Informed Consent Form

The Second Xiangya Hospital of Central South University

The Second People's Hospital of Dali Bai Autonomous Prefecture
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Clinical Research Informed Consent Form

Dear Participant/Volunteer,

Greetings!

We invite you to participate in a medical study titled " Effects of intermittent theta burst stimulation (iTBS) on appetite change and body weight in inpatients with schizophrenia in China: study protocol for a randomized controlled trial." The study is led by the Department of Psychiatry at Central South University Xiangya Second Hospital. Your participation in this study is entirely voluntary. To help you understand this research, this informed consent form will provide you with detailed information about the study's purpose and process and the possible risks and benefits of your participation. If you are interested, please read the following content carefully. The researchers and medical staff will answer any questions you may have. If all your questions are satisfactorily answered and you decide to participate, you may sign this consent form.

I. Study Background

Schizophrenia is a severe mental illness that significantly impacts an individual's health and social life. Its clinical manifestations are complex and diverse, including various types of psychotic symptoms. The core symptoms can be divided into positive symptoms (hallucinations, delusions, etc.), negative symptoms (reduced willpower, emotional blunting, social withdrawal), cognitive symptoms, and affective symptoms. Epidemiological studies suggest that individuals with schizophrenia have a life expectancy that is 15-30 years shorter than that of the general population, with approximately 60% of these deaths caused by cardiovascular diseases rather than central nervous system disorders. The prevalence of type 2 diabetes among schizophrenia patients is 10-15%, which is 2-3 times higher than that of the general population. Patients with severe mental illness are twice as likely to die from cardiovascular diseases compared to healthy individuals. Consequently, there is increasing attention among scholars on the physical health of mental illness patients, especially metabolic syndrome, cardiovascular diseases, and bone metabolism disorders.

Patients with schizophrenia often need to take antipsychotic medications long-term, but nearly all antipsychotic drugs lead to weight gain. Currently, there is a consensus in the academic community that the metabolic side effects of antipsychotic medications, such as weight gain and glucose-lipid metabolism disorders, need to be closely monitored. These metabolic side effects not only affect patients' medication adherence, increasing the risk of relapse, but also significantly raise the risk of comorbid diabetes, cardiovascular diseases, and cerebrovascular diseases, potentially shortening life expectancy. In recent years, the

prescription of antipsychotic drugs for children and adolescents has increased significantly, posing potential risks for their long-term health. Most studies indicate that Olanzapine, Clozapine, and Quetiapine have the most significant effects on glucose and lipid metabolism, while Aripiprazole and Ziprasidone have relatively more minor effects. In contrast, the CATIE study, tracking for 10 years, suggests that Olanzapine and Quetiapine significantly increase the risk of cardiovascular diseases, while Risperidone and Ziprasidone have a lesser impact.

The specific mechanism by which antipsychotic drugs cause metabolic syndrome is not yet clear. Some studies suggest that the weight gain induced by Olanzapine is primarily influenced by an increase in appetite and food intake in the early stages, possibly related to the drug's antagonistic effects on the serotonin H1 and 2C receptors. Moreover, antipsychotic drugs may inhibit insulin pathways and glucose metabolism in specific target cells, such as muscle cells, liver cells, and adipocytes, increasing insulin resistance independent of weight gain and increased food intake. This phenomenon occurs both in schizophrenia patients and in healthy individuals who take antipsychotic medications. At the same time, obesity caused by antipsychotic drugs also increases the levels of fatty acids and inflammatory factors, further exacerbating insulin resistance. Studies suggest that Olanzapine may directly damage pancreatic beta cells, leading to dysfunction or even apoptosis.

Previous research indicates that non-invasive brain stimulation activating the dorsolateral prefrontal cortex (DLPFC) can effectively suppress appetite and control food intake within a reasonable range, with certain therapeutic effects on bulimia and binge eating disorders. Most studies target the left DLPFC, as this region is believed to be associated with inhibitory control processes, thus affecting self-control in eating behavior. However, the results of related studies remain controversial, with most indicating that both single and repeated stimulation can alleviate appetite increase and eating disorders. Currently, there is no effective treatment for appetite increase caused by antipsychotic drugs. Transcranial magnetic stimulation (TMS) to activate specific brain regions is a promising and safe method for appetite control. Our research team aims to validate this hypothesis.

