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ORIGINAL ARTICLE

Randomized Controlled Trial

Effect of comprehensive intervention model based on drug-psychology-society-skills on medication compliance and cognitive ability of chronic schizophrenia patients

Hai-Jun Wang, Wei Chen, Xiao-Lin Yan, Qian-Ying Huang, Wei-Dong Xu

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Abstract

BACKGROUND

The intervention value of a drug-psycho-social-skill model on medication compliance and cognitive ability in patients with chronic schizophrenia was unknown.

AIM

To explore the intervention value of a drug-psycho-social-skill model on medication compliance and cognitive ability in patients with chronic schizophrenia.

METHODS

Overall, 98 out-patients and in-patients with chronic schizophrenia treated in our hospital from February 2022 to January 2023 were included and randomly divided into the study (50 patients) and control groups (48 patients). For 3 months, the control group was treated with conventional drugs, and the research group with a comprehensive intervention model of drug-psychology-society-skills. Data were obtained for the mini mental assessment scale (MMSE), Montreal cognitive assessment scale (MoCA), positive and negative symptom scale, insight and treatment attitude scale, cognitive ability scale and social skills [personal and social function scale (PSP)]. The adverse reactions were observed.

RESULTS

After the intervention, the MMSE and MoCA scores improved in both groups. MoCA scores in the study group (26.58 ± 3.21) were significantly ($P < 0.05$) higher than those in the control group (24.68 ± 3.02), MMSE scores were not significantly higher. Post-intervention, positive and negative symptom scores improved in both groups, and the positive and negative symptom scores in the study group [(12.01 ± 2.58) and (32.51 ± 2.11)] were significantly ($P < 0.05$) different than those in the control group [(14.54 ± 2.33) and (33.74 ± 2.55)]. Post-intervention, insight and treatment attitudes questionnaire scores of both groups were improved and compared with the control group (7.97 ± 3.02), the study group (13.56 ± 6.35) had significantly ($P < 0.05$) higher scores. Post-intervention, the MATRICS consensus cognitive battery score of both groups was improved and compared with the control group (38.44 ± 6.23), the score of the study group was significantly ($P < 0.05$) increased (43.51 ± 6.01). Post-intervention, the PSP score of the study group (78.38 ± 6.63) was significantly ($P < 0.05$) higher than that of the control group (74.52 ± 7.01). During the intervention period, the incidence of adverse reactions in the study group was 6.25%, not significantly different from that in the control group (8.33%). During the intervention, both groups experienced adverse reactions, with no significant difference between groups ($P > 0.05$).

CONCLUSION

The comprehensive intervention model based on drug-psychology-society-skills has obvious intervention effects on patients with chronic schizophrenia, which improves their cognitive ability and reduces their positive and negative symptoms. Simultaneously, it improves the self-knowledge of patients, improves their attitude toward treatment, effectively promotes the recovery of patients' social functions, and is safe. Therefore, it is worthy of being vigorously promoted and widely used in clinics.

Key Words: Drug-psychology-society-skill; Comprehensive intervention model; Medication compliance; Self-knowledge; Cognitive ability

Core Tip: The comprehensive intervention model based on drug-psychology-society-skills has obvious intervention effect on patients with chronic schizophrenia, which not only improves the cognitive ability of patients, but also reduces the positive and negative symptoms of patients.

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INTRODUCTION

Chronic schizophrenia, a disease in the field of mental health, is characterized by apathy, lack of motivation, and other negative symptoms[1]. With the gradual extension of the course of the disease, patients' cognitive ability is impaired to some extent, which affects their mental health and adversely affects their quality of life[2]. In China, patients with schizophrenia are treated centrally and managed in a closed manner. However, patients with schizophrenia generally have poor medication compliance owing to a lack of correct understanding of their own diseases and treatments, which leads to patients' unwillingness to cooperate, thus causing treatment difficulties[3]. Simultaneously, poor medication compliance is also one of the main reasons that directly lead to the gradual chronicity of the course of schizophrenia. To a certain extent, it not only reduces social function but also consumes many medical resources and imposes a burden on families[4]. Current treatment models tend to focus on medication and neglect psychological, social, and skill training interventions. This single treatment approach is difficult to meet the full needs of people with chronic schizophrenia, therefore, exploring a comprehensive intervention model is of great significance for the rehabilitation of patients with chronic schizophrenia. Recently, with changes in medical models, people have gradually realized the complexity of mental illnesses and their multidimensional treatment. Drug therapy, combined with psychotherapy, social support, and skill training, provides patients with a comprehensive, personalized treatment plan. This intervention model not only focuses on symptom relief but also emphasizes the recovery of patients' psychological and social functions and the improvement of their quality of life. With regard to drug therapy, patient symptoms can be effectively controlled through a scientific and reasonable medication scheme that lays the foundation for the implementation of other treatment measures[5]. Psychotherapy focuses on helping patients establish positive self-awareness and improve their ability to cope with stress and challenges, thus reducing the recurrence and deterioration of symptoms[6]. In terms of social support, family, community, and other forces are used to provide the necessary help and support for patients and

