Promoting Therapeutic Alliance in Clozapine Users: An Exploratory Randomized Controlled Trial

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Abstract

Objective: To pilot a brief cognitive behavioral therapy-based intervention designed to enhance client empowerment and the therapeutic alliance with the aim of reducing clozapine discontinuation. **Design:** Randomized controlled trial with two conditions: therapy (Alliance Enhancement Therapy [AET]) and control (psychoeducation alone). Assessments took place at: baseline, twelve weeks and twenty-four weeks (follow-up). The primary outcomes were levels of empowerment, alliance with the clinical team and clozapine discontinuation. Secondary outcomes included insight and other clinical measures. **Methods:** Treatment-resistant patients who had a diagnosis of schizophrenia, had been registered for clozapine in the previous month and who consented, were independently randomized to active versus control therapy. **Results:** Thirty-nine patients entered the study. Both groups improved on the main measures with no differential effects of AET intervention. However, patients who attended for more than five sessions showed a differential enhancement of working alliance. **Conclusions:** Although the active therapy showed no general improvement, it did provide some added value over psychoeducation alone when patients attended several sessions. Effective methods of reducing clozapine discontinuation and engaging patients in psychosocial interventions are needed.

Key Words: Schizophrenia, Clozapine, Adherence, Randomized Controlled Trial (RCT), Compliance, Cognitive Behavioral Therapy (CBT)

Introduction

Patient adherence to therapeutic regimes is far from optimal (1). Nonadherence in schizophrenia has been estimated to account for increased rates of hospitalization, increased inpatient stays and hospital costs (2). Clozapine is an effective antipsychotic, and is judged by many patients to be more acceptable than other medications (3-5). Recent trials have demonstrated its superiority to other second-generation antipsychotics (6, 7), and it is the only agent proven to be effective in treatment-resistant schizophrenia (8). However, the necessity for periodic blood monitoring for neutropenia makes it more invasive and expensive to administer than other antipsychotics. Unfortunately, many patients discontinue clozapine before they can experience the benefits of its lower side effect profile and antipsychotic action (9, 10).

Given this background, there is scope for a psychological intervention aimed at reducing the number of patients discontinuing their clozapine prematurely. Previous research on adherence therapy with people with schizo-

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Clinical Implications

Interventions that augment medical input with psychosocial approaches and promote empowerment and therapeutic alliance are valued by service users. Our results suggest some possible benefits, but, in particular, they point to barriers which must be overcome in future research. First, consideration needs to be given to engaging patients at the outset whose adherence is already fragile. Patients with schizophrenia frequently show suboptimal adherence in relation to other psychiatric and medical patient populations (40). Treatment-resistant schizophrenia patients have, by definition, failed to experience a positive benefit from medication so are an especially difficult group to help. Second, there is a need to define the specific ingredients of an intervention (e.g., therapeutic alliance enhancement), if indeed there are any, which lead to a therapeutic effect on adherence. Until alternatives to clozapine are developed, it is worth applying resources to increase the numbers of patients who might benefit from the drug, particularly those who drop out of therapy before its beneficial effects could have been perceived.

phrenia with varied medications has been equivocal, with some studies showing a benefit (11-15) whereas other studies showed no benefit (16-18). However, no study has concentrated on clozapine users who are known to have high rates of early dropout from the treatment regime (19).

The differing results from studies of adherence might also be the result of a lack of measurement of key mediating factors that are addressed by the therapeutic approaches. Specifically, adherence may be improved through a better therapeutic alliance with the treating team facilitating feelings of empowerment through a discussion of the patient's personal recovery aims (20, 21), and this mirrors our service users' experience. Recent reviews have also suggested insight as a mediating factor (22). Our intervention, Alliance Enhancement Therapy (AET), was designed explicitly to increase user empowerment and therapeutic alliance between user and treating team, rather than directly promoting continued use of clozapine.

In order to detect specific treatment effects, we offered a comparison treatment that would equate for the amount of information that the participant might receive about clozapine. This was provided through psychoeducation, offering patients a summary of such information, including therapeutic effects, side effects, advantages and disadvantages. Previous trials of psychoeducation do not reliably increase adherence to medication regimes in patients with psychosis (e.g., 23) so it is clearly a placebo. However, this control treatment still offers consumers a positive treatment intervention. We hypothesized that a cognitive behavioral therapy (CBT) based therapeutic intervention would be superior in increasing empowerment, therapeutic alliance and adherence to clozapine.

