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A randomized controlled trial of cognitive-behavior therapy for persistent symptoms in schizophrenia: A five-year follow-up

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Abstract

Meta-analyses of randomized controlled trials support the efficacy of cognitive behavioral therapy (CBT) in the treatment of symptoms of schizophrenia refractory to antipsychotic medication. This article addresses the issue of medium term durability. A five-year follow-up was undertaken of a sample of 90 subjects who participated in a randomized controlled trial of CBT and befriending (BF). Patients received routine care throughout the trial and the follow-up period. Intention to treat multivariate analysis was performed by an independent statistician following multiple imputation of missing data. Fifty-nine out of ninety patients were followed up at 5 years (CBT=31, BF=28). In comparison to BF and usual treatment, CBT showed evidence of a significantly greater and more durable effect on overall symptom severity (NNT=10.36, CI −10.21, 10.51) and level of negative symptoms (NNT=5.22, CI −5.06 −5.37). No difference was found between CBT and BF on either overall symptoms of schizophrenia or depression. The initial cost of an adjunctive course of CBT for individuals with medication refractory schizophrenia may be justified in light of symptomatic benefits that persist over the medium term.

Keywords: Cognitive-behavior therapy; Schizophrenia; Medium term follow-up

1. Introduction

1.1. The need for psychosocial interventions in schizophrenia

Schizophrenia is usually a recurrent disorder, and despite treatment with first-generation antipsychotic drugs (FGAs), the illness has a poor course and outcome in around half of those with the diagnosis (Gaebel and Frommann, 2000; Harrison et al., 2001). The symptomatic burden of many patients may have been ameliorated by the introduction of the second-generation antipsychotics (SGAs), which have a lower liability for extrapyramidal side effects (Geddes et al., 2000) and may provide a greater protection against relapse than FGAs (Leucht et al., 2003). Further, the SGA clozapine is effective in a proportion of patients whose illness has proved unresponsive to other

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antipsychotic medications (NNT = 7 for 20% symptomatic improvement) (Williams et al., 2002). Nevertheless, the best estimates still suggest that 30%–40% of all those who develop schizophrenia will develop chronic distressing symptoms despite the availability of such medication (Cannon and Jones, 1996). Also, the CATIE trial demonstrated that discontinuation of antipsychotic medication and relapse occurred in the majority of patients at short-term follow-up (Lieberman et al., 2005). The recent NIMH MATRICS initiative called for the urgent need to describe and research new treatments for negative symptoms of schizophrenia and cognitive deficits (Kirkpatrick et al., 2006). CBT has shown benefits in relapse prevention and delay as well as on negative symptoms (Turkington et al., 2006). This paper explores the medium term durability of any such benefits.

1.2. CBT benefits over the short-term in schizophrenia

CBT can be fully manualised (Kingdon and Turkington, 2005) with clear protocols for training and supervision (Kingdon and Turkington, 2003). Quality assurance in terms of therapists' adherence to therapy style and proposed interventions can be independently rated (Haddock et al., 2001). The primary outcomes for all CBT trials to date have been overall symptoms, positive symptoms or relapse. In comparison to control treatments, CBT has been shown to have a greater effect on overall severity of symptoms in the short-term (Pilling et al., 2002), and there is evidence to suggest it may delay relapse and reduce days hospitalised (Gumley et al., 2003). CBT has also been shown to have a significant effect (ES = 0.65) on positive symptoms (delusions and hallucinations) at the end of therapy that persists in the short-term (9 months) (ES = 0.93) (Gould et al., 2001). However, the most recent meta-analysis shows more modest effect sizes, is more guarded concerning the specific versus the non-specific effect of CBT and advocates head-to-head trials with other effective psychosocial treatments (Zimmerman et al., 2005). The five-year follow-up of CBT reported by Drury et al. (2000) failed to show durable effects except in those who did not relapse. In comparison the five- and eight-year follow-up of family CBT (Tarrier et al., 1994) confirmed protection against relapse but only in the high expressed emotion group.

