Adherence therapy for schizophrenia: a randomised controlled trial

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KEY MESSAGES

1. Compared with routine care, adherence therapy is an effective alternative for people with schizophrenia with poor medication adherence and short duration of illness.
2. Adherence therapy can significantly improve patient adherence to antipsychotic medication, insight into illness/treatment, and re-hospitalisation rate, as well as psychotic symptoms and functioning over 12-month follow-up.
3. Adherence therapy can be cost-effective over the 12-month follow-up.

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Introduction

People with schizophrenia spectrum disorders account for 60% to 70% of all psychiatric cases worldwide. Their non-adherence rate to antipsychotic medication is 25% to 70%.[1] New (atypical) antipsychotics have little evidence in improving medication adherence because of side-effects of tardive dyskinesia and metabolic and weight problems.

Medication adherence in patients with schizophrenia spectrum disorders during the early stage of illness can be enhanced by effective psychosocial and relapse prevention interventions that improve understanding/coping with the illness and medication use. A systematic review suggested inconsistent and short-term effects of adherence therapy in schizophrenia.[2] Nonetheless, adherence therapy based on motivational interviewing technique showed evidence to improve both insight and adherence to medication over 6-month follow-up.[3] Therefore, further research with longer-term follow-up and diverse patient populations is recommended.

This randomised controlled trial aimed to evaluate the effects of motivational interviewing adherence therapy (and its cost-effectiveness) for Chinese patients with schizophrenia spectrum disorders on medication adherence, re-hospitalisation rate, and psychosocial outcomes over 12-month follow-up; and to examine its strengths and weaknesses from the perspectives of participants and therapists. Primary outcomes were medication adherence rate, mental status, and number and length of psychiatric re-hospitalisations. Secondary outcomes included patients' insight into medication/treatment and functioning.

Methods

This study was approved by the Human Research Ethics Committee of The Chinese University of Hong Kong (HEARS20120008112) and the Clinical Research Ethics Committees of the New Territories East Cluster (NTE2012.258) and Kowloon West Cluster (KW2012.3.0183) of Hospital Authority. Patients with schizophrenia who were non-adherent to medication were recruited from two community psychiatric nursing services centres (at New Territories West and Kowloon West) and were referred by psychiatrists. Non-adherence was defined as cessation of oral antipsychotics prescribed at admission or complete cessation of medication for at least 1 month after discharge based on reports from the psychiatrist, community psychiatric nurse (CPN), and/or patient.[2,3] Inclusion criteria were (1) Hong Kong Chinese residents aged 18 to 65 years, (2) primary diagnosis of schizophrenia or its subtypes for ≤3 years, (3) taking oral antipsychotics for >1 month, and (4) with Positive and Negative Syndrome Scale (PANSS) score of >60 and judged by a CPN/psychiatrist as non-adherent. Patients were excluded if they had co-morbidity of learning disability, organic brain disease, and/or visual/language/communication difficulty, or participated in any medication management programme.

Of 380 eligible patients, 67 were stratified according to the two services centres and randomly selected from each centre by matching random numbers with the potential participant list. The participant list was concealed to the outcome assessors, centre staff (except the trained CPNs for adherence therapy), and researchers. With a study power of 80% and a significance level of 0.05, 67 patients in each group (n=134) were recruited

to detect a medium effect size of 0.48),[2,3] with an estimated attrition rate of 20%.

Adherence therapy was based on motivational interviewing technique and in-depth behavioural analysis. Six 2-hour sessions (over 3 months) focused on principles of expressing empathy, developing discrepancies between client's beliefs and evidence, supporting self-efficacy, avoiding argumentation, and rolling with resistance to behavioural change.[3] Fidelity of the six CPNs to the treatment protocol was ensured with supervised practice and examination of audio-taped sessions by using a validated adherence therapy competency scale (ie, 91% to 95% rated to be competent).[3]

Routine care consisted of monthly home visits, mental health assessment, administration of medications, and brief education (2 hours every 3-4 weeks) by CPNs, psychiatric consultations by psychiatrist, and referrals to community care, and welfare services by psychiatrist/medical social worker.

Participants were assessed on: medication adherence, using the Adherence Rating Scale (ARS); symptom severity, using PANSS; number and lengths of re-hospitalisations; symptom remission; insight into illness/treatment; and functioning at baseline (T0) and at one week (T1), 6 months (T2), and 12 months (T3) after completion of the interventions. Participants' demographic and clinical data were collected at baseline. All instruments demonstrated satisfactory internal consistency and construct validity.[1] Internal consistency and inter-rater reliability were strongly correlated with the results (Cronbach's α=0.85-0.94; intraclass correlation coefficients for ARS and PANSS were 0.81 and 0.89, respectively). Process evaluation was performed to identify the strengths and limitations of adherence therapy with (1) observation of two randomly selected sessions to assess the quality of adherence therapy implementation and (2) semi-structured interviews with 19 selected participants (13 in adherence therapy and 6 in routine care) based on different levels of medication adherence at post-test T1, and all six CPNs conducted the adherence therapy.