Method

Design

Participants were independently randomized using specific software to two conditions: experimental therapy (CBT and psychoeducation [AET]) or control therapy (psychoeducation alone [PE]). They were assessed on three occasions: baseline, twelve weeks (post therapy) and twenty-four weeks (follow-up).

Participants

Participants were eligible for the study if they had a diagnosis of schizophrenia and were registering or re-registering on clozapine in one of five pharmacy departments in a large geographical catchment area in South London. Registration occurred if there were a clinical need and patients were considered to be treatment resistant by their treating team. Patients were included if they had *International Statistical Classification of Diseases and Related Health Problems, 10th edition* schizophrenia, were aged between 18 and 65, and could be contacted within four weeks of registration. They were excluded if they did not comprehend English or were too symptomatic to give informed consent. All participants gave written informed consent.

Primary Outcome Measures

1. The Empowerment Scale (24). This is a 28-item scale measuring the personal construct of empowerment as defined by mental health users. The key measure is the total score.

2. The Working Alliance Inventory (25). This 36-item scale consists of a set of seven-point Likert scales measuring aspects of the construct of working alliance. The measure refers to the participant's alliance with his clinical team, which is independent of the therapist providing either AET or PE. The key measure is the total score.

3. Remaining on clozapine was assessed, and if not, whether this was due to the patient's choice, as far as we could determine, or other factors (e.g., problematic blood test results).

Secondary Outcome Measures

4. The Birchwood Insight Scale (26)—a self-report questionnaire.

5. The Drug Attitude Scale (DAS) (27), a 30-item questionnaire.

6. The Attitudes to Medication Questionnaire (AMQ) (28). This 12-item structured interview asks patients to express their favorable and unfavorable views of medications; the total maximum score is 25.

7. Knowledge of Clozapine Quiz. Created for this study, this quiz consists of 9 interview questions and 12 multiple-choice questions. It is designed to measure patient knowledge of basic facts about clozapine and is the basis for the psychoeducation in the programs. The key score is the total number of correct items (maximum score 21).

8. Global Assessment of Functioning (GAF) Scale *(DSM-III-R).*

9. Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS [29]). It was completed by an independent assessor who was blind to treatment condition.

Treatment Interventions

"Alliance Enhancement Therapy" (AET)

This CBT-based intervention was modeled on so-called "compliance therapy," as described in (11) and in more detail in (30) and (31). AET is presented in a manual and described in detail by the treatment initiators Kemp et al. (30). It involves up to seven sessions of a CBT-based therapy package, modeled on the type of motivational interviewing used in the substance-abuse field. The seven sessions covered the following three phases: patient's stance toward treatment, exploration of ambivalence toward treatment and treatment maintenance. For this study, sessions were extended from six to seven in order to encompass some education on clozapine. Users were asked to review their medication history and to consider the pluses and minuses of medication use. The client's concerns and worries were elicited and medication use was presented as a freely chosen strategy to enhance quality of life. Reflective, empathic listening was emphasized and pressure and directive interventions were avoided. Emphasis was placed on the user's freedom to either accept or reject medication, which was intended to avoid creating reactance (the natural tendency to reject treatments when one feels pressured to accept them [see 32]).

Psychoeducation (PE)

This was based on the best knowledge available about clozapine. It was decided that it would be impossible to make it last as long as the therapy package without a considerable amount of uninteresting filler material so it was, therefore, limited to two sessions. The intervention was delivered factually in a didactic manner. No attempt was made to elicit the individual concerns and resistances of participants although, of course, any questions were answered in a factual manner.

Both therapies were carried out by a nurse therapist trained in "Alliance Enhancement Therapy" by the main author of the therapy manual. Fidelity was achieved through initial training, as well as recorded sessions with practice patients, and was maintained through close clinical supervision (P.H.). Contamination was unlikely as the PE intervention only consists of two sessions of knowledge provision.

Statistical Analysis

As this was an exploratory study with new measures and a new therapy, formal power calculations were not possible, but with twenty people per group there was 80% power to detect effect sizes in the region of 0.58 and an odds ratio of 0.05 in clozapine dropout.