2. Methods

2.1. Subjects

Ninety individuals with established schizophrenia who were willing and able to give written informed consent were recruited in London and the North of England (Cleveland, Durham and Newcastle) to a randomized controlled treatment trial of 20 sessions of CBT or BF (Kingdon and Turkington, 1989). This was a geographical convenience sample. Referrals of patients with persistent hallucinations and delusions were sought from psychiatric outpatient clinics. The DSM-IV (APA, 1993) and ICD-10 diagnoses of schizophrenia and presence of persistent hallucinations and/or delusions was confirmed using the diagnostic checklists. All patients had positive symptoms of such severity as to have caused distress and/or dysfunction for a minimum of 6 months despite adequate trials of antipsychotic medication. An adequate trial of antipsychotic medication was defined as regular use of antipsychotic medication, with no evidence of poor adherence, at or above the equivalent of 300 mg daily of chlorpromazine, including a minimum period of at least 2 weeks of treatment with the equivalent of 600 mg of chlorpromazine unless this was precluded by side effects or contraindications (Kane et al., 1988). Patients were included if their use of cannabis or alcohol was intermittent, but were excluded if their primary diagnosis was of one of alcohol or substance dependence. After complete description of the study to the subjects written informed consent was obtained. The subjects were followed up immediately post-therapy (9 months) at 18 months and at 5 years.

2.2. Interventions

Both therapists were experienced psychiatric nurses trained in CBT and BF and given regular supervision. CBT and BF were both delivered by the same therapist to control for non-specific factors. An attempt was made to deliver the same amount of face-to-face contact to each group. Patients randomized to each treatment limb were offered 20 sessions over a nine-month period. Sessions were variable in length but an attempt was made to aim for 45 min of therapy time.

2.2.1. CBT

The CBT approach has been described in manualised form (Kingdon and Turkington, 2005). Early sessions focused on engaging, normalising and developing explanations for distressing psychotic symptoms. Thereafter vulnerability–stress formulations were jointly constructed. Auditory hallucinations were tackled by developing coping strategies backed up by voice diaries. Paranoid delusions were dealt with using the development of alternative explanations and reality testing homework. Negative symptoms were worked on using activity

scheduling and mastery and pleasure recording. Affect and cognition recognition and labelling were worked on in session. Anxiety and depression which often worsen positive and negative symptoms were addressed using recognition of cognitive distortions and the development of rational responses. Negative attitudes to medication were explored and modified through guided discovery. Very negative personal beliefs (schemas) which often perpetuate voice hearing and underlie delusional systems were collaboratively modified. Lastly a personal relapse prevention plan was agreed.

2.2.2. BF

This approach has been previously described and is based on the principles of social support (Milne, 1999). The approach depended on a high quality interpersonal relationship which focused on neutral i.e. non-psychotic issues. BF as delivered was non-confrontational and non-collusive and conversation was always directed away from symptoms to everyday activities such as hobbies, the weather, holidays and sports. No homework was given and no techniques used except those of keeping the conversation going, personal disclosure and maintaining an interest in the patient's current opinions and activities.

2.3. Assessments and procedures

The assessment measures used in the original study were repeated at the five-year follow-up. These included the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981), and the Comprehensive Psychopathological Rating Scale (CPRS) (Asberg et al., 1978), from which can be derived the Schizophrenia Change Scale (SCS) (Montgomery et al., 1978) and the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The summary scores described in the analysis included the following — CPRS total score, SANS total score (including attention and inappropriate affect items), SCS and MADRS. Ratings were completed by two independent raters blind to treatment group following a period of training by an expert. These were not the same raters who took part in the original trial but they were trained in the use of the same scales by the same expert (TRB) using the same training methods and inter-rater reliability of 0.954 was achieved. Ratings were independently completed by both raters on six patients. Permission to interview the patients was sought from their consultant psychiatrists, care managers/community key workers and general practitioners. Assessments were undertaken via face-to-face interviews and, in addition, data on relapse, hospitalisation and medication (changes in drug and dosage in chlorpromazine equivalence) were extracted from the psychiatric notes using a coded proforma. The primary outcome was a statistical and clinically significant improvement in overall symptoms at the five-year follow-up point. Secondary outcomes included statistical and clinically significant improvements in negative symptoms, symptoms of schizophrenia (including positive symptoms), depression and days spent re-hospitalised during the five-year period.

2.4. Statistical analysis

Summary statistics such as mean standard deviations together with the 95% C.I. were used to find the overall difference between the main four outcomes CPRS, SANS, SCSS and MADRS with the two treatments (BF and CBT). The multi-variable regression models were fitted to locate the change in the five-year follow-up for each outcome adjusting for the baseline measure, and gender. As a completer analysis may not be representative of the study population, multiple imputation using all previous time points was applied to account for missing data in the multivariate regression analysis of each of the four continuous outcome measures. In this method each missing value is replaced by $m > 1$ plausible values. The multiple imputation method is implemented under the assumption that the missing data are missing at random (MAR) (Rubin, 1987). This is when incomplete data differs from cases with missing data, but the pattern of data missing is traceable or predictable from other observed variables in the database. For each incomplete outcome variable 20 imputed variables were generated conditional on the baseline scores for that variable, gender and treatment condition. This was generated using multiple imputation routines written in STATA 8. Multivariate regression was applied to the 20 imputed variables. Results were combined using multiple imputation rules (Rubin, 1987), which take into account the uncertainty due to missing values. Repeated measures modelling was adequate to analyse the data set without a need for hierarchical modelling. Statistical significance was represented using 95% confidence intervals and also as $p < 0.05$ for continuous variables. The number needed to treat (NNT) is the number of patients who need to be treated with an experimental treatment (in this case CBT) as compared to a control treatment (in this case BF) in order for one additional patient to benefit. It is calculated on the basis of an *a priori* standard for a good clinical outcome (in this case, an improvement of 50% or greater in symptom score from baseline). The NNT is calculated

Table 1
Means and confidence intervals at baseline, end of therapy, nine-month and five-year follow-up for CBT and BF

		Baseline mean (SD) [95% C.I.]	Therapy end mean (SD) [95% C.I.]	Nine-month follow-up mean (SD) [95% C.I.]	Five-year follow-up mean (SD) [95% C.I.]
CPRS	CBT	36.2 (13.9) [32.1, 40.4]	23.4 (9.64) [20.6, 26.3]	19.4 (15.4) [14.9, 23.9]	24.4 (11.7) [20.1, 28.7]
	BF	36.3 (14.5) [31.9, 40.8]	27.7 (13.9) [23.5, 32.0]	32.3 (22.2) [25.5, 39.2]	29.0 (14.0) [23.5, 34.5]
SANS	CBT	36.7 (21.7) [30.3, 43.1]	24.7 (14.0) [20.5, 28.8]	20.7 (15.2) [16.2, 25.1]	22.8 (14.5) [17.4, 28.1]
	BF	30.6 (25.4) [22.8, 38.5]	24.7 (19.0) [18.8, 30.6]	24.7 (24.6) [23.7, 38.8]	33.1 (22.6) [24.4, 41.9]
SCS	CBT	10.7 (5.1) [9.2, 12.2]	5.4 (3.9) [4.2, 6.5]	4.6 (3.0) [3.7, 5.5]	6.5 (5.2) [4.6, 8.4]
	BF	10.7 (5.4) [8.9, 12.3]	8.0 (6.1) [6.1, 9.9]	8.6 (7.0) [6.5, 10.8]	7.5 (4.5) [5.7, 9.3]
MADRS	CBT	9.5 (4.9) [8.0, 10.9]	4.9 (3.5) [3.9, 5.9]	4.3 (2.6) [3.5, 5.0]	5.5 (4.3) [3.9, 7.1]
	BF	10.3 (4.4) [8.9, 11.6]	7.4 (4.6) [5.9, 8.8]	8.2 (6.4) [6.2, 10.2]	7.0 (4.6) [5.2, 8.7]

Outcome measures are CPRS (overall symptoms), SANS (negative symptoms), SCS (symptoms of schizophrenia) and MADRS (depression).

as the reciprocal of the risk difference (Laupacis et al., 1988).

3. Results

3.1. Sample characteristics

At the five-year follow-up point, 31 of the 90 patients could not be re-assessed (17 refused or had relocated, access was refused for 12, and 2 had died): 31 of the 46 patients in the CBT treatment group, and 28 of the 44 assigned to the BF group were successfully followed up. All of the 12 patients to whom access was refused were in the London centre, as such, significantly fewer patients were followed up at the London centre (16/33) as compared to the Newcastle centre (43/57). There was no significant baseline difference in total CPRS, SANS, SCS or MADRS found between those patients who were lost to follow-up and those who were retained in the trial in each group.

3.2. Durability of CBT and BF effects on overall and negative symptoms at 5 years

Table 1 illustrates the mean scores with standard deviations and confidence intervals for CBT and BF at baseline, end of therapy, nine-month and five-year follow-up. The mean score for the primary outcome (overall symptoms) in the CBT group at five-year follow-up is 24.4 as compared to 29.0 in the BF group. CBT showed a significantly more durable benefit on overall symptoms (group × time, CI −12.85, −1.56) than BF at the five-year follow-up point. The mean scores for negative symptoms (SANS) at five-year follow-up are 22.8 for CBT and 33.1 for BF. There was a significant baseline difference between the two groups on this secondary outcome with a higher baseline mean score in the CBT group. However, this is a statistically significant effect (group × time, CI −23.62, −7.34).

3.3. Good clinical outcomes at 5 years with CBT and BF

On the basis of a worst case scenario, taken from a position of clinical equipoise, i.e. that none of those patients with missing data achieved a good clinical outcome, the number needed to treat (NNT) for the primary outcome is 10.36 (CI −10.21, −10.51). This indicates a moderate effect size for CBT over an active psychological treatment comparator (BF) in terms of a durable effect on overall symptoms at five-year follow-up. The NNT in relation to the clinical significance of this result in favour of CBT over BF for negative symptoms is 5.22 (CI 5.06, 5.37) indicating a moderate to strong effect.

3.4. Results for CBT and BF on symptoms of schizophrenia and depression at 5 years

In terms of the other secondary outcomes, results of the regression analysis do not show a statistically significant difference for symptoms of schizophrenia or depression ratings between the treatment groups. Symptoms of schizophrenia were rated using a subscale of the CPRS (the Schizophrenia Change Scale Score)(SCS) (Montgomery et al., 1978). However, both CBT and BF groups had maintained significant improvements in relation to baseline for symptoms of schizophrenia and depression. In relation to all symptoms of schizophrenia (SCS), the five-year mean for CBT was 6.6 and for BF the figure was 7.5. This was not statistically significant (group × time, −3.02, 1.20). The depression mean score at 5 years was 5.0 for the CBT group and 5.9 for the BF group. This was not statistically significant (group × time, −3.16, 0.50) Table 2.

3.5. Hospitalisation results over 5 years

There was no significant difference between the two groups available for study on the number of re-hospitalisations or total days spent in hospital. There was a trend in favour of CBT (CBT total days

Table 2
Regression analysis with baseline measure of variables as covariates

	Coefficient	SE	*p*-value	95% C.I.
Baseline CPRS	0.17	0.114	0.15	−0.05 to 0.40
Cognitive therapy	−5.82	2.861	0.04	−11.42 to −0.21
Gender	4.71	3.158	0.21	−1.48 to 10.90
Baseline SANS	0.32	0.08	0.01	0.16 to 0.49
Cognitive therapy	−15.47	4.15	0.01	−23.62 to −7.34
Gender	6.03	4.11	0.42	−2.02 to 14.09
Baseline SCS	0.21	0.01	0.06	−0.02 to 0.43
Cognitive therapy	−0.91	1.16	0.63	−3.02 to 1.20
Gender	0.11	1.39	0.78	−2.20–2.42
	5.41	4.16		1.41–9.41
Baseline MADRS	0.28	0.09	0.01	0.09–0.47
Cognitive therapy	−1.33	0.93	0.11	−3.16–0.50
Gender	1.18	0.98	0.18	−0.76–3.11

hospitalised = 1323, BF total days hospitalised = 2947). The hospitalisation data was heavily skewed. Analysis was undertaken using log transformation and then with non-parametric methodology. The actual number of patients admitted was 26 (CBT = 14, BF = 12) with the total number of admissions being 41 (CBT = 22, BF = 19). There were no statistically significant differences between the groups on type or dose of antipsychotic medication. Switches to atypical medication (CBT = 5, BF = 4) indicated no significant between group differences. No switch data was imputed.

4. Conclusions

4.1. Discussion of CBT benefits over 5 years

Our first publication (Sensky et al., 2000) showed that both CBT and BF had significant effects on the primary and secondary outcome measures at the end of therapy, but that only the CBT group maintained these improvements when the groups were re-assessed 9 months post-therapy. It was hypothesized that individuals receiving CBT had gained a greater understanding of their symptoms and acquired additional strategies that they could independently employ to cope more effectively with the disorder than those individuals who received a supportive intervention. The NNT for a good clinical outcome on overall symptoms at nine-month follow-up was 4. The present study attempted to answer the question as to whether these benefits would last over the medium term. Presuming a worst clinical case scenario in relation to imputed data (i.e. that all patients who could not be followed up failed to have a good clinical outcome) the NNT for overall symptoms being improved by 50% at five-year follow-up in relation to baseline was 10.36 (CI 10.21, 10.51) for CBT in relation to BF. The effect on negative symptoms was even stronger with an NNT of 5.22 (CI 5.06, 5.37) for a good clinical outcome of a 50% improvement in SANS between baseline and five-year follow-up favouring CBT over BF. Given that there was no difference between the groups on symptoms of schizophrenia or on depression it is possible that the result on overall symptoms may be accounted for by the difference in negative symptoms. Many of the techniques described in the manual were targeted at hallucinations and delusions but it would seem that the short-term effect of CBT on symptoms of schizophrenia (SCS) although durably maintained at medium term follow-up were not significantly better than BF. Similarly the greater reduction in depression seen with CBT as compared to BF that was present at nine-month follow-up was not present at the five-year follow-up assessment. This was a stable community based patient group so it was not predicted that there would be any impact on number of readmissions to hospital or days spent in hospital. There was however a trend in favour of CBT in terms of aggregate days hospitalised (1323 days versus 2947 days) over the extended five-year follow-up period.