promote their reintegration into society. Skill training is designed to help patients improve their daily self-care ability, vocational skills, life skills, and social ability so that they can better adapt to the social environment and promote their rehabilitation[7]. Comprehensive interventions improve functional outcomes in patients with chronic schizophrenia[8]. However, there are few reports on integrated drug-psycho-social-skill intervention models. Therefore, this study aimed to explore the intervention value of a drug-psycho-social-skill integrated model for medication compliance and cognitive ability in patients with chronic schizophrenia to provide a new perspective and practical basis for the clinical treatment of chronic schizophrenia. This study also aimed to provide a reference for future mental health policy formulation and service system improvement to achieve more comprehensive and humanized care and support for patients with schizophrenia. The remainder of this paper is organized as follows.

MATERIALS AND METHODS

General information

In this study, 98 patients with chronic schizophrenia who were treated at our hospital between February 2022 and January 2023 were selected as research subjects, and the study was approved by the ethics committee of the hospital. Inclusion criteria: (1) Patients satisfying the diagnostic criteria of the international classification of diseases[9], 10th edition, and diagnosed as chronic schizophrenia by psychiatrists; (2) Age ≥ 18 years old, regardless of sex or education level; (3) Patient should be in a relatively stable period of the disease; (4) Have certain cognitive function, and be able to understand and abide by the research requirements; and (5) Patient or their legal guardian shall sign an informed consent form and agree to participate in the study. Exclusion criteria: (1) Patients with severe physical, nervous system, or infectious diseases; (2) Patients with a history of drug abuse or dependence; (3) Patients who had recently experienced major life events (such as divorce and bereavement); (4) Patients who switched to other antipsychotics or added other antipsychotics midway; (5) Serious adverse reactions that occurred, the disease obviously worsened, and the patient or his family refused to continue to treat the patient; and (6) Pregnant or lactating women. Patients were randomly divided into a study group (n = 50) and a control group (n = 48). As two patients in the study group were lost to follow-up, they were finally divided into a study group (48 cases) and a control group (48 cases).

Among the 48 patients in the control group, the ratio of men to women was 27:21. The age range was 33–45 years, with an average age of (40.21 ± 4.32) years. The course of disease is 5-10 years, with an average of 7 ± 2.5 years and an average of (3.36 ± 0.48) years. Of the 48 patients, 7, 14, and 9 had major depression, schizophrenia, and bipolar disorder, respectively.

Among the 48 patients in the research group, the men-to-women ratio was 29:19. The age range was 34-44 years, with an average age of (39.12 ± 4.54) years. The course of the disease was 5-9 years with an average of 6.5 ± 3.0 years. There was no significant difference in the clinical data between the two groups, therefore, a targeted clinical comparison could be made (P > 0.05).

Methods

Control group: Intervention with second-generation antipsychotics. The dosage of most clozapine tablets was 200-600 mg/day, the dosage of quetiapine combined with quetiapine was 400-600 mg/day, the dosage of risperidone tablets was 4-6 mg/day, or the dosage of ziprasidone tablets was 80-120 mg/day. The dosage was individualized, considering the effective dosage and safe blood concentration range. Further, patients adherence to the dosage schedule (timing and quantity) was supervised, their families were guided on how to take drugs accurately, any changes in patients' conditions were identified, community doctors were consulted on time under abnormal circumstances, patients' possession of drugs was observed, and patients with suicidal tendencies were closely monitored.

Study group: Based on the control group, a drug-psychological-social-skill comprehensive intervention was administered.

Drug intervention and drug management training: Treatment drugs and control groups. Simultaneously, the adverse reactions of drugs and basic knowledge of psychotropic drugs were explained to the patients and their families to improve patients' ability to manage drugs.

Psychological intervention: Patients were supported and encouraged to help them face reality faster and live actively. According to the individual mood and ideological changes of patients, humor and positive language was used to stimulate patients' interest in life, a self-reliant and confident outlook on life was established, patients were encouraged to establish support networks, actively expand social circles, and gradually return to normal life.

Socio-skill intervention: (1) Life skills training: Using one-to-one behavior correction guidance, patients were trained in terms of daily self-care ability such as diet, personal hygiene, dressing and grooming, 2-3 times a day, and each training time was controlled within half an hour. At the same time to actively participate in the patient to give timely encouragement and affirmation. Patients were trained in daily living activities such as shopping and washing clothes, and their family members accompanied and assisted them throughout the training process, training once or twice a day, and each time was controlled to about 15 minutes; (2) Social employment skills training: For patients with functional disabilities, based on their previous occupations, occupational therapy and systematic labor simulation training were used to carry out individualized training in combination with their individual conditions. Each training time lasted for 1 hour, twice a week. Patients were encouraged to use household work or community services accompanied by family members, and the

time was also controlled at approximately 1 hour each time; (3) Emotional control training: Patients' interests and hobbies were combined and they were encouraged to participate in recreational activities such as chess, playing ball, singing, *etc.*, to help patients integrate into the normal life track. The patients were guided in finding appropriate ways of emotional catharsis by playing tai chi, practicing Wuqin play, *etc.* Additionally, basic emotional regulation skills, such as, deep breathing, appropriate physical exercise, and other ways to control emotions were taught. Psychologists conducted a psychological intervention for patients once a week, and specialists explained the general symptoms and treatment measures of schizophrenia to patients and their families, and reflect to doctors when necessary to get active treatment; and (4) Social skills training: Patients were encouraged to introduce themselves and their interests and hobbies in an appropriate way. General life events such as birthdays, dining, shopping were simulated to let patients learn how to get along with others, express their inner thoughts, and master the method of praising others and self-praise. They were also allowed to learn how to regularly carry out team cooperation games by encouraging and praising the patients in order to affirm correct behavior.

Both groups underwent intervention continuously for 3 months.

Observation indicators

The mini mental status examination and Montreal cognitive assessment were used for joint assessment: Mini mental status examination (MMSE)[10] evaluates seven components: Language, attention, computing power, immediate memory, delayed memory, time orientation, spatial orientation, and visual space. The Montreal cognitive assessment (MoCA)[11] evaluates language, naming, memory, execution, attention, orientation, abstract thinking, and delayed recall. The total score on both scales was 30, and the higher the score, the stronger the cognitive ability.

Positive and negative syndrome scale: Positive and negative syndrome scale (PANSS)[12] scores before and after treatment were compared between the groups. Negative symptoms mainly include poor speech, concentration defects, emotional retardation, apathy, and social withdrawal, while positive symptoms mainly include hallucinations and delusions; each item is scored according to 1-7 grades. Grade 1 was asymptomatic, with symptoms worsening gradually, grade 7 was the most serious, and the final score was counted.

Insight and treatment attitudes questionnaire: The scale[13] has 11 questions, including the patients' knowledge of diseases and their attitudes towards treatment. The evaluation doctor asks each question to the patient and answers and explains the question. The doctor gave a score of 0-2 based on the patient's answers. The score 2 = completely self-aware, 1 = partially self-aware, and 0 = not self-aware. The lowest score on the questionnaire was 0 and the highest score was 22. The higher the score, the better the patient's insight into and attitude towards treatment.

Cognitive ability scale: Before and after the intervention, patients' cognitive ability was evaluated using the MATRICS consensus cognitive battery (MCCB)[14], which included eight subtests, including number symbol, number span, visual memory, maze, visual reproduction, verbal fluency, short-term language memory, and continuous operation, and cognitive functions of patients, such as association, perception, and memory.

Social skills: Through the personal and social performance scale (PSP)[15], activities, personal and social relationships, self-care, and disturbing and aggressive behaviors are useful to patients in society were evaluated. The first three items are scoring standards and the fourth item is a scoring standard. The total score ranges from 0 to 100. Divided into 10 grades, 71-100 points: The patient's social and interpersonal skills are good and only slightly affected; 31-70: There are different degrees of defects in social skills; < 30: Patient's ability is low and needs active support or monitoring.

Adverse reactions in the two groups during the intervention period were evaluated, including extrapyramidal reactions, weight gain, elevated blood sugar and blood lipid levels, abnormal liver function, and leukopenia.

Statistical analysis

Statistical product and service solutions 26.0 was used for data processing. The counting data obtained from the experiment is expressed as %, and the measurement data is expressed by the mean ± SD by the χ^2 test. Data were normally distributed, the variance was homogeneous, and the difference was statistically significant according to the *t*-test, $P < 0.05$.

RESULTS

MMSE and MoCA score comparison

Before the intervention, there were no significant differences in the MMSE and MoCA scores between the two groups ($P > 0.05$). After intervention, the scores of both groups significantly improved, and the MoCA score of the study group (26.58 ± 3.21) was significantly higher than that of the control group (24.68 ± 3.02), the difference was statistically significant ($P < 0.05$), but there was no statistically significant difference in MMSE score between the two groups ($P > 0.05$). See Table 1.

PANSS score comparison

Before the intervention, there was no significant difference in the scores of positive symptoms and negative symptoms between the two groups ($P > 0.05$). After intervention, both positive and negative symptom scores were improved in the two groups, and the positive symptom scores (12.01 ± 2.58) and negative symptom scores (32.51 ± 2.11) in the study

Table 1 Comparison of mini mental assessment scale and Montreal cognitive assessment scale scores between the two groups, mean ± SD

Group	Number of cases	MMSE score		MoCA score	
		Before intervention	After intervention	Before intervention	After intervention
Research group (n = 48)	48	22.25 ± 2.47	27.15 ± 2.58	23.31 ± 2.14	26.58 ± 3.21[a]
Control group (n = 48)	48	22.33 ± 2.71	26.24 ± 2.36	23.44 ± 2.09	24.68 ± 3.02[a]
t value		0.151	1.803	0.301	2.987
P value		0.880	0.075	0.764	0.004

[a]P < 0.05.

MMSE: Mini mental assessment scale; MoCA: Montreal cognitive assessment scale.

group were more significantly changed than those in the control group [(14.54 ± 2.33) and (33.74 ± 2.55)]. This difference was statistically significant (P < 0.05). See Table 2.

Insight and treatment attitudes questionnaire score comparison

Before the intervention, there was no significant difference in the insight and treatment attitudes questionnaire (ITAQ) scores between the two groups (P > 0.05). After intervention, ITAQ scores of both groups were improved, and compared with control group (7.97 ± 3.02) scores, the score of study group (13.56 ± 6.35) scores was significantly increased, and the difference was statistically significant (P < 0.05). See Table 3.

MCCB score comparison

Before the intervention, there was no significant difference in the MCCB scores between the two groups (P > 0.05). After intervention, the MCCB score of both groups was improved, and compared with the control group (38.44 ± 6.23), the score of the study group was significantly increased (43.51 ± 6.01), and the difference was statistically significant (P < 0.05). See Table 4.

Comparison of social skills

Before the intervention, there was no significant difference in PSP scores between the two groups (P > 0.05). After intervention, the PSP score of the study group (78.38 ± 6.63) was significantly higher than that of the control group (74.52 ± 7.01), and the difference was statistically significant (P < 0.05). See Table 5.

Comparison of adverse reactions

The incidence of adverse reactions in the study group was 6.25%, which was not significantly different from that in the control group (8.33%), P > 0.05. See Table 6.

DISCUSSION

The continuous prolongation of chronic schizophrenia can cause great damage to the patient's body and mind in the long run, especially in terms of cognitive ability and social adaptability. As patients with schizophrenia easily lose confidence in treatment after long-term medication, medication compliance is an important factor in the treatment of patients with schizophrenia[16]. The main factors that affect patients' medication compliance are a lack of cognitive ability, the importance of continuous treatment to a certain extent, and the wrong cognition of adverse drug reactions, which leads patients to refuse to take medication[17]. If patients take their medication on time, they can better control their symptoms and reduce the possibility of recurrence, thus improving their quality of life[18]. Currently, the universal free medication policy has increased medication compliance to some extent and reduced the recurrence of diseases and further aggravation of disabilities; however, other methods and strategies are still needed to further strengthen this effect. Therefore, this study explored medication compliance and cognitive ability in patients with chronic schizophrenia, using a comprehensive intervention model of drug, psychological, and social skills. In order to avoid the impact of confounding factors on the study results, this study randomly grouped the patients after inclusion and compared the baseline data of the two groups of patients. The results showed no significant difference in the baseline data between the two groups, which further provided the basis for the study and ensured its feasibility. At the same time, after the successful completion of this study, it also showed a relatively satisfactory result.

The MMSE and MoCA rating scales mainly evaluate patients' cognitive function. The comprehensive intervention of drug-psychology-society-skills can reduce the interruption rate of antipsychotic drug treatment, effectively improve the patient's disease status and quality of life and bring new hope to the treatment of chronic schizophrenia[19]. Insisting drugs are the most effective means of preventing the recurrence of chronic schizophrenia. Hattabi *et al*[20] reported that the combination of psychological, social, and skill intervention training based on drug treatment can reduce the

Table 2 Comparison of positive and negative syndrome scale score between two groups, mean ± SD

Group	Number of cases	Positive symptom score		Negative symptom score	
		Before intervention	After intervention	Before intervention	After intervention
Research group (n = 48)	48	15.38 ± 2.45	12.01 ± 2.58[a]	35.22 ± 2.65	32.51 ± 2.11[a]
Control group (n = 48)	48	15.66 ± 1.94	14.54 ± 2.33[a]	35.53 ± 2.01	33.74 ± 2.55[a]
t value		0.621	5.042	0.646	2.575
P value		0.536	0.000	0.520	0.012

[a]P < 0.05.

Table 3 Comparison of insight and treatment attitudes questionnaire scores before and after treatment, mean ± SD

Group	ITAQ score	
	Before intervention	After intervention
Research group (n = 48)	5.23 ± 3.45	13.56 ± 6.35[a]
Control group (n = 48)	5.79 ± 3.04	7.97 ± 3.02[a]
t value	0.843	5.508
P value	0.402	0.000

[a]P < 0.05.
ITAQ: Insight and treatment attitudes questionnaire.

Table 4 Comparison of MATRICS consensus cognitive battery scores between the two groups, mean ± SD

Group	Number of cases	Before intervention	After intervention
Research group (n = 48)	48	34.45 ± 5.22	43.51 ± 6.01[a]
Control group (n = 48)	48	34.24 ± 5.62	38.44 ± 6.23[a]
t value		0.190	4.058
P value		0.850	0.000

[a]P < 0.05.

Table 5 Comparison of personal and social performance scale scores between the two groups, mean ± SD

Group	PSP		t value	P value
	Before intervention	After intervention		
Research group (n = 48)	46.79 ± 7.31	78.38 ± 6.63	22.177	0.000
Control group (n = 48)	45.51 ± 7.26	74.52 ± 7.01	19.916	0.000
t value	0.861	2.772		
P value	0.382	0.007		

PSP: Personal and social performance scale.

recurrence rate of patients with chronic schizophrenia and restore their damaged social functions, such as life, work, and study. The results of this study showed that the MMSE score was not statistically significant, which may be related to the insensitivity of the indicators. Although chronic mental illness results in cognitive impairment, it has not yet reached the level of dementia. The MoCA score and the complete cognitive function test for schizophrenia (MCCB) in the study group were statistically higher than those in the control group, suggesting that the comprehensive intervention model of drug-

Table 6 Comparison of the incidence of adverse reactions during treatment, *n* (%)

Group	Extrapyramidal reaction	Put on weight	Elevated blood sugar	Hyperlipidemia	Incidence rate
Research group (n = 48)	1 (2.08)	0 (0.00)	0 (0.00)	2 (4.17)	3 (6.25)
Control group (n = 48)	2 (4.17)	0 (0.00)	0 (0.00)	2 (4.17)	4 (8.33)
χ^2	0.205				
P value	0.36				

psychology-society-skills has a certain positive significance for patients with chronic schizophrenia and the two scales may be more useful for evaluating cognitive impairment. The reason is that the second-generation antipsychotic drugs show high affinity for α1 and α2 receptors by acting on 5-hydroxy tryptamine (HT) 2 and D2 receptors. On the one hand, they block D2 receptors in the midbrain marginal pathway, thus changing patients' attention[21], on the other hand, they block 5-HT2 receptors in the midbrain cortical pathway and the substantia nigra striatum pathway, improving the functions of D1 receptors in the prefrontal cortex and D2 receptors in the striatum, thus improving the cognitive function of patients with chronic schizophrenia[22]. Through psychosocial and skill interventions, patients can learn to rationally vent their emotions and relax, and correctly express their emotions and needs. Simulation training of employment skills was developed according to the patients' own conditions to improve their ability to deal with problems and cultivate their learning habits and ability to accept new things. They must be encouraged to actively participate in social activities and naturally integrate into them[23] and foster self-affirmation, thereby helping them regain confidence in recovery and indirectly helping them improve their quality of life.