Transcranial magnetic stimulation is a non-invasive, cost-effective, and widely used physical therapy method. It uses electromagnetic induction to convert current in a coil into a magnetic field that stimulates neurons in the local cortex, leading to subtle electrical changes that affect brain metabolism and neural activity. Repetitive transcranial magnetic stimulation (rTMS) is a rhythmic and regular stimulation. Low-frequency stimulation (≤1Hz) inhibits cortical function, while high-frequency stimulation (>1Hz) increases cortical activity. Different patterns of rTMS can trigger various physiological and biochemical responses, influencing brain function and neural regulation. An 8-week high-frequency rTMS intervention has been shown to effectively improve cognitive performance in chronic schizophrenia patients. The iTBS stimulation pattern is a newer rTMS intervention model, which includes a 50Hz intrapulse stimulation frequency and a 5Hz burst stimulation frequency, with each burst lasting 2 seconds and an 8-second interval. It allows for more frequent stimulation sessions in a shorter period while maintaining long-lasting effects. Recent randomized clinical studies suggest that iTBS is more effective than other traditional stimulation methods, with no significant differences in side effects. Clinical studies have shown that iTBS targeting the dorsolateral prefrontal cortex can significantly alleviate the negative symptoms of chronic schizophrenia patients. fMRI results indicate enhanced functional connectivity between the left dorsolateral prefrontal cortex and the right occipital cortex, angular gyrus, and midbrain regions following iTBS stimulation. Thus, this experiment aims to use rTMS to intervene in

the appetite-related brain regions of schizophrenia patients on antipsychotic medication, modify cortical neuron excitability, and further investigate the efficacy of rTMS in preventing antipsychotic-induced appetite and weight gain. This intervention uses 90% subthreshold stimulation, which is safe and well-tolerated, with the most common side effect being mild headaches during the stimulation.

II. Research Process

2.1 Study Plan

About 60 participants will be enrolled in this study, which will be conducted at the Department of Psychiatry, Xiangya Second Hospital, Central South University and the Second People's Hospital of Dali Bai Autonomous Prefecture.

This study is a randomized, double-blind, placebo-controlled trial, enrolling 60 patients who have gained weight due to antipsychotic drugs. The participants will be randomly assigned to either the treatment group or the control group, with follow-up assessments at baseline, immediately after treatment, 2 weeks post-treatment, and 4 weeks post-treatment. The study will evaluate the effectiveness and safety of iTBS in improving appetite and weight gain induced by antipsychotic drugs by measuring changes in BMI, weight, brain structure and function related to appetite, cognitive control, glucose-lipid metabolism, and gut microbiota. Multimodal imaging and metabolomics will be used to develop a predictive model for iTBS efficacy in alleviating antipsychotic-induced appetite and weight gain.

III. Related Rights

Costs:

If you agree to participate in this study, the experimental equipment application and related laboratory tests (including rTMS treatment, blood sample collection, microbiome testing, liver function, kidney function, MRI, cognitive tests) will be provided free of charge by the Second Xiangya Hospital. If additional blood samples are collected during follow-up, participants will be compensated 100 yuan. A transportation fee of 50 yuan per visit will also be provided.

Possible Benefits:

The assessments and rTMS treatments performed in this study are free of charge. As a participant, you will receive professional follow-up assessments. If any abnormalities are discovered during the research, we will inform you and arrange for more detailed tests or treatment. The research team will also help schedule appointments with specialists at the hospital to facilitate your care. If hospitalization is required, we will assist with the arrangement. This study will not involve any other interventions or alter your current medication regimen. No additional transportation or meal subsidies will be provided.