4.2. Possible explanations of a durable effect on negative symptoms

These results however seem paradoxical. Why was there a durable and stronger effect of CBT on negative symptoms? The particular techniques used in relation to negative symptoms included graded activity scheduling, mastery and pleasure recording, thought recording and emotional labelling and linked homework exercises. There are a number of possible explanations. Such techniques may directly lead to a 'switching on' of the prefrontal cortex via biological mechanisms. CBT may act to reduce social withdrawal by reducing stigma. It is also possible that those patients who can challenge avoidance behaviours can improve their range of activities and interactions in a durable manner. Such patients with high levels of negative symptoms may also have benefited from the introduction of atypical antipsychotics over the period in question further enhancing their gains. On the other hand very isolated patients with negative symptoms initially benefiting with BF may have further deteriorated with the removal of that intervention.

4.3. Comparison with other medium term follow-up studies of CBT in schizophrenia

We clearly need prospective, independent, follow-up data regarding the impact of the various psychological treatments available. Paykel et al., 1999 in a five-year, follow-up study of CBT in chronic depression showed a

lasting benefit of a course of CBT for 3.5 years, making the intervention clearly cost-effective. Only one other five-year follow-up has as yet been published in the CBT of schizophrenia literature (Drury et al., 2000). This study followed up an RCT of patients in acute relapse who were treated with CBT or recreational activities and support in an inpatient setting. At follow-up, no statistically significant 'between group' differences were found in relapse rates, positive symptoms or degree of insight. However, in those patients who had experienced one relapse or less, the CBT group did show evidence of significantly less residual positive symptoms. No durable benefit was found for overall or negative symptoms. Hogarty et al. (1997) described the use of personal therapy with outpatients with schizophrenia: this involves some CBT components including psychoeducation, adherence work and social skills training. Over the three years of the trial, there were benefits in terms of symptomatic control and relapse, however patients treated without the support of a carer showed signs of deterioration at follow-up. The importance of continuing input was again stressed. Our trial was similarly unimpressive in reducing positive symptoms in a durable way as compared to BF, but showed a differential benefit for CBT in the reduction of overall and negative symptoms. This study adds to the above literature as the only five-year follow-up study of patients with schizophrenia with persisting symptoms in the literature at the current time.

4.4. Methodological weaknesses and implications of this study

In our study we may have missed a durable benefit on symptoms of schizophrenia or depression due to a lack of intermediate assessments at 2, 3 and 4 years. The main methodological weaknesses of this study were that it did not have a treatment as usual limb, employed a single cross-sectional assessment of symptoms rather than prospective annual longitudinal ratings of outcome and that 31 of the 90 baseline patients could not be re-assessed. Two patients had died; one of pneumonia, one in an accident and 17 patients refused follow-up. In the case of 12 patients, permission was not granted for us to make contact. These patients were not demographically or symptomatically different from the rest of the cohort at baseline and the proportion of patients followed up from each treatment limb was not significantly different. These results were achieved with a reasonable dose of therapy but without booster sessions. It is possible that, in routine practice, booster sessions would be given, thus further enhancing these effects. These results support the meta-analyses which conclude that CBT should be made available for those patients with schizophrenia with antipsychotic resistant symptoms (Pilling et al., 2002; Gould et al., 2001; NICE, 2002). This trial represents a possible indication of CBT efficacy in schizophrenia and should now be followed up by a definitive multi-centre trial. Such a trial should use a more sensitive measure of positive symptoms and also focus on social outcomes such as occupational recovery and quality of life.

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Contributors

Professors Turkington, Sensky, Kingdon, Barnes and Scott were involved in study design and wrote the protocol. Dr Nur undertook the statistical analyses. Tom Sensky, Ronald Siddle, Katherine Hammond and Neshika Samarasekara were involved in data collection, literature searches and analysis. Professor Turkington wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The only disclosures relate to Professors Turkington, Kingdon and Barnes.

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