Beijing Science and Technology Program Project Implementation

Topic Title: Research on Early Standardized Electronic Cognitive Training Technology for Elderly Depression with Cognitive Impairment

Project Name: Advantageous Discipline Cultivation Project

Field: Healthcare

Category: Public welfare applications

Municipal Science and Technology Commission In charge of the office: Medical and Health Science and Technology Division

The version number: 2.0

Document date: September .30.2021

Starting and ending years: January 2020-august 2023

Purpose, significance and necessity of the study

1. Significance and necessity of the study

Age-related depression (LLD) is the most common mental disease in the old age. Because of the increasing prevalence of population aging, it has become one of the important factors affecting the quality of life of the elderly. 50-70% of senile depression is accompanied by cognitive impairment of different degrees. The patients with senile depression with cognitive impairment have higher risk of dementia transformation, worse prognosis and higher recurrence rate, which seriously endanger the quality of life and social function of patients and increase the economic burden of society and families. Therefore, it is urgent to provide evidence-based early intervention strategies for senile depression with cognitive impairment.

At present, the domestic and foreign guidelines do not provide a clear and effective treatment plan for the elderly patients with cognitive impairment, and the clinical research and practice also lack evidence-based treatment. Selective serotonin reuptake inhibitors (SSRIs), the most used antidepressant in elderly depression, cannot significantly improve the cognitive impairment of elderly patients with depression, and may even aggravate the cognitive impairment of elderly patients with depression. The overall efficacy and tolerability of drug therapy for elderly patients with depression and cognitive impairment are poor. Studies have confirmed that cognitive training can significantly improve the overall cognitive function and the functions of multiple cognitive domains of healthy elderly, patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). The previous research results have also initially confirmed the cognitive improvement effect of cognitive training on elderly patients with depression, providing a new idea for clinical diagnosis and treatment.

Therefore, based on the urgent needs of the clinic and the foundation of the preliminary work, the development and clinical validation of a set of standardized cognitive training methods suitable for elderly depressive patients with cognitive impairment will help improve the overall efficacy of elderly depressive patients, improve the prognosis of patients, save health resources, provide evidence-based medical basis for improving the

diagnosis and treatment guidelines of elderly depressive patients, It conforms to the concept of patient-centered bio psychological social medical model.

2. Research purpose:

(1) To compare the efficacy of conventional SSRIs combined with electronic cognitive training (intervention group) and single conventional SSRIs treatment/Blank electronic training (control group) on cognitive impairment in elderly patients with depression.

(2) To establish a set of standardized and operable electronic cognitive intervention technology for elderly depression patients with cognitive impairment, which is applicable to various psychiatric hospitals at all levels.

3. Project basis

1.China's population aging situation is severe, the prevalence of senile depression is high, and the cognitive function is seriously damaged

The aging situation of China's population is grim. By the end of 2017, the elderly population in Beijing had exceeded 20% of the total population. Senile depression is the most common mental disorder in the elderly [1], and the prevalence rate has increased year by year. Studies have reported that the global prevalence rate of senile depression is 0.2% ~ 29% [2-4], while the prevalence rate of senile depression in China is about 2.8% [5]. Compared with other age groups, the onset of senile depression is more concealed and cognitive function is more likely to decline. 50-75% of senile depression patients have cognitive function impairment [6], which is more likely to lead to the decline of quality of life and social function impairment [7, 8].

2.Elderly depression with cognitive impairment has poor treatment effect, high recurrence risk and lack of evidence-based treatment

Clinical studies have found that the effect of antidepressants in elderly patients with cognitive dysfunction is poor, and cognitive impairment may be one of the important factors for poor efficacy [9]. Tam [10] et al. Found that the ability of daily living of

elderly patients with depression decreased significantly, and the severity of depressive symptoms and the degree of cognitive impairment were significantly related to the ability of daily living. Persistent cognitive impairment may increase the risk of relapse of depression [11]. In terms of the treatment and intervention of senile depression with cognitive impairment, there are few relevant studies at present, and the domestic and foreign depression treatment guidelines do not involve the treatment suggestions on senile depression with cognitive impairment. The first-line treatment recommendations for senile depression are still based on drug treatment to control symptoms, and there is no evidence-based evidence to support the treatment of cognitive impairment. Studies have shown that intelligence promoting drugs such as cholinesterase inhibitors have no obvious effect on senile depression with cognitive impairment [12]. The drug treatment of senile depression with cognitive impairment is not optimistic. There is an urgent need to explore a suitable intervention mode for the elderly depression patients with cognitive impairment to improve their prognosis.

