ORIGINAL ARTICLE

A Randomized Controlled Trial of Cognitive-Behavioral Therapy for Persistent Symptoms in Schizophrenia Resistant to Medication

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Background: Research evidence supports the efficacy of cognitive-behavioral therapy in the treatment of drug-refractory positive symptoms of schizophrenia. Although the cumulative evidence is strong, early controlled trials showed methodological limitations.

Methods: A randomized controlled design was used to compare the efficacy of manualized cognitive-behavioral therapy developed particularly for schizophrenia with that of a nonspecific befriending control intervention. Both interventions were delivered by 2 experienced nurses who received regular supervision. Patients were assessed by blind raters at baseline, after treatment (lasting up to 9 months), and at a 9-month follow-up evaluation. Patients continued to receive routine care throughout the study. An assessor blind to the patients' treatment groups rated the technical quality of audiotaped sessions chosen at random. Analysis was by intention to treat.

Results: Ninety patients received a mean of 19 individual treatment sessions over 9 months, with no significant between-group differences in treatment duration. Both interventions resulted in significant reductions in positive and negative symptoms and depression. At the 9-month follow-up evaluation, patients who had received cognitive therapy continued to improve, while those in the befriending group did not. These results were not attributable to changes in prescribed medication.

Conclusion: Cognitive-behavioral therapy is effective in treating negative as well as positive symptoms in schizophrenia resistant to standard antipsychotic drugs, with its efficacy sustained over 9 months of follow-up.

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SCHIZOPHRENIA causes persistent or recurrent symptoms that are often distressing and socially disabling. Antipsychotic medication is often helpful in attenuating positive symptoms and reducing the risk of relapse, but some patients fail to respond adequately, even to newer antipsychotic drugs. Therefore, adequate clinical treatment of people with schizophrenia should include nonpharmacologic treatments. Particularly relevant in this respect are psychosocial interventions that can be readily incorporated into the training of health care professionals and integrated into routine clinical practice.

Cognitive-behavioral therapy (CBT) is such an intervention. It is a structured psychological therapy initially applied to the management of depression[1] but now used for wide range of psychiatric diagnoses.[2] Early case studies demonstrated benefits from CBT in treating persistent psychotic symptoms,[3-5] and later case series and open studies have provided further support for the potential benefits of CBT for schizophrenia in reducing distress, disability, and hospitalization.[6,7]

Several controlled trials have now been published regarding the use of CBT for schizophrenia,[8] to improve adherence,[9,10] as an adjunctive treatment among inpatients admitted for short-term treatment,[11] and for psychotic symptoms unresponsive to medication.[8,12,13] Two of these studies have also reported 18-month follow-up data.[14,15] These results have been reported as promising in a recent Cochrane review[16] and in the American Psychiatric Association guidelines.[17] However, there are limitations in the published studies and questions about their generalizability. Methodological problems include paucity of published methodological details,[9] small sample size,[12] problems keeping clinicians blind to the intervention,[8,11] failure to report treatment changes that might mediate observed clinical improvements,[8] and possible difficulties with the chosen control conditions.[8,11,12] Two studies involved in-

SUBJECTS AND METHODS

SAMPLE

Patients were recruited into the study from 5 clinical services: 2 in West London and 3 in the north of England (one each in Newcastle, Cleveland, and Durham). Patients were included if they were aged 16 to 60 years; had a diagnosis of schizophrenia according to both *International Classification of Diseases, 10th Revision* (*ICD-10*) research and *DSM-IV* criteria; and had symptom(s) causing distress and/or dysfunction that had persisted for at least 6 months despite adequate trials of antipsychotic medication. An adequate trial was defined as regular use of antipsychotic medication for 6 months or more, with no evidence of poor adherence, at dosages 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 daily of chlorpromazine, unless this was precluded by side effects or contraindications. Exclusion criteria were a primary diagnosis of alcohol or drug abuse; current abuse of drugs or alcohol warranting specific clinical intervention, such as attendance at a specialist substance misuse clinic; exclusively negative symptoms; or not complaining of any positive symptoms or of depression.