Homogeneity of study groups was checked at baseline, and outcome analysis was based on intention to treat. With violations of multivariate normality, multicollinearity and outliers for MANOVA test found among the outcome variables and very few missing data noted, the interaction [group x time] treatment effects on mean scores of the primary outcomes were examined using repeated-measures ANCOVA test, followed by Helmert contrasts tests. The co-variants included the nature of readmission, duration of illness, number and dose of antipsychotics, and Drug Attitude Inventory mean score. The numbers of patients' re-hospitalisations over each follow-up period were converted to average times of re-admissions per month, which were normally distributed. The percentages of patients being hospitalised over each follow-up period were compared between the two study groups, as were the numbers and percentages of patients with symptom remission. Comparisons of outcomes between two services centres and comparisons of adherence therapy participants with attendance of >3 sessions and those with ≤3 sessions were performed using ANCOVA test. Levels of significance for baseline and post-tests (using Bonferroni correction) were set at 0.05 and 0.01, respectively.

The qualitative interview data were content analysed immediately after each interview. Cost-effectiveness analysis was performed to verify the value of the additional resources associated with adherence therapy, using an incremental cost-effectiveness ratio on each of the primary outcomes at three post-tests as follows[4]:

$$\frac{\textit{cost with the AT} - \textit{cost of the routine care}}{\textit{outcome with the AT} - \textit{outcome of the routine care}}$$

Results

Characteristics and baseline scores of study participants

Of 134 participants at baseline, 128 were included in data analysis (attrition rate, 4.5%). Three participants failed to attend >3 adherence therapy sessions. One participant in routine care and two participants in adherence therapy withdrew from the study. One participant in adherence therapy declined to complete T1. The mean attendance to sessions was 4.8 (standard deviation [SD], 1.0; median, 5.0; range, 2-6). Participants of the two groups at baseline were comparable (P>0.12, Table 1); 86% to 88% of participants were deemed poorly adherent to medication at baseline, with a mean ARS score of 1.39 to 1.48.

Treatment effects of adherence therapy

Repeated-measures ANCOVA tests on the outcome measures indicated significant interaction (group x time) treatment effects in the adherence therapy group, which had greater improvements over time than the routine care group in terms of insight into illness/treatment (P=0.009, effect size=0.58), symptom severity (P=0.008; positive symptoms, P=0.008; negative symptoms, P=0.005; effects sizes=0.69-0.73), functioning (P=0.009, effect size=0.63), medication adherence (P=0.008, effect size=0.71), and average number of re-hospitalisations (P=0.01, effect size=0.52) [Table 2]. The adherence therapy group had greater improvement in symptom remission at post-tests (P=0.005, effect size=0.60).

Results of Helmert contrasts test indicated that the adherence therapy group had greater

TABLE 1. Demographic and clinical characteristics of participants at baseline (n=134)*