3.The results of previous small sample studies suggest that cognitive training can improve the cognitive dysfunction of senile depression

In recent years, more and more researchers have begun to pay attention to the role of cognitive training in improving cognition. Studies on the general elderly population have found that cognitive training can improve the overall cognitive function and multiple cognitive domain functions of healthy elderly and MCI patients [13]. Evidence based medicine evidence supports the effect of multi cognitive domains and multi-modal cognitive training on the overall cognitive function. The cognitive domains covered by cognitive training should include but not limited to orientation, perceptual ability, attention, memory, executive function, logical reasoning, processing speed and language function. At present, the research on cognitive training is mainly focused on ad, MCI, healthy elderly and schizophrenia, and the related research on senile depression with cognitive impairment is less. Some researchers provided memory training for elderly patients with depression and found that the 10-week intervention not only improved the cognitive level of patients, but also alleviated their depressive symptoms [14]. Cognitive training can improve the attention pre-processing of elderly

patients with depression and improve the prognosis of patients [15]. The previous small sample study of our research group also obtained the same research results.

This study intends to further screen and optimize the cognitive training technology in the previous study and make it electronic. Through an RCT study, the efficacy and compliance of the electronic cognitive training technology on the elderly depression with cognitive impairment are verified. The purpose is to provide convenient and reliable treatment technology for the clinic and solve the dilemma of "no medicine to cure" cognitive impairment associated with the elderly depression, to improve its prognosis and reduce the disease burden.

4. Scientific problems

Cognitive training can improve the cognitive function of elderly depression: the previous small sample study found that cognitive training can improve the cognitive function of elderly depression patients with cognitive impairment. At present, there is no RCT study with strict design to further verify the improvement of cognitive function of elderly depression patients by cognitive training, The successful implementation of this study can solve the bottleneck problem of "no drug can be treated" in the current clinical treatment of cognitive impairment associated with senile depression, provide treatment ideas for clinicians to treat senile depression, and provide evidence-based support for the clinical treatment guidelines of depression.

Current situation and trend of research and development at home and abroad in relevant industries and fields of the subject, as well as the work foundation of the unit in relevant fields

1. Research status at home and abroad

(1) Senile depression with cognitive impairment may persist

For a long time, most studies on cognitive impairment have focused on schizophrenia, MCI, ADand other diseases. It is believed that the cognitive impairment of patients with depression is slight, and that the cognitive impairment can be improved with the alleviation of depression, and the cognitive impairment associated with depression is

called "pseudodementia". However, with the deepening of the research, experts and scholars at home and abroad have found that cognitive function damage of some depressed patients is prominent and persists after the depression symptoms are relieved, especially for the elderly patients with depression. They also found that the elderly patients with depression without cognitive function damage may also have cognitive function damage after the depression mood improves over time [16]. Recent studies have found that persistent cognitive impairment may increase the risk of relapse of depression. Depression often leads to severe and comprehensive social function decline. The degree of social function damage of patients is related to the severity of depressive symptoms. Some patients' social function decline persists after the depressive symptoms are relieved [17].

Studies have shown that cognitive impairment in elderly patients with depression mainly involves multiple cognitive domains, including episodic memory, information processing speed, executive function, and visuospatial ability [18] [19]. Cognitive functions such as speech learning, memory function, psychomotor speed, and executive function of elderly patients with depression are more severely damaged than those of young patients with depression [20].

(2) The treatment effect of senile depression patients with cognitive impairment is worse

At present, the treatment of senile depression with cognitive impairment often pays attention to the treatment of depressive symptoms and neglects the treatment of cognitive impairment. However, the effect of antidepressant therapy alone is not satisfactory for senile depression with cognitive impairment. The study found that the short-term efficacy of tricyclic and tetracyclic antidepressants and SSRIs antidepressants was generally poor in elderly patients with executive function impairment. Some studies have also found that elderly patients with depression, if accompanied by information processing speed, episodic memory and language function impairment, may have poor antidepressant treatment effect [21]. SSRIs antidepressant treatment cannot significantly improve the cognitive impairment of elderly patients with depression and may even aggravate the degree of cognitive impairment. Recent

studies have found that the psychomotor speed and speech learning ability of elderly patients with depression continue to decline after treatment with citalopram hydrobromide, suggesting that the cognitive impairment of elderly patients with depression may be secondary to drug factors [22]. At present, clinicians with cognitive impairment in elderly depression are more inclined to choose different kinds of intelligence promoting drugs. However, the study found that even if cholinesterase inhibitors were added to elderly patients with depression, it had only a small impact on the improvement of concurrent cognitive impairment and the conversion rate of AD. it also found that cognitive impairment may lead to an increase in the risk of relapse of depression. At present, there is no evidence-based drug for cognitive impairment in senile depression.

(3) Previous studies have confirmed that cognitive training can improve cognitive impairment

In recent years, the intervention of cognitive training on brain diseases has been favored by experts, scholars and clinical workers at home and abroad for its convenience, safety and effectiveness. The results of randomized controlled clinical trials and meta-analysis all support that cognitive training can improve the overall cognitive function and cognitive domains such as memory and attention function of healthy elderly and MCI patients [13, 23, 24]. The research shows that for the elderly with cognitive health, the cognitive enhancement effect brought by traditional cognitive training is quite stable, although it is affected by training methods, training duration, suitability, and other factors. And cognitive training for MCI and AD patients has also been proved to have "moderate to high effect amount" [25]. For mild to moderate AD patients, the implementation of cognitive training in the whole cognitive field can be an effective supplement to drug treatment and maintain the "recovery" effect of this cognition for at least 1 year after the training. Most of the existing cognitive training studies focus on MCI and ad, but few studies on cognitive impairment associated with senile depression. Meta-analysis shows that cognitive training can improve the attention, working memory and social function of elderly patients with depression [26]. It has been found that cognitive training can improve the executive function and visuospatial ability of

patients with stable senile depression and reduce the residual symptoms of depression [27]. Some researchers provided electronic memory training for elderly patients with depression, and found that the intervention lasting for 10 weeks, once a week, for 60-75min, not only improved the memory level of patients, but also alleviated their depressive symptoms [14]. Memory specific training 6 times a week, once for 20min, 2h a week can improve the episodic memory function of senile depression [28]. However, the sample size of these studies is generally small, and the cognitive training methods adopted are not designed for the elderly with depression, and they only focus on a certain module of the cognitive field for training, lack of intervention research on the elderly with depression in the acute phase, and the follow-up time is short. It is impossible to judge the long-term efficacy and compliance of cognitive training for the elderly with depression. The preliminary open research results of this research group have also obtained similar results. The cognitive training methods developed by the research team around various cognitive fields such as episodic memory, executive function, working memory, attention processing, speech ability, reasoning and judgment have accumulated tens of thousands of data in the elderly population in the community. The results show that the training is conducted four times a week for 60min every day, Training for 12 weeks can significantly improve the cognitive function of the elderly in the whole and various cognitive fields. At present, this training method has been widely used in AD, MCI, senile schizophrenia, and senile depression in our hospital.