The analysis was on an intention-to-treat basis, with all participants randomized entering the analysis even if they did not receive all the treatment sessions. The continuous repeated measures were analyzed using a linear mixed model with fixed effects of group, time and group by time and a random effect for subjects. A significant group-by-time interaction would indicate that the treatment had an effect on the rate of improvement over time. If the interaction was not significant, the null hypothesis that the groups improve at the same rate could not be rejected, so the interaction was removed from the model to estimate the main effect of time (the average improvement for the two groups). All available observations contributed to the analysis even if some data points for an individual were missing. As outcomes will be affected by changes in positive symptoms as a result of clozapine treatment, the analyses were repeated using the PANSS Positive Symptom scores as a time-varying covariate. The PANSS Negative scores were log-transformed when analyzed as a response variable to make their distribution more symmetrical. Compliance was an ordinal outcome and was modeled using a random effects proportional odds model. A 5% level of significance was used for all analyses. All analyses were carried out in Stata 8.0; the random effects proportional odds model was estimated using the Stata program generalized linear latent and mixed models (gllamm) (33) for generalized linear latent and mixed models.

Results

Participant Description

Overall, 89 referrals met criteria for the study, but only 39 (44%) consented to take part: 22 men and 17 women. Their mean age was 37.9 years (range 20–64). The majority (64.1%) were Caucasian, with Afro-Caribbean (20.5%) as the second largest group. Their mean initial score on the PANSS was 67.9 (standard deviation [SD] 13.5) and on the GAF their mean score was 40.3 (SD 12.0), suggesting a moderate level of symptoms along with impairment in several areas of social functioning. The mean clozapine dose was 233 mg, and 17 out of 39 were not on other medications. The remaining 22 were also taking other antipsychotic, mood stabilizer or anticholinergic drugs. Nineteen participants were randomized to AET and 20 to PE and, as would be expected, there were no significant differences in age, sex or ethnic group between the two groups. The dependent variables for each group are presented in Table 1. The AET patients received an average of 4.5 sessions of therapy (range 0 to 7), and the PE group received an average of 1.6 therapy sessions (range 0 to 2).

Effects of Type of Treatment

All primary and secondary outcomes were analyzed to investigate interaction effects that would suggest a differential effectiveness of the two interventions. The rate of dropout from clozapine treatment, tested by a chi-square statistic, did not differ between treatment groups (X^2 (1)=0.16, p=.41). However, the overall clozapine dropout rate from our study was slightly better than that previously reported (9) in a previous naturalistic study of clozapine users from the same hospital trust (20.5% vs. 31.5%, mean difference 11%; 95% CI -6.7–28.7). Reasons given for discontinuation included: nonadherence, no improvements noted and problematic blood test results.

None of the predicted interaction effects were found (see Table 1 for all means and SDs at the three time points). Although we expected that there would be a variable reduction in positive symptoms, in fact there was a significant differential effect. The mean decrease for PE was 2.34 points per three-month period (p=0.004) compared with 0.07 (p=0.90) in the AET group. When positive symptoms were covaried in the analyses, there was a trend for a group by time interaction for Knowledge of Clozapine (p=.07), with knowledge increasing by only 0.13 per three-month period in the PE group (p=0.86) compared to an estimated 1.85 points in the AET group (p=.002). A group by time interaction for the PANSS Negative Symptoms also approached significance (p=.051), with the AET group showing the greater decline. There was a significant decline of 0.09 points (on a log scale) per three-month period in the AET group (p=0.01), but no significant change in the PE group (p=0.61).

There were improvements in a number of the variables, including Working Alliance Inventory, Knowledge of Clozapine, the DAS, the AMQ, the GAF and PANSS Negative Symptoms (see Table 2), but all these changes occurred across both treatment groups. There were no changes over time in one putative mediating variable: insight (baseline=7.96, post treatment=7.42, follow-up=7.90).

Table 1 Data on Group Changes over Time

	Dropouts/ Total Number		Empowerment Scale Mean (SD)		Working Alliance Inventory Mean (SD)		Drug Attitude Scale Mean (SD)	
	PE	AET	PE	AET	PE	AET	PE	AET
Time 1	0/20	1/19	78.9 (8.3)	75.4 (7.6)	22.2 (37.7)	16.1 (37.6)	11.4 (10.3)	6.9 (13.1)
Time 2	0/20	2/19	76.3 (6.0)	76.7 (6.1)	43.6 (38.2)	29.1 (35.3)	12.3 (11.9)	11.1 (12.5)
Time 3	0/20	2/19	76.1 (6.7)	75.5 (3.3)	37.4 (34.7)	48.1 (24.7)	12.2 (12.5)	10.0 (12.2)