IV. Potential Risks and Discomforts

By participating in this study, you may experience the following discomforts:

1. **Blood Collection Risks:** You might notice bruising or temporary pain at the site where blood was drawn. There is a slight risk of a local infection or dizziness.
2. **Repetitive Transcranial Magnetic Stimulation (rTMS) Risks:** During rTMS treatment, you may experience the following:
    1. **Physical Risks:** While undergoing TMS stimulation, you may feel twitches in your scalp or facial muscles, which could lead to discomfort or pain. After stimulation, you might experience mild headaches, tinnitus, or other sensations of discomfort. Rare side effects can include serious psychiatric changes or the triggering of seizures. Therefore, individuals with a history of epilepsy, sleep deprivation, intoxication, or extreme fatigue will be carefully assessed for the potential risks of rTMS. If you experience unbearable discomfort during the stimulation, we will stop immediately rTMS.
    2. **Electromagnetic Safety:** The TMS coil generates a magnetic field that attracts ferromagnetic materials while repelling non-ferromagnetic ones. Consequently, people with metal implants or electronic devices—for example, cochlear implants, pacemakers, and medical pumps—near the stimulation area are not eligible for rTMS. To prevent interference from the powerful magnetic field, all jewelry, including necklaces, earrings, glasses, and watches, should be removed prior to rTMS treatment.

V. Management of Related Issues during the Study

The research team will closely monitor each participant for any adverse effects during the study. However, not all potential side effects are known, and these may range from mild to severe. Your treating physician may prescribe medication to alleviate any adverse reactions, and all treatment-related side effects will be addressed with free medical care.

VI. Confidentiality of Information

In China, relevant legislation safeguards privacy, data protection, and controlled access. We will rigorously follow these legal standards when gathering and processing your research data to maintain your confidentiality. Your personal information, including your name, ID number, address, and phone number, will only be disclosed to the research team and not shared externally unless legally mandated. Blood and stool samples collected during this study will be managed in line with China's human genetic resource regulations. Any information shared with testing companies will be anonymized with a coding system to shield your identity. This coded data will be securely stored at the Department of Psychiatry in Second Xiangya Hospital. Your identity will remain confidential in all research outputs, whether presented at scientific conferences or published in journals. That said, your records may still be subjected to review by relevant authorities, including the ethical review committee at the National Clinical Research Center of Second Xiangya Hospital, as required by law.

VII. Withdrawal from the Study

Your participation in this study is completely voluntary. You have the right to refuse or withdraw from the study at any time, without needing to provide a reason, and you will not face any discrimination or retaliation. Your rights and medical treatment will remain unchanged. However, you must return any unused research medications and devices.
If you experience severe side effects, or if your doctor believes that it is not in your best interest to continue, you may be withdrawn from the study. In such instances, we will inform you immediately, and your study doctor will discuss alternative options with you. If the doctor believes that abruptly discontinuing the study may affect your health, you may be asked to visit the hospital for a check-up before your withdrawal. After you withdraw, no further data regarding you will be collected.
Regardless of the withdrawal reason, we will still attempt to gather effectiveness and safety data for participants who have withdrawn. The reason will be documented in your original medical records.

VIII. Related Inquiries

If you have any questions about this study, please contact Dr. Qin at 18670775091.

If you have any concerns regarding your rights or would like to express dissatisfaction or concerns about the process of participating in this study, please contact the Ethics Committee Office at 0731-85295391.

Participant's Statement and Signature:

I have thoroughly reviewed this informed consent form and had the chance to ask questions. The researchers have given clear explanations and answered my questions. I recognize that participating in this study is completely voluntary, and I can withdraw at any time without needing to explain, with no impact on my medical or legal rights. I permit the sponsor, researchers, and health monitoring authorities to access my medical records, and I am aware that reasonable precautions will be taken to safeguard my privacy. I consent to participate in this study and will receive a signed copy of this consent form.

Participant's Name (Printed):
Signature (Handwritten):
Date:
Contact Number:

Legal Guardian's Name (Printed):
Signature (Handwritten):
Date:
Contact Number:

Primary Investigator's Statement and Signature:

I and my research team have thoroughly explained the purpose, process, and possible risks and benefits of this clinical trial to the participant and answered all related questions.

Principal Investigator's Name (Printed):
Signature (Handwritten):
Date:
Contact Number:

Designated Contact Person's Name (Printed):
Signature (Handwritten):
Date:
Contact Number: