

A Randomized, Parallel-group, Placebo-controlled, Double-blind Clinical Trial to Evaluate the Efficacy and Safety of Ethosuximide in Chinese Patients with Treatment-Resistant Depression

Informed Consent Form

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Dear patients:

Welcome to participate in the study of the efficacy and safety of ethosuximide in patients with treatment-resistant depression. The study had been approved by the ethics committee of our hospital that approved research doctors to start it.

Before deciding to participate in this research, please read the following carefully which can help you understand the significance, procedure and duration of the research, and the potential benefits and risks of participating in the study. If you have some questions about the study, your doctor will answer them for you in time. You can also discuss with your relatives and friends to help you make decisions. It is up to you to decide whether or not to participate in this clinical trial on the basis of your understanding of this study.

Introduction

Depression is a major disease with the highest prevalence of mental disorders, characterized by a high rate of self-mutilation and suicide. Conventional antidepressants have slow onset and poor efficacy, and only approximately 70% of all patients with depression respond to these drugs therapies, the remaining 30% may be patients with treatment-resistant depression. In recent years, ketamine, as a new antidepressant, has been hailed as the largest discovery in the past half century because of its rapid antidepressant effect (rapid improvement of mood in a few hours) and its efficacy in patients with treatment-resistant depression. However, the potential addiction of ketamine limits its application in clinical antidepressant therapy.

Latest research elucidated the neurological mechanism of ketamine's rapid antidepressant effect, that was, ketamine blockaded the N-methyl-D-aspartate receptor (NMDAR) and low-voltage-sensitive calcium channel (T-VSCCs)-dependent cluster discharges in the lateral habenular nucleus located in the reward center, which led excessive inhibition of downstream monoamine reward brain regions, and ultimately caused rapid antidepressant effects. This series of studies provides a new idea for the rapid development of antidepressant drugs, that is, inhibiting T-VSCCs to achieve rapid antidepressant. This clinical trial drug is ethosuximide, that can produce rapid antidepressant effect by inhibiting T-VSCCs on lateral habenular nucleus neurons. The aim of this study is to evaluate the clinical efficacy and safety of ethosuximide in patients with treatment-resistant depression.

Research information

This study which will be conducted in the First Affiliated Hospital of Medical College of Zhejiang University is co-sponsored by Professor Yi Xu of the First Affiliated Hospital of Medical College of Zhejiang University and Professor Hailan Hu of Zhejiang University. About 40 patients with treatment-resistant will participate in this study, including 20 patients in the ethosuximide+escitalopram group and 20 patients in the placebo + escitalopram group. Escitalopram is currently the first-line antidepressant which ensure the effective treatment for all patients. The research will last six weeks, including nine research visits within screening. Considering the scientific, legal and ethical factors, this experiment preliminarily plans to enroll 40 subjects. If the number of subjects has reached the target but you are being screened, you may not be enrolled in the study.

You will be randomly assigned to the following two experimental groups according to the chronological sequence of participation in the study: 1 group: A+C, 2 group: B+C [A. Ethosuximide (capsule, 250mg/capsule); B. placebo (capsule, 250mg/capsule); C. Escitalopram (tablet, 10mg/pill). Usage and dosage: Drug A, 2 times/day, take it orally after breakfast/dinner; take 500mg in the morning and 500mg in the evening on day1, 500mg in the morning and 750mg in the evening on day2, 750mg in the morning and 750mg in the evening on day3, 750mg in the morning and 1000mg in the evening on day4, 1000mg in the morning and 1000mg in the evening on day5, maintain this dose until the end of treatment for 2 weeks. The usage and dosage of Drug B are the same as above. Drug C, 1 time/day, 10mg/day, take it orally after