In a pilot study using different patients, after 8 weeks' treatment, the Comprehensive Psychiatric Rating Scale (CPRS)[18] mean (SD) total scores for CBT and BF were 14 (9) and 22 (12), respectively. On this basis, a sample size of 86 would demonstrate a significant difference between the 2 treatments with 90% power.

ASSESSMENTS AND PROCEDURES

The main outcome assessments were the CPRS total score, global score, and schizophrenia change score,[19] the Montgomery-Åsberg Depression Rating Scale,[20] and the Scale for Assessment of Negative Symptoms (SANS).[21] The CPRS and SANS were chosen as the main outcome measures because they had been used in the earlier pilot study,[22] both are widely validated, and both are used in other intervention studies in schizophrenia. Interrater reliability was high; for the CPRS, the intraclass correlation coefficient after training was 0.92.

Clinicians were asked to refer patients to the study, and those referred had their eligibility confirmed by one of the researchers. The *DSM-IV* and *ICD-10* research diagnoses of schizophrenia were confirmed by clinical interview, including information gathered for the CPRS and SANS ratings. After written informed consent was obtained, patients were then assigned to one of the treatment arms using simple randomization applied independently for the London patients (the London center) and for those from Newcastle, Cleveland, and Durham (the Newcastle center). The randomization was by members of the research team not involved with either the assessments or the treatments. Further assessments were carried out approximately 9 months later, after completion of the intervention, and again at 9-month follow-up assessment. The assessors were independent of the randomization procedure and remained blind to each patient's assigned group throughout the study.

Further data were abstracted from clinical records. As both psychological interventions were being applied against a background of maintenance antipsychotic medication, it was important to exclude the possibility that improvements were attributable to changes in antipsychotic drug treatment. Total dose of antipsychotic drugs at each assessment was calculated as chlorpromazine equivalents (milligrams per day).[23] Prescription of atypical antipsychotic drugs was noted.

INTERVENTIONS

Patients received individual treatment from 1 of 2 therapists (M.O. and R.S.). One therapist was based at each study center, and each offered CBT or BF, according to the patient's assigned group. The therapists, both experienced psychiatric nurses, underwent recognized training in CBT, and were registered as therapists by the United Kingdom Council for Psychotherapies. Both duration and frequency of the sessions were flexible to accommodate the needs of individual patients, but the initial aim was to offer each patient at least 45 minutes of therapy each week. After this phase, which could last up to 2 months, the session frequency could be reduced, with the aim of completing each patient's course of therapy within 9 months. Interviews were audiotaped for supervision and for quality control (see below). Patients in either group who attended fewer than 6 therapy sessions were considered to have failed to engage in treatment.

Cognitive-Behavioral Therapy

The CBT interventions followed the treatment manual developed by 2 of us (D.K. and D.T.),[24] who also provided regular supervision.

The general approach, as in other applications of CBT, was a collaborative understanding of the development of symptoms and work toward reducing distress and disability.

tensive CBT,[11,13] which might be difficult to provide outside research settings.

The present study was designed to overcome many of the limitations of previously published work. The aim was to compare individual CBT with a nonspecific befriending (BF) intervention in reducing psychiatric symptoms among people with schizophrenia who had experienced distressing positive symptoms refractory to conventional antipsychotic medication. The hypotheses tested were that a course of CBT is superior to BF in reducing psychiatric symptoms and that the benefits of CBT endure 9 months after the intervention has ended.

RESULTS

SAMPLE

Ninety patients were randomized: 57 from Newcastle, Cleveland, and Durham and 33 from London. Although the 2 groups were well matched overall in their baseline

The therapy followed distinct stages, including engagement, examining the antecedents of the emergence of the psychotic disorder, developing a normalizing rationale, treating coexisting anxiety or depression, and generating a shared case formulation. Thereafter, specific techniques were used with positive psychotic symptoms. For auditory hallucinations, collaborative critical analysis of beliefs about the origin and nature of the voice(s) was followed by the use of voice diaries, reattribution of the cause of the voices, and generation of possible coping strategies. Delusions were elucidated by guided discovery and graded homework tasks. Thereafter, Socratic questioning was used, and for grandiose or systematized delusions, linked underlying beliefs were identified using inference chaining (the downward arrow technique[25]). Interventions to improve thought disorder included focusing on specific themes, clarification of neologisms, and thought linkage (this last technique involves the therapist persistently requesting that the patient attempt to explain the jumps between topics). Interventions for negative symptoms were usually instituted only after work on positive symptoms, using paced activity scheduling and diary recording of mastery and pleasure.

Befriending

This intervention was designed to provide patients with approximately the same amount of therapist contact as the CBT group, with sessions spaced at similar intervals. The therapists aimed to be empathic and nondirective. Psychotic or affective symptoms were not directly tackled in any way. The sessions focused on neutral topics, such as hobbies, sports, and current affairs.

Quality Control

A random sample of 87 audiotaped therapy sessions was assessed by a member of the research team (J.L.S.) blind to all patient data and to the audiotape selection procedure. The tapes selected were stratified according to therapist (R.S. and M.O.), therapy (CBT or BF), stage of individual therapy (early, middle, or late session), and time of entry to the study (early, middle, or late recruit). The assessor assigned each tape to either the CBT or the BF group. To determine the technical quality of the CBT sessions and to confirm that the BF intervention was unlikely to have incorporated CBT techniques, all 87 audiotaped sessions were rated using an assessment based on the Cognitive Therapy Rating Scale (CTRS).[1,26] A score of 39 or more was defined as an adequate level of technical competency in the CBT sessions. The CTRS includes a general section as well as items focusing specifically on cognitive therapy; in the absence of any cognitive or behavioral techniques, good interviews are expected to score up to 20 through 24. In addition, records were kept of the duration of each treatment session and the number of sessions each patient received.

Patients were asked to complete a 10-item questionnaire eliciting their satisfaction with different aspects of their therapy, each item being rated on a fully anchored 6-point scale (rated 1-7). Only 55 completed questionnaires were received.

STATISTICAL ANALYSIS

Analysis of the main outcome measures was by intention to treat, using multilevel modeling techniques.[27] Multilevel modeling was chosen in preference to multivariate analysis of variance because the former is able to model more accurately the clustered or hierarchical nature of the study data (patients within treatment groups within centers). The 3 assessment occasions were treated as a 3-level repeated-measures factor. Among-subjects factors used in the analyses were sex and center as well as treatment. Up to 3-way interactions were tested of center and treatment with time, and 2-way interactions were tested of sex with the other factors. Multilevel modeling yields a fitted mean (the intercept) for the reference level of all the factors in the analysis (for these analyses, the reference group was Newcastle, BF, female) plus estimates of the extent to which each factor alters the analysis.

Differences between means may be difficult to interpret clinically. A further analysis examined the proportion of patients by treatment group who showed an improvement between baseline and follow-up evaluations of 50% or greater in scores on each outcome measure. The absolute benefit increase[28] attributable to CBT is the difference in proportions of cases showing 50% or greater improvement in the CBT group vs appropriate comparisons. Two comparisons were used: the first compared improvements in the CBT and BF groups and the second assumed that the spontaneous rate of symptom reduction of 50% or greater would be 10%, as reported by Tarrier et al.[13] These absolute benefit increase figures were used to calculate 2 estimates of the number of patients who need to be treated with CBT for one patient to show improvement.[29]

Results from data other than the main outcome variables did not require the hierarchical approach described above, and therefore relied on analysis of variance or χ^2 tests, as appropriate.

All analyses involved 2-tailed tests, with α set at .05.

characteristics (**Table 1**), there were more women in the BF group than in the CBT group ($\chi^2_1 = 6.3$; $P = .01$) among the Newcastle patients. Although entry criteria for the study precluded people with thought disorder likely to interfere with assessment or therapy, no patients were actually excluded based on this criterion. Thirteen patients (14% of the sample) were rated on the CPRS as having clinically significant incoherent speech. The presence of significant substance misuse was not ascertained at baseline, but clinical records indicated that up to 13 patients (14%) warranted a dual diagnosis of schizophrenia plus substance misuse.

Data at the 3 points (baseline, treatment outcome, and 9-month follow-up evaluation) were collected for all the patients randomized, except that SANS data were not collected for 2 patients from Newcastle. This was because of the assessors rather than because of any bias caused by the patients.

As the multilevel modeling results indicate (**Table 2**), there were small but significant differences

Table 1. Baseline Characteristics of the Sample*

	Treatment Group		
	CBT (n = 46)	BF (n = 44)	Total (N = 90)
Men, No. (%)	31 (67)	22 (50)	53 (59)
Ethnic group, No. (%)			
White	40 (87)	40 (91)	80 (89)
Nonwhite	6 (13)	4 (9)	10 (11)
Age, y, mean (95% CI)	39 (35-42)	40 (35-45)	39 (37-42)
Time since diagnosis, y, mean (95% CI)	14 (12-17)	15 (11-18)	14 (12-17)
Previous admissions, median	3	3	3
Psychopathology at initial assessment, No. (%)†			
Delusions‡ and hallucinations§	27 (59)	27 (61)	54 (60)
Delusions‡ or hallucinations§	18 (39)	16 (36)	34 (38)

*CBT indicates cognitive-behavioral therapy; BF, befriending; and CI, confidence interval.

†Based on relevant Comprehensive Psychiatric Rating Scale (CPRS) items.

‡Measured using CPRS items 31, 33, and 36.

§Measured using CPRS items 37 through 40.

between the centers in CPRS and Montgomery-Åsberg Depression Rating Scale scores (Table 2). Men had higher baseline SANS scores (mean, 38; 95% confidence interval [CI], 32-44) than women (mean, 26 [95% CI, 18-35]). Initial CPRS total scores were also higher for men (mean, 38 [95% CI, 34-42]) than women (mean, 33 [95% CI, 28-38]). This, together with the excess of men in the CBT group in Newcastle, probably contributed to the significant center × treatment interaction in CPRS total score. Patients recruited in Newcastle had higher CPRS total scores (mean, 38 [95% CI, 34-42]) than those in London (mean, 33 [95% CI, 29-37]). Similar differences between centers were found for CPRS schizophrenia change and Montgomery-Åsberg Depression Rating Scale scores. Such between-center differences would be expected, given that randomization was done independently at the 2 centers, hence effectively stratifying the sample by center.

OUTCOME MEASURES

The 4 principal outcome measures all showed a similar pattern (**Figure**) (Table 2). Both CBT and BF resulted in significant symptom improvements at the end of the treatment period (shown by significant time 2 main effects in Table 2). At the end of treatment, there were no significant differences between the 2 interventions (indicated by the absence of significant treatment × time 2 interactions in Table 2). However, at 9-month follow-up, CBT resulted in significantly greater improvements than BF for all 4 outcome measures (shown in Table 2 by treatment × time 3 interactions making significant contributions to each of the models). Between outcome and follow-up evaluation, those in the CBT group continued to show improvements, while those in the BF group lost some of their earlier gains (Figure). As shown in **Table 3**, using the outcome criterion of 50% or greater reduction in symptom scores, both treatments led to substantial percentages of patients improving, with CBT superior to BF in reducing CPRS total scores, and a trend in the same direction for the schizophrenia change scores. Depending on the assumed rate of improvement in the absence of CBT treatment, the number of patients needed to recruit into CBT treatment to show one successful outcome varied between 2 and 6.

Improvements at follow-up evaluations in CPRS schizophrenia change and SANS scores differed between the centers (shown by the significant center × treatment × time 3 interactions in Table 2). In the CBT group, the Newcastle patients showed greater reduction in CPRS schizophrenia change scores (mean difference between baseline and follow-up, –8 [95% CI, –9 to –6]) than did the London patients (mean difference, –4 [95% CI, –7 to –1]). In the BF group, in Newcastle, only small changes were found between baseline and follow-up on both the CPRS schizophrenia change score (mean difference, –2 [95% CI, –5 to 0.2]) and the SANS (mean difference, 5 [95% CI, –10 to 20]). By contrast, much greater changes were found in the CPRS schizophrenia change score (mean difference, –5 [95% CI, –8 to –2]) and the SANS (mean difference, –25 [95% CI, –34 to –16]) for patients in the BF group in London.

MEDICATION USE

The mean dosages of antipsychotic medication within the treatment groups changed very little between baseline and follow-up evaluations (**Table 4**), although there was a wide range of dosage within the treatment groups and mean dosages varied between individuals and centers. Nevertheless, comparing the CBT and BF groups, similar proportions of patients had their drug dose increased during the study, or were given atypical antipsychotic drugs.

QUALITY ASSURANCE

Only 6 patients (4 assigned to CBT and 2 to BF) failed to engage in treatment. An additional 9 patients (5 in the CBT group and 4 in the BF group) had less therapist contact than the therapists aimed to offer and were judged to have ended the intervention prematurely. For the whole sample, the mean total session time was 698 minutes (95% CI, 628-770 minutes), but ranged from 60 to 1655 minutes. Overall, the mean number of sessions was 19 (95% CI, 17-21 sessions [range, 2-33 sessions]). The CBT and BF groups did not differ significantly in total session time or number of sessions. For those patients who did not end the intervention prematurely, the mean total session time was 775 minutes (95% CI, 706-844 minutes [range, 222-1655 minutes]), and the mean number of sessions was 21 sessions (95% CI, 20-22 sessions [range, 6-33 sessions]). The mean patient satisfaction score (theoretical range, 7-70) was 47 (95% CI, 44-50 [range, 26-63]). Patients were more satisfied with the CBT intervention (mean, 50 [95% CI, 47-53]) than

Table 2. Summary and Statistical Analyses of Main Outcome Measures by Treatment Group*

Outcome Measure	Assessment	CBT, Mean (95% CI)	BF, Mean (95% CI)	Variables Making Significant Contribution to Model†	Parameter Estimate (SE)
CPRS total	Initial	35.6 (31.6-39.7)	36.1 (31.7-40.5)	Intercept	40.8
				Center‡	−16.1 (3.9)
				Time 2§	−14.7 (1.8)
	Outcome	20.5 (17.7-25.5)	22.9 (17.7-28.2)	Treatment‖	−11.8 (3.5)
				Center × treatment	23.7 (5.4)
				Sex¶	5.6 (2.7)
	Follow-up	15.1 (12.0-19.1)	26.6 (18.9-34.3)	Time 3#	−10.5 (2.4)
				Treatment × time 3	−10.2 (3.1)
CPRS schizophrenia change**	Initial	10.7 (8.9-12.0)	10.7 (9.1-12.4)	Intercept	3.0
				Center	0.4 (0.3)
				Time 2	1.1 (0.1)
	Outcome	5.2 (4.2-6.7)	6.6 (4.6-8.7)	Treatment	0.5 (0.2)
				Center × treatment	1.1 (0.4)
				Time 3	1.7 (0.2)
	Follow-up	4.0 (3.0-5.2)	7.1 (4.8-9.5)	Treatment × time 3	0.9 (0.3)
				Center × time 3	0.7 (0.3)
				Center × treatment × time 3	1.2 (0.5)
MADRS	Initial	9.6 (8.0-10.9)	10.1 (8.8-11.5)	Intercept	12.0
				Center	−3.9 (1.1)
				Treatment	−2.5 (1.0)
	Outcome	4.8 (4.0-6.1)	6.0 (4.4-7.7)	Center × treatment	4.2 (1.6)
				Time 2	−4.5 (0.6)
				Time 3	−3.6 (0.7)
	Follow-up	3.7 (2.8-4.7)	6.7 (4.6-8.9)	Treatment × time 3	−2.2 (0.9)
SANS**	Initial	35.9 (29.3-42.5)	31.0 (22.9-39.1)	Intercept	4.7
				Sex	1.1 (0.4)
				Time 2	−1.2 (0.3)
	Outcome	22.0 (16.9-27.0)	20.7 (14.3-27.0)	Center × time 2	−1.6 (0.6)
				Center × treatment × time 2	1.7 (0.7)
				Treatment × time 3	−1.9 (0.4)
	Follow-up	18.2 (12.9-23.4)	25.1 (16.7-33.4)	Center × time 3	−3.4 (0.6)
				Center × treatment × time 3	3.3 (0.9)