Compared with traditional cognitive training, computer-based electronic cognitive training is easier to obtain. A meta-analysis shows that there are individual differences in the effects of comprehensive cognitive training and single domain cognitive training - the improvement of memory function of MCI patients by comprehensive cognitive training is not as good as that by simple memory training [29, 30], while in the healthy elderly, the improvement of memory function by memory training is not as good as that by executive control or comprehensive cognitive training [13]. Computer based cognitive training has been applied to the healthy elderly, MCI patients, AD patients and vascular cognitive impairment patients, and its effect has also been confirmed,

because it has the advantages of personalization and adaptation, and can consider comprehensive training programs and individual differences in plasticity in different cognitive fields. Personalized computer cognitive training can enhance subjective perception of cognitive changes, and higher-level cognitive training may bring additional benefits [31]. In consideration of individual differences, when designing cognitive training schemes, the advantages of big data and artificial intelligence algorithms can be brought into play and the training schemes can be adjusted individually. There are many ways to implement cognitive training, such as training with paper and pen materials or computer-aided programs, and training through virtual reality, biofeedback, etc. Immersive and interactive cognitive training based on virtual reality has been proved to have good effects, but no research has applied this training method to the elderly with depression. In terms of training dose, the research based on the healthy elderly shows that each training time is not less than 30 min, three times a week, and the total training time is more than 20 h, which can achieve more obvious training effect.

To sum up, combining the basis of previous work, screening cognitive training tasks suitable for the elderly with depression, developing electronic cognitive training tasks, and further verifying them in the clinic, with a view to making up for the defects of current clinical treatment, improving the prognosis and reducing the disease burden, which has great social significance.

2. The research team is supported by the preliminary research results directly related to the project

The applicant and the main members of the team have rich experience in the clinical diagnosis, treatment, and research of senile depression, have undertaken many clinical studies related to senile mental diseases, and have high scientific research ability. The members of the research team are reasonable, and there are experts in clinical, psychological, rehabilitation, testing, statistics, and other aspects. The above provides sufficient technical and personnel conditions to ensure the development of the research. The research team has long carried out research work related to cognitive rehabilitation

training. At present, a set of comprehensive training tools suitable for the elderly in China has been developed around various cognitive fields such as executive function, working memory, episodic memory, and continuous attention. It can formulate personalized cognitive training programs based on the cognitive evaluation results of the elderly and adjust the training programs in time according to the training results and follow-up evaluation, so as to achieve the effect of improving the cognitive function of the elderly. At present, this cognitive training system has been applied and popularized in many domestic institutions and communities. The preliminary results show that it can significantly improve the cognitive function of the elderly healthy population, MCI and early AD population. The research team has accumulated extensive experience in promoting aging research in China and the practice of dementia prevention and control in communities and hospitals.

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Task:

Task 1: optimization and electronation of cognitive training program for senile depression

Task 2: through an RCT study, verify the cognitive improvement effect of electronic cognitive assessment tools on elderly patients with cognitive impairment

Subject objective

1 Qualitative objective:

1) Optimize the cognitive training program of senile depression and form a set of electronic cognitive training technology.

2) To compare the improvement of cognitive function of elderly depressive patients with cognitive impairment treated with conventional SSRIs antidepressants combined with electronic cognitive training technology and single conventional SSRIs antidepressants.

2 Quantitative objectives:

1) 64 elderly depressive patients with cognitive impairment completed 52 weeks of SSRIs antidepressants combined with electronic cognitive training (once a day, 60min each time);

2) 64 elderly depressive patients with cognitive impairment were treated with SSRIs antidepressants Blank electronic training for 52 weeks (once a day, 60min each time);

3) To form a cognitive training process for elderly patients with depression, including training content, training duration, training guidance and other key contents.

Research design

1) Overall design scheme

This study is a prospective, randomized, controlled study. The screened qualified subjects were randomly divided into two groups. One group was the control group, receiving clinical routine SSRIs drug treatment combined with blank control method (that is, subjects were allowed to use electronic products to browse the web and watch the news for 1H every day), and the other group was the intervention group, receiving SSRIs drug treatment combined with electronic cognitive training. The whole study lasted 52 weeks.

At each visit, the scale evaluation (cognitive function, psychosocial function evaluation), the level of Alzheimer associated neurofilament protein (AD7C NTP) in urine and the concentration of antidepressants in blood were performed. The investigator quantitatively adjusted the patient's medication regimen (including dose and type) according to the evaluation results and adjusted the cognitive training regimen according to the evaluation results.

2) Drug therapy intervention

The subjects who met the screening criteria did not need cleaning and entered the study directly. Considering that the overall efficacy of various antidepressants is similar, and to maximize the simulation of the actual situation of clinical treatment, SSRIs treatment drugs are used in this study, including fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram and escitalopram. The specific types of drugs are not limited. During the study, the drug dose was quantitatively adjusted according to the results of each visit evaluation combined with the drug concentration.

The researcher will comprehensively evaluate the effectiveness of the treatment according to the above data results, and then make corresponding adjustments according to the treatment plan. If the score reduction rate of the Hamilton Rating Scale for depression (hrsd-17) is >50% and the drug concentration is within the recommended

range, the current treatment will be continued; 50% > hrds-17 score reduction rate > 30% or the drug concentration is lower than the minimum recommended concentration, the current treatment can be continued or the dose can be adjusted; If the score reduction rate of hrds-17 is less than 30% and the drug concentration is lower than the minimum value of the recommended concentration, the dosage should be adjusted. If the score reduction rate of hrds-17 is less than 30% and the drug concentration is higher than the minimum value of the recommended concentration, the dressing should be changed. If intolerable side effects occur, the dose can be reduced, or the dressing can be changed.

Design method of cognitive training program

Intervention implementation plan

The total duration of this intervention was 52 weeks, during which training tasks were carried out in weeks, and patients were arranged to carry out cognitive training in different fields. During the intervention period, patients need to complete a total of 52 weeks of training plan, including 4 training days per week (it is recommended to ensure the frequency of every other day). Each training day includes at least 3 different cognitive training. The duration of each training is about 60min, and the total duration of each month shall not be less than 16 hours.

Intervention scheme generation rules

The cognitive training program will push personalized cognitive training according to the performance of the subjects in the six areas of episodic memory, executive function, working memory, processing speed, speech ability and reasoning judgment. Patients need to be evaluated once a month and update the training program according to the evaluation performance.

The specific recommendation principles of the training program in the intervention group are as follows: the areas with poor cognitive performance (1.5 standard deviations lower than the average value of the norm) are recommended first, and more than one and no more than four times in each training cycle; Secondly, recommend areas with poor cognitive performance (1 standard deviation lower than the norm), and

no more than 2 times in each training cycle; In addition to the above fixed training, if the training content does not reach 16 items / week, cognitive training in other fields will be randomly pushed; Within each training day, only one cognitive rehabilitation training is arranged for each cognitive field; The difficulty of each cognitive rehabilitation training depends on the last training level of the subject.

Training scheme of the control group: to keep the same electronic use time as that of the intervention group, the subjects in the control group are required to open the electronic products for 60 minutes every day, 4 days a week.

Intervention mode

Tablet computer or mobile phone to be used in this intervention training. The training will take the principles of psychology and cognitive neuroscience as the core, and interactive games as the carrier, covering the cognitive training in six fields: episodic memory, executive function, working memory, processing speed, speech ability and reasoning judgment, to ensure the scientific on the premise of enhancing interest.

According to their own conditions, the subjects can choose to go to the hospital to use the tablet computer provided by the hospital for training within the reserved time or can use their own tablet computer or mobile phone for independent training. The training mode of this intervention is flexible. The subjects can start training on different terminal devices, and the training records can also be updated in real time. The research team will monitor the whole training process.

Research object

Inclusion criteria: 1. written informed consent signed by patients and their families; 2. Age ≥60 years; 3. Meet the diagnostic criteria for single or recurrent major depressive disorder in the diagnostic and Statistical Manual of mental disorders Fourth Edition (DSM-V); 4. Currently in the acute phase, the total score of hrds-17 at baseline is ≥ 18 points. 5.There were cognitive impairment symptoms, and the Montreal Cognitive Assessment Scale (MoCA) was < 26 points. 6/Education level above primary school.

Exclusion criteria: 1.patients with history of epilepsy or coronary heart disease or other serious unstable physical diseases; 2. Participated in another intervention clinical study in the past 1 month; 3. The following mental diseases have been or are currently diagnosed by DSM-V: organic mental disorder, Alzheimer's disease, secondary dementia caused by other causes, schizophrenia, schizophrenic affective disorder, bipolar disorder, delusional disorder, undefined mental disease, patients with drug abuse history, including alcohol and active drug abuse in the past 12 months, except nicotine; 4.He has been taking antidepressants, mental retardants and other psychiatric drugs for the past 2 weeks; 5. Severe aphasia, visual and hearing impairment, etc. unable to complete the scale evaluation; 6. Pregnant, lactating women or those planning to conceive.

The subject may withdraw from the study for any of the following reasons: the investigator considers that it is best for the subject to terminate the treatment due to safety factors (such as adverse events); The subjects were lost to follow-up; The subject withdrew informed consent. If a subject is lost to follow-up, the staff of the research center shall make every effort to contact the subject and determine the reason for his withdrawal. Follow up examinations must be recorded. When a subject withdraws before completing the study, the reason, date, and final evaluation of withdrawal shall be recorded in the CRF and original documents.

Symptomatic assessment

1) Hamilton Anxiety Rating Scale (HAMA): in the baseline period, at the end of the 2nd, 4th, 8th, 12th, 26th, 38th and 52nd weeks, the rater assessed the anxiety symptoms of the subjects.

2) The Hamilton Rating Scale for depression (hrsd-17): subjects were assessed for depressive symptoms at the end of the baseline period, 2 weekends, 4 weekends, 8 weekends, 12 weekends, 26 weekends, 38 weekends and 52 weekends.

3) The Geriatric Depression Scale (GDS): subjects were evaluated for depressive symptoms at the end of the baseline period, 2 weeks, 4 weeks, 8 weeks, 12 weeks, 26 weeks, 38 weeks, and 52 weeks.

4) Neuropsychiatric Inventory (NPI): subjects were assessed for cognitive function at the end of the baseline period, 2 weeks, 4 weeks, 8 weeks, 12 weeks, 26 weeks, 38 weeks, and 52 weeks.

5) Activities of daily living (ADL): the cognitive function of the subjects was assessed in the baseline period, 2 weekends, 4 weekends, 8 weekends, 12 weekends, 26 weekends, 38 weekends and 52 weekends.

Safety evaluation

1) Vital signs: the temperature, pulse and blood pressure of the subjects were monitored at the end of the baseline period, 2 weekends, 4 weekends, 8 weekends, 12 weekends, 26 weekends, 38 weekends and 52 weekends.

2) Adverse event report: adverse event records were made on the subjects at the end of the baseline period, the end of the 2nd week, the end of the 4th week, the end of the 8th week, the end of the 12th week, the end of the 26th week, the end of the 38th week and the end of the 52nd week.

3) Treatment Emergent Symptom Scale (TESS): during the baseline period, the subjects were evaluated for side effects at the end of 2 weeks, 4 weeks, 8 weeks, 12 weeks, 26 weeks, 38 weeks, and 52 weeks.

4) Laboratory examination and electrocardiogram: routine blood test, biochemical examination and electrocardiogram examination were conducted at the end of the

screening period, the end of the 4th week, the end of the 12th week, the end of the 38th week and the end of the 52nd week.

Efficacy index

1) Main efficacy indicators:

At the end of the 12th week after treatment, the change value of ADAS cog scale scores of the subjects in the two groups compared with the baseline.

2) Secondary efficacy indicators:

1.At each follow-up point, the change value of ADAS cog scale scores of the two groups compared with the baseline.

2.At each follow-up point, the change value of hrsd-17 score of the subjects in the two groups compared with the baseline;

3.At each follow-up point, the change value of HAMA scale scores of the two groups compared with the baseline.

4.At each follow-up point, the change value of GDS score of the subjects in the two groups compared with the baseline.

5.At each follow-up point, the change value of NPI scale scores of the subjects in the two groups compared with the baseline.

6. At each follow-up point, the change value of ADL scale scores of the subjects in the two groups compared with the baseline.

7. Complete remission rate: the difference in the proportion of patients with a total score of hrds-17 ≤ 7 at each visit point between the two groups.

8. Effective rate of treatment: the proportion difference between the two groups of subjects in the reduction rate of hrds-17 scale at each visit point and the baseline ≥ 50%.

9.Recurrence rate and recurrence time: recurrence is defined as any of the following conditions: the subject meets the DSM-IV diagnostic criteria for depressive episode; The subject was hospitalized again due to depression; After the treatment was effective (ham-d17 score decreased by ≥ 50% compared with the baseline), ham-d17 score increased by more than 30% compared with the baseline at any visit point; During the maintenance treatment period, after the treatment of the subjects is effective or remission, the proportion of relapse and the time of relapse between the two groups at each visit point;

Safety index:

i. Abnormal values of vital signs, laboratory examination and electrocardiogram examination during the study period.

II. Adverse events and adverse reaction reports during the study period.

Basis for determining sample size

According to the main research hypothesis of this study, the effect of comprehensive intervention group on improving patients' cognition is better than that of conventional treatment group. According to the previous similar research results and the expected efficacy hypothesis, the difference between the groups of the study group and the control group in terms of ADAS cog score reduction after 12 weeks of treatment is about 2.2, and the combined standard deviation is 4. Set α= 0.025 (one side), β= 0.20, and set the superiority and effectiveness limit value as 3 in combination with the

previous research and clinical significance, The ratio of the number of cases in the study group to the control group was 1:1. The sample size of the study group was 51 cases, and the sample size of the control group was 51 cases. Considering the 20% rejection rate of similar items, 64 cases need to be included in the study group and the control group.

Statistical analysis methods

Full Analysis Set (FAS): A collection of all randomized cases with valid baseline assessments. FAS is the main analysis set. Secondary efficacy measures were analyzed using only FAS without carry-over.

General principles: Statistical analysis was performed using SAS.9.4 statistical analysis software. P value < 0.05 was statistically significant (unless otherwise specified).

Statistical description: Measurement data are described using mean (standard deviation), median (interquartile range), minimum value, and maximum value; skewed distribution indicators are normally corrected before analysis, unless otherwise specified. Enumeration data were described using the number of cases (percentage).

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1) Efficacy analysis:

Primary Endpoint Analysis

The between-group difference in the change from baseline in the total score of the two groups of subjects (ADAS-cog) at the end of 12 weeks

Statistical analysis of changes from baseline in ADAS-cog total scores at the end of 12 weeks was performed using MMRM (mixed model for repeated measures). The model takes the change of ADAS-cog total score at each time point after treatment relative to the baseline as the dependent variable, the baseline ADAS-cog total score is a covariate, and the grouping is a fixed effect. Each fixed effect factor and covariate is nested in each visit. Inside. According to the model, the adjusted mean of the total ADAS-cog total score at the end of treatment in each group compared with the baseline, as well as the difference of the adjusted mean between the two groups and its 95% confidence interval, the lower limit of the confidence interval and the set optimal value were calculated. The comparison of the effect-media value was used as the criterion for superiority.

Secondary endpoint analysis:

Efficacy evaluation indicators include HRSD-17, HAMA, GDS, NPI, ADL and other scales. The differences between groups at the visit point relative to the baseline value were analyzed using the same analysis method as the main efficacy indicators. The cumulative complete remission rate, treatment response rate, recurrence rate and other outcome indicators during the study period were compared between groups using the Kaplan-Meier curve, and the COX proportional hazards model was used to evaluate the impact of the intervention while controlling for confounding factors such as disease duration.

Safety analysis: The incidence of adverse events and adverse reactions was tested by chi-square and described in a list.