Cognitive impairment is a typical symptom in chronic schizophrenia[24]. An increase in the MMSE and MoCA scores indicates that the cognitive function of the patients has recovered to some extent. However, this study found that the scores of positive and negative symptoms in the study group were lower than those in the control group, indicating that the comprehensive drug-psychology-society-skills intervention can reduce positive and negative symptoms in patients with chronic schizophrenia. This is because clozapine can stimulate the serotonin receptor and promote dopamine release, thus increasing dopamine content in the synaptic cleft[25]. Clozapine also has an anticholinergic effect that can effectively improve the conversion efficiency of dopamine in the central nervous system and increase dopamine levels in the substantia nigra-striatum, thus strengthening dopamine nerve function and reducing cholinergic nerve function[26]. Furthermore, the drug can be taken for a long time. Training patients in society and skills, encouraging patients to communicate with others, and enhancing patients' confidence are conducive to the improvement of the disease.

There is a positive correlation between medication compliance and insight, and the improvement of insight is related to cognitive ability. Therefore, we can infer that improving cognitive ability can improve insight, and thus improve medication compliance. Improvements in cognitive ability are closely related to the rehabilitation of social functioning. The results of this study showed that the ITAQ and MCCB scores of patients in the study group were significantly higher than those in the control group after the comprehensive intervention of drug-psychology-society-skills, showing that the comprehensive intervention of drug-psychology-society-skills can improve patients' cognitive ability, improve patients' treatment attitudes, and relieve mental symptoms. This is because drug treatment can directly affect neurotransmitters in the brain and relieve patients' mental symptoms and psychological states[27]. Psychological intervention can effectively improve patients' cognition of their own diseases, improve their self-management ability, and help alleviate patients' negative emotions, such as anxiety and depression[28]. Moreover, through social intervention, providing patients with a good social support network can effectively reduce the sense of social isolation of patients; in addition, by training patients' drug management ability, life ability, interpersonal skills, work ability, *etc.*, patients can help to identify adverse drug reactions, and patients can be provided comprehensive health education and psychological treatment, which can help patients understand the importance of treatment and improve their self-care ability and social adaptability, so as to reduce patients' dependence. This will help them improve quality of life, thereby improving ITAQ and MCCB scores.

This study also found that, after treatment, the PSP score of patients in the study group was significantly higher than that in the control group. The reason for this was that the mental symptoms and psychological state of patients were effectively alleviated through the control and improvement of symptoms of severe mental illness by drugs. A comprehensive treatment system was formed with the intervention of society and skills to improve the symptoms of patients more comprehensively and improve the score on the social skills scale. Furthermore, the results of this study also showed no significant difference in adverse reactions between the two groups, which may be due to individual differences in patients related to personal physique, age, and long-term medication use.

CONCLUSION

In summary, the comprehensive intervention mode based on drug-psycho-social-skills can reduce the disease state of patients with chronic schizophrenia, enhance the cognitive ability of patients, reduce the positive and negative symptoms of patients, and improve the self-knowledge of patients and their attitude toward treatment. This model provides more comprehensive support for patients and new ideas and directions for the development of the mental health field. However, this study also has some limitations: (1) The sample size of patients was small, which may affect the universality of the study results, so it is still necessary to carry out further research and observation of large samples; (2)

Observation of results by means of scale statistics may cause the results to be affected by subjective factors, so the analysis of objective indicators should be added in subsequent studies; (3) Patients were not followed up, and the potential impact of comprehensive intervention on patients' long-term life could not be clarified. Therefore, the study period should be further extended to clarify the clinical application value of comprehensive intervention; and (4) This study only observed the clinical treatment outcome of patients, and the specific mechanism of action was not clearly explained. Therefore, further research should be conducted to improve intervention mechanisms.

FOOTNOTES

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