*CBT indicates cognitive-behavioral therapy; BF, befriending; CI, confidence interval; CPRS, Comprehensive Psychiatric Rating Scale; MADRS, Montgomery-Åsburg Depression Rating Scale; and SANS, Scale for the Assessment of Negative Symptoms.

†All variables were tested in each model, but only those making a significant contribution are listed.

‡Newcastle, 0; London, 1.

§Outcome assessment.

‖Cogitive behavioral therapy, 1; BF, 0.

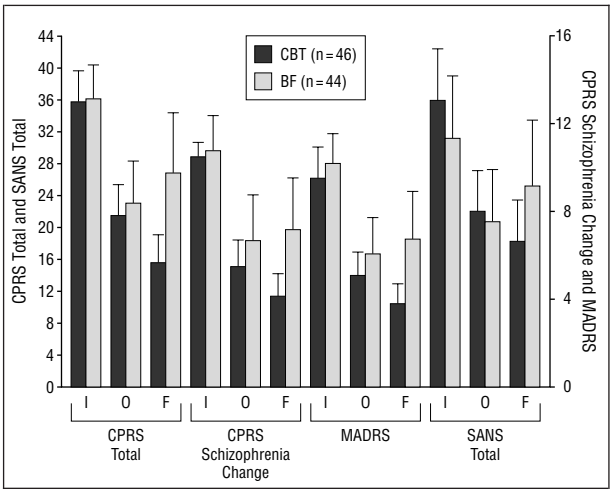
¶Female, 0; male, 1.

#Follow-up assessment.

**Because the CPRS schizophrenia change and SANS data were skewed, a square root transformation was applied; the models apply to the transformed data.

with BF (mean, 43 [95% CI, 38-47]) but this difference did not reach significance.

The independent assessor correctly assigned all 87 taped sessions (58 conducted by R.S. and 29 by M.O.) to the appropriate treatment group (43 to CBT and 44 to BF). The mean CTRS scores demonstrated highly significant differences (analysis of variance, $F_{1,84} = 2995$; $P<.001$) between mean CTRS ratings for CBT (45.8 [95% CI, 44.8-46.8]) compared with BF (16.2 [95% CI, 15.7-16.7]). The BF scores were within the range expected of good interviews using no cognitive or behavioral techniques. There was also a significant overall difference between the 2 therapists in CTRS ratings ($F_{1,84} = 6.1$; $P = .02$), one therapist receiving higher mean CTRS ratings for both CBT (46.1 [95% CI, 44.9-47.3] vs 45.1 [95% CI, 43.2-47.0]) and BF (16.8 [95% CI, 16.4-17.2] vs 14.9 [95% CI, 13.7-16.1]). Although significant, these differences are probably not clinically meaningful. When a separate post hoc analysis was undertaken comparing mean CTRS scores for CBT only, there were no significant differences between therapists ($F_{1,41} = 0.88$; $P = .35$).



Means and 95% confidence intervals (error bars) of main outcome measures. CBT indicates cognitive-behavioral therapy; BF, befriending; CPRS, Comprehensive Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; MADRS, Montgomery-Åsberg Depression Rating Scale; I, initial assessment; O, outcome; and F, follow-up.

Table 3. Patients Who Showed 50% or Greater Reduction in Outcomes Scores at Follow-up Examination*

Outcome Measure	Patients Showing ≥50% Improvement, No. (%)		Rate of Symptom Reduction Because of CBT			
			Relative to BF		Assuming 10% Spontaneous Improvement	
	CBT (n = 46)	BF (n = 44)	ABI, %†	NNT, No.‡	ABI, %†	NNT, No.‡
CPRS total	29 (63)§	17 (39)§	24	4	53	2
CPRS schizophrenia change	32 (70)‖	22 (50)‖	20	5	60	2
MADRS	31 (67)	22 (50)	17	6	57	2
SANS total	23 (52)	23 (53)	–6	. . .	42	2

*CBT indicates cognitive-behavioral therapy; BF, befriending; ABI, absolute benefit increase; NNT, number needed to treat; CPRS, Comprehensive Psychiatric Rating Scale; MADRS, Montgomery-Åsburg Depression Rating Scale; and SANS, Scale for the Assessment of Negative Symptoms.

†The difference in proprtion of cases showing a 50% or greater reduction of symptoms in the CBT group vs the comparison groups.

‡The number of patients who needed to be treated with CBT for 1 patient to show a 50% or greater reduction in symptoms.

§$\chi^2_1 = 5.36$; P = .02.

‖$\chi^2_1 = 3.59$; P = .06.

Table 4. Changes in Prescribed Antipsychotic Drugs*

	Assessment	CBT (n = 46)	BF (n = 44)	Total Sample (N = 90)
Chlorpromazine equivalents, dosage, mg/d (95% CI)	Initial	633 (430-836)	597 (407-788)	615 (497-751)
	Outcome	618 (445-791)	558 (390-726)	588 (470-707)
	Follow-up	592 (452-732)	649 (465-834)	620 (507-733)
Patients changing total antipsychotic drug dose at follow-up evaluation, No. (%)	Reduced	12 (26)	12 (27)	24 (27)
	Increased	15 (33)	15 (34)	30 (33)
Patients changing atypical antipsychotic drug prescription at follow-up evaluation, No. (%)†	Discontinued	2 (4)	3 (7)	5 (6)
	No change	31 (67)	31 (70)	62 (69)
	Started during study	9 (20)	5 (11)	14 (16)

*CBT indicates cognitive-behavioral therapy; BF, befriending; and CI, confidence interval.

†Atypical antipsychotic drugs were considered separately in view of their reputed effects on symptoms refractory to standard antipsychotic drugs.

COMMENT

In this comparison of the effectiveness of CBT and BF in treating patients with medication-resistant symptoms of schizophrenia, both forms of therapy led to significant clinical improvement at the end of treatment, but at 9-month follow-up, the improvements were sustained only in the CBT group. Given that negative symptoms can be particularly resistant to treatment, the observed improvements in SANS scores are potentially important clinically.

Strengths in the design of the present study include randomized treatment allocation with intention-to-treat analysis; assessors who were blind to the patients' assigned treatment group; use of manual-based treatment, the technical quality of which was monitored; comparison of CBT with an appropriate comparative intervention controlling for therapist contact; and monitoring of prescribed medication.

A potential limitation of the study was that patients were recruited by repeatedly canvassing local services for referrals, rather than systematically screening patient populations (see the study by Tarrier et al[13]). Nevertheless, systematic bias in patient selection is unlikely because the patients were recruited from numerous clinical teams in 5 different clinical services. Also, in their sociodemographic and clinical profiles, patients in this study closely resembled those in the study by Tarrier et al.[13] Although there were some baseline differences between the treatment groups that were significant, they were subtle and probably unimportant clinically. In any case, these differences alone cannot account for the main findings of the study. That the therapists carried out both types of intervention may have controlled for some nonspecific therapist factors, but could also have contaminated the BF intervention with cognitive or behavioral techniques. However, analysis of the audiotaped interviews found no evidence of this.

Patients were recruited into the study because of persistent symptoms not attributable to poor treatment adherence. That 100% follow-up was achieved supports the good adherence of the sample, since there is usually a high correlation between adherence to different aspects of clinical care.[30] This also suggests that the clinical improvements because of the interventions cannot be attributed to better treatment adherence. Although CBT is effective in improving adherence among people with schizophrenia,[10,15] the present study was designed to assess the efficacy of CBT directly for persistent symptoms. The patients included were not intended to be representative of all outpatients with schizophrenia, but to represent the group most likely to benefit from direct effects of cognitive therapy on their symptoms.

The study did not include a health economic analysis. However, on the basis of 24 hours of therapist time for one clinically successful outcome, this intervention probably compares favorably with other currently available treatment options.

Some differences in outcomes were found between the 2 centers. The magnitude of differences between the therapists in CTRS ratings, although significant, is too small to be clinically important. It remains possible that some therapist factors not measured by the CTRS influenced outcomes. However, therapist factors alone are very unlikely to account for the between-center differences, not least because some were apparent at baseline. Patients in the study came from a variety of settings and it is possible that the outcomes were influenced by interactions between the treatment and the patient's circumstances.

The results of the present study compare well with those previously published. As noted above, Kuipers et al[8] reported significant benefits for CBT compared with routine clinical care, but these results become more difficult to interpret in the light of our own results with the nonspecific BF control group. Tarrier and colleagues[13] reported a 33% improvement rate (defined as in the present study) 3 months following an intensive course of cognitive therapy. This may be an underestimate, as improvement is likely to continue during follow-up (Figure).

The most surprising result in the present study was the substantial short-term improvement in the BF group. This seemed to be dependent on continuing therapist input and was not sustained after this contact ended. It might be expected that patients would benefit from regularly meeting with someone attentive to their interests and who seemed willing to interact with them socially and allowed them, if they wished, to talk about distressing ideas and experiences without making value judgments. Such interaction requires experience of working with people with schizophrenia, and both therapists were experienced psychiatric nurses. The therapists found the BF intervention difficult, not least because they were aware of the need to keep patients engaged in their treatment. There may be scope to introduce elements of BF into routine clinical practice, but until more is known about how BF might operate in improving symptoms, it remains likely that this is another example of benefits to patients that are attributable to participating in a research trial.

One particular problem raised by the BF results is the optimal design of control interventions in studies of the efficacy of psychological therapies. The present results throw doubt on the arguments applied to support comparisons of routine clinical treatment either alone or in combination with CBT.[31] Given that BF was chosen because it is nonspecific and its benefits for people with schizophrenia do not have any underlying theoretical or empirical basis, its effects complicate the attribution of therapeutic benefit to specific psychological techniques or mechanisms in studies that lack appropriate control groups. It has been argued that research designs aiming to assess therapeutic outcomes (ie, outcome or pragmatic studies) and those intending to explain mechanisms of change (explanatory studies) are incompatible and will actually conflict under some circumstances.[32] Influenced by these arguments, this study was designed as a pragmatic trial to measure therapeutic outcomes, without collecting data specifically relevant to explanatory mechanisms. However, our BF findings make a strong case for the inclusion whenever possible in CBT studies of cognitive variables, predicted a priori by the cognitive model to mediate change in the main outcome variables.

Our study contributes to the growing evidence of the efficacy of cognitive interventions in schizophrenia. A key feature of CBT is that it teaches patients a range of skills that enable them to manage their difficulties more effectively. Consistent with this is the prophylactic effect of CBT in depression. Challenges now include characterizing more adequately patient and therapeutic factors most likely to influence outcome, and integrating CBT interventions into standard clinical practice.

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