	Knowledge of Clozapine Mean (SD)		Attitudes to Medication Mean (SD)		PANSS Negative Mean (SD)		PANSS Positive Mean (SD)	
	PE	AET	PE	AET	PE	AET	PE	AET
Time 1	15.8 (6.6)	15.2 (6.2)	17.9 (4.2)	18.5 (3.4)	21.0 (8.7)	18.1 (5.3)	17.5 (3.2)	14.3 (3.5)
Time 2	18.7 (6.0)	18.4 (6.6)	20.9 (3.8)	20.8 (3.2)	17.0 (7.6)	16.5 (4.8)	13.8 (4.2)	14.2 (4.1)
Time 3	19.2 (4.1)	18.3 (6.3)	20.7 (2.7)	20.6 (3.2)	17.8 (6.3)	15.1 (3.8)	13.0 (3.9)	14.5 (4.2)

SD=standard deviation; PE=Psychoeducation; AET=Alliance Enhancement Therapy

Table 2 Changes over the Whole Sample

Outcome	Mean Change 3 Months	p Value
Working Alliance Inventory	10.85	.001
Knowledge of Clozapine	1.28	.008
Drug Attitude Scale	1.50	.01
Attitudes to Medication	0.97	<.001
Log PANSS Negative	-0.07	.03
GAF	2.81	.03

Does the Treatment Effect Depend on Dose?

The effect of the two treatments was considered for those who received an adequate dose of treatment (>4 sessions AET or 2 sessions PE). Controlling for PANSS Positive score, there was a significant interaction for Working Alliance Inventory ($F(2, 16)=5.1$, $p=0.019$) only. The main difference was at follow-up, when the group who had received AET therapy had higher scores (estimated marginal means 32 vs. 59).

Discussion

The sample is representative of the population that is prescribed clozapine in the same large catchment area (10), and the study has a high methodology score as measured on CTAM (34). The proportion entering the study was low, but similar to equivalent studies of nontreatment-resistant patients (e.g., 18). This factor results in a selection bias which is undoubtedly the biggest barrier to demonstrating the value of adherence-enhancing clinical interventions since the very population for whom the intervention is designed is the least likely to take it up, especially in the context of a randomized controlled trial.

The results do not suggest that there is a beneficial effect for AET over PE alone in terms of clozapine adherence. Both groups showed substantial gains on many of the outcomes. The AET group showed a differential benefit for a few variables and only in special circumstances (controlling for symptom improvement or only in those who received the majority of the dose of therapy). The improvement in Working Alliance Inventory associated with receiving an adequate dose of AET is clearest at follow-up, three months after the end of therapy. This suggests that the skills acquired during therapy take some time to show benefit, thus producing a lagged effect.

This study replicates the findings of three others (16-18) that showed no clear effects for AET-like therapies over a simple education intervention. The latter is the largest of its kind and, like the current study, included an active comparison treatment arm rather than "treatment as usual" or "nonspecific counseling" as in the positive studies (12, 34). There is, therefore, a possibility that both interventions encouraged continuation with clozapine. In addition, improving insight into illness—not achieved by AET—may be a prerequisite of a more effective adherence intervention (e.g., 13, 36). What is clear is that AET did not confer additional benefits in regard to clozapine continuation detectable with our sample size. Nonadherence increases annual costs per patient by over £5,000 (approximately $8,200) (36); hence, if a 10% reduction of the order we found was confirmed then this would yield considerable savings for the health service. Further, given the high cost of relapse both in monetary (37, 38) and social effects these results warrant further study.

The current study is limited in that there was no control for the amount of extra contact that the participants received in the AET arm of the study. Others have also shown that contact does reduce dropout (39), although dropout in that study was much higher (49–58%) than in the current one. The effect of increasing contact in comparison to an active arm of therapy also needs further investigation.

Interventions that augment medical input with psychosocial approaches and promote empowerment and therapeutic alliance are valued by service users. Our results suggest some possible benefits but, in particular, they point to barriers which must be overcome in future research. First, consideration needs to be given to engaging patients at the outset whose adherence is already fragile. Patients with schizophrenia frequently show suboptimal adherence in relation to other psychiatric and medical patient populations (40). Treatment-resistant schizophrenia patients have, by definition, failed to experience a positive benefit from medication so are an especially difficult group to help. Second, there is a need to define the specific ingredients of an intervention (e.g., therapeutic alliance enhancement), if indeed there are any, which lead to a therapeutic effect on adherence. Until alternatives to clozapine are developed it is worth applying resources to increase the numbers of patients who might benefit from the drug, particularly those who drop out of therapy before its beneficial effects could have been perceived.

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