Characteristics	Adherence therapy (n=67)	Routine care (n=67)	χ^2	P value
Gender			1.50	0.26
Male	37 (55.22)	36 (53.73)		
Female	30 (44.78)	31 (46.27)		
Age, y	28.87±9.54	29.53±9.96	1.48	0.28
18-29	21 (31.34)	22 (32.84)		
30-39	28 (41.79)	27 (40.30)		
40-49	11 (16.42)	10 (14.93)		
≥50	7 (10.45)	8 (11.94)		
Diagnosis			1.02	0.39
Schizophrenia	35 (52.24)	36 (53.73)		
Other psychotic disorders	32 (47.76)	31 (46.27)		
Nature of last admission			1.58	0.23
Voluntary	40 (59.70)	42 (62.69)		
Compulsory/involuntary	27 (40.30)	25 (37.31)		
Employment status			1.58	0.24
Employed (full-time)	23 (47.76)	25 (37.31)		
Employed (part-time)	13 (19.40)	11 (16.42)		
Unemployed	14 (20.90)	12 (17.91)		
Others (eg, intermittent job)	7 (10.45)	8 (11.94)		
Education level			1.81	0.19
Primary school	12 (17.91)	13 (19.40)		
Secondary school	42 (62.69)	39 (58.21)		
University/college	13 (19.40)	15 (22.39)		
Duration of illness, mo	22.91±12.68	23.42±14.38	2.15	0.12
<6	18 (26.87)	17 (25.37)		
6-12	21 (31.34)	23 (34.33)		
13-24	12 (17.91)	15 (22.39)		
25-36	10 (14.93)	12 (17.91)		
Treatment setting			1.31	0.30
Outpatient department	66 (98.51)	67 (100.00)		
Day hospital/centre	10 (14.93)	11 (16.42)		
Others (eg, sheltered workshop and social club)	17 (25.37)	18 (26.87)		
Living situation			1.01	0.31
Supervised care	10 (14.93)	9 (13.43)		
Family residence	39 (58.21)	38 (56.72)		
Living alone	18 (26.87)	20 (29.85)		
Monthly household income, HK$			1.02	0.31
5000-10 000	10 (14.93)	11 (16.42)		
10 001-20 000	20 (29.85)	21 (31.34)		
20 001-30 000	21 (31.34)	19 (28.36)		
>30 000	16 (23.88)	16 (23.88)		
Accommodation			1.83	0.18
Private household	24 (35.82)	29 (43.28)		
Public housing	28 (41.79)	24 (35.82)		
Others (eg, hostel and long-stay care home)	15 (22.39)	14 (20.90)		

* Data are presented as mean±standard deviation or No. (%) of participants

TABLE 2. Repeated-measures ANCOVA (group x time) tests for outcomes at baseline (T0), immediately after completion of intervention (T1), 6 months post-intervention (T2), and 12 months post-intervention (T3)*

Instrument	Adherence therapy (n=63)				Routine care (n=65)				F†	P value	Effect size
	T0	T1	T2	T3	T0	T1	T2	T3			
Insight and Treatment Attitudes Questionnaire	9.12±4.14	11.18±6.67	12.88±6.80	13.96±7.01	9.33±3.31	9.91±5.45	9.57±6.12	11.01±6.82	6.98	0.009	0.58
Positive and Negative Syndrome Scale	80.19±11.10	74.01±15.10	68.12±14.81	60.01±13.92	81.13±12.01	80.18±15.11	82.45±12.03	80.01±14.31	7.32	0.008	0.70
Positive symptoms	18.02±4.89	16.13±4.54	14.65±3.98	13.02±4.13	18.21±4.12	18.23±4.65	19.79±5.56	18.02±6.98	7.21	0.008	0.69
Negative symptoms	20.68±5.01	18.23±5.91	16.70±5.67	15.12±6.01	20.82±5.76	20.90±5.87	20.38±6.43	21.13±9.87	7.78	0.005	0.73
Symptom remission		(f=4, 6.35%)	(f=8, 12.70%)	(f=10, 15.87%)		(f=2, 3.08%)	(f=2, 3.08%)	(f=3, 4.62%)	5.61	0.005	0.60
Specific Level of Functioning Scale	140.01±18.22	150.91±22.35	169.23±27.65	173.13±29.11	138.34±17.18	138.65±19.71	146.01±30.34	143.88±29.81	7.00	0.009	0.63
Adherence Rating Scale	1.48±0.98	2.21±1.06	3.10±1.20	3.31±1.50	1.39±1.01	1.47±1.02	1.71±1.23	1.56±1.43	7.34	0.008	0.71
Re-hospitalisation											
Number	1.41±0.98	1.30±0.90	1.12±1.01	1.01±0.88	1.50±0.92	1.39±1.11	1.58±1.00	1.82±1.10	5.12	0.010	0.52
Duration	9.12±2.98	8.90±5.88	8.70±5.11	9.83±5.98	10.01±4.02	12.05±8.98	10.01±9.84	12.12±10.88	3.20	0.097	0.23

* Data are presented as mean±standard deviation or No. (%) of participants

improvements than the routine care on the three primary outcomes at post-tests: (1) psychotic symptoms (PANSS score) decreased at T1, T2, and T3 (mean difference=6.17, 14.33, and 20.00; standard error [SE]=0.05, 2.80, 1.70; P=0.001, P=0.005 and P<0.001, respectively); (2) medication adherence rate (ARS score) increased at T1, T2, and T3 (mean difference=0.74, 1.39, and 1.75; SE=0.05, 0.04, and 0.07; P=0.02, P=0.01, and P=0.007, respectively); and (3) number of re-hospitalisations reduced at T2 and T3 (mean difference=0.46 and 0.81; SE=0.02 and 0.30; P=0.03 and P=0.01, respectively). The adherence therapy group also indicated greater improvements in secondary outcomes in terms of functioning and treatment insight at T2 and T3 (P=0.03–0.001). The percentages of patients being hospitalised over T1 to T4 were 45%, 32%, 24%, and 17% in the adherence therapy group and 44%, 40%, 38%, and 48% in the routine care group, respectively. The difference between groups was significant (P=0.008, Kruskal Wallis test). However, the types and doses of psychotropic medication, nature of admission (voluntary/compulsory), frequency of defaulted follow-up, and types/frequency of participation in other psychosocial interventions did not differ significantly between groups at post-tests (P>0.20). All mean outcome scores did not differ significantly between the six adherence therapy subgroups and two services centres at post-tests (P>0.10), and between adherence therapy participants who attended ≤3 sessions and those who attended >3 sessions (P>0.08).

Cost-effectiveness of adherence therapy

The total costs of adherence therapy (n=63) were higher than those of routine care (n=65) by HK$85 500 and HK$12 380 at T1 and T2, respectively, but lower than those of routine care by HK$51 065 at T3 (Table 3). The average cost per case of adherence therapy was higher than that of routine care at T1 and T2 but similar to routine care at T3. At T1, T2, and T3, the number of patients with clinically significant improvements in medication adherence (n=10, 21, and 28, respectively) and symptom severity (n=20, 28, and 35, respectively), and reduction in numbers of re-hospitalisations in the past 4 months (-20, -30, and -43 re-hospitalisations, respectively) were consistently higher in the adherence therapy group than in the routine care group (P<0.001, χ^2 test).

Compared with routine care, adherence therapy resulted in additional 1, 12, and 21 cases with significant improvement on medication adherence at extra costs of HK$85 500 and HK$952 and (reduced) HK$1824 per case, and additional 13, 23, and 25 cases with significant improvement on symptom severity at extra costs of HK$7125, HK$538 and (reduced) HK$1548 per case at T1, T2, and T3, respectively. In addition, adherence therapy resulted in 10, 48, and 75 fewer re-hospitalisations at additional costs of HK$8550 at T1 and HK$258 at T2, and reduced cost of HK$681 per case for one admission at T3. In sum, adherence therapy was an effective intervention with low extra costs, particularly saving costs for outcome improvements at the 12-month follow-up.

Strengths and weaknesses of the interventions used

From the interview and observation data, three themes concerning perceived benefits (strengths) of the adherence therapy were identified, including

TABLE 3. Cost, effectiveness, and cost-effectiveness ratios at baseline (T0), immediately after completion of intervention (T1), 6 months post-intervention (T2), and 12 months post-intervention (T3)

Item	Means for calculation	Adherence therapy (n=63)			Routine care (n=65)		
		T1	T2	T3	T1	T2	T3
Costs (in HK$)							
Cost of adherence therapy	Sum of salary of research assistants (~250 hrs), general expenses (eg, travelling and copying) and facilities and venue fees (15 hrs)	205 000	-	-	-	-	-
Cost of health care services used by patients	Total costs of health care services as required in each intervention, including those requested by patients (and their family caregivers), not for routine care provided by the community nursing service	194 000	216 000	183 000	221 000	224 080	223 000
Cost of patients' hospital stay	Total number of days of hospital stay multiplied by average cost per day (~HK$1500) in psychiatric hospital/unit	810 000 (540 days)	847 500 (565 days)	928 935 (619 days)	892 500 (595 days)	930 000 (620 days)	1 155 000 (770 days)
Total costs of intervention		1 209 000	1 268 500	1,326 935	1 123 500	1 154 080	1 378 000
Cost of intervention per case		19 190± 1098	20 135± 1510	21063± 170	16 977± 1388	17 755± 1692	21 200± 2103
Effectiveness							
No. of cases who indicated significant improvement in medication adherence	Significant change in mean score of Adherence Rating Scale between baseline and each of the three post-tests over 12 months follow-up if the change at post-tests were >1 standard deviations of baseline	10	21	28	9	9	7
No. of cases who indicated significant improvement in symptom severity	Significant reduction of mean score of Positive and Negative Syndrome Scale if the change measured at any of the three post-tests was not >1 standard deviations of baseline	20	28	35	7	5	10
Total reduction of number of patients' re-hospitalisations	Difference on total number of patients' hospitalisations in the past 4 months between the baseline measurement and the three post-tests	-20	-30	-43	-10	18	32
		Adherence therapy vs routine care					
Cost-effectiveness ratio (in HK$)		T1	T2	T3			
Incremental cost per additional case with significantly improved medication adherence	Additional cost per case required for one extra patient in adherence therapy with significant improvement in medication adherence than routine care	85 500	952	-1824			
Incremental cost per additional case with significant reduction of symptom severity	Additional cost per case required for one extra patient in adherence therapy with significant reduction of level of psychotic symptoms than routine care	7125	538	-1548			
Incremental cost per additional case with reduction of one psychiatric hospitalisation	Additional cost per case required for one extra patient in adherence therapy with one hospital admission less than that of routine care	8550	258	-681			

(1) enhanced knowledge about the illness and medication, (2) perceived support from mental health professionals/services, and (3) adoption of effective coping (and problem-solving) strategies in medication adherence. In addition, two themes on difficulties in participation and medication adherence were identified, including (1) challenges in overcoming serious side-effects and (2) symptoms and perceived social stigma and family burden.

There were recommendations for improvements of adherence therapy, including (1) more sessions/opportunities for engaging and discussion about adherence attitude, (2) increasing family and social support, (3) more inputs/

collaborations with health professionals and services to enhance psychosocial resources and support, and (4) more practice and home assignments for improving patients' adherence behaviours.

Discussion

The six-session adherence therapy based on motivational interviewing technique can be effective to improve the medication adherence and subsequently mental health of people with schizophrenia spectrum disorders. Compared with routine care, adherence therapy significantly improved patient outcomes with moderate to large effect sizes (Cohen's d=0.49-0.73) over 12-month follow up. Adherence therapy (originally for addictive and behavioural problems) can be effective in people with schizophrenia.[2,5] Adherence therapy can improve both positive symptoms (hallucination and delusion) and treatment-resistant negative symptoms (anhedonia and social withdrawal). Qualitative interview data indicated that many participants in adherence therapy could perceive/experience the benefits of adherence therapy to their knowledge and skills in medication adherence and illness management.

The completion rate of the intervention was very high (only three participants failed to attend >3 sessions) and the attrition rate was low (4%). Adherence therapy showed clear benefits in terms of psychopathology and treatment insight and adherence for younger adults with schizophrenia at early stage of illness with poor medication adherence (>80%, which is comparable to 60% to 80% of people with schizophrenia being poorly adherent)[1,2] and moderate levels of psychotic symptoms and functioning at recruitment. In contrast, recent studies on medication adherence recruited >50% of participants with fair to satisfactory adherence to medication.[2,5]

Increase in motivation and initiative in treatment adherence is the essence of adherence therapy, in which motivational interviewing helps resolve ambivalence and engage intrinsic motivation and specific goals with participants in order to change their problem behaviours.[6,12] In addition, the cost-effectiveness ratios in reducing number of re-hospitalisations and improving medication adherence and symptom severity favour adherence therapy. As no economic evaluation of adherence therapy for patients with psychotic disorders has been performed,[3] this finding provides evidence that adherence therapy can be cost-effective for people with schizophrenia in community care.

Limitations of this study include: (1) small and selective sample recruited from two services centres only; participants were voluntary to participate and with satisfactory family support and ≤3 years of illness; (2) some confounders of adherence therapy such as 30% of refusal rate, side-effects, and changes in types and dosages of medication, and other community services used over the study period were not examined; and (3) participants and CPNs were not blind to adherence therapy and routine care and might have caused subjective biases on preconceived benefits of adherence therapy.

Conclusion

Adherence therapy for people with schizophrenia spectrum disorders can improve symptom severity, medication adherence, functioning, insight to illness/treatment, and number of re-hospitalisations, as well as cost-saving for outcome improvements over a 12-month follow-up. Adherence therapy in addition to psychopharmacological and other psychiatric treatments has benefits to Chinese patients. Further research on its wider implementation in community-based rehabilitation for diverse patient groups and across cultures is warranted.

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References

1. Chien WT, Yip AL. Current approaches to treatments for schizophrenia spectrum disorders, part I: an overview and medical treatments. Neuropsychiatr Dis Treat 2013;9:1311-32.
2. McIntosh AM, Conlon L, Lawrie SM, Stanfield AC. Compliance therapy for schizophrenia. Cochrane Database Syst Rev 2006;3:CD003442.
3. Gray R, White J, Schulz M, Abderhalden C. Enhancing medication adherence in people with schizophrenia: an international programme of research. Int J Ment Health Nurs 2010;19:36-44.
4. Drummond MF, Sculpler MJ, Torrance GW, O'Brien B, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes, 3rd ed. Oxford: Oxford University Press; 2005.
5. Gray R, Wykes T, Gournay K. From compliance to concordance; a review of the literature on interventions to enhance compliance with antipsychotic medication. J Psychiatr Ment Health Nurs 2002;9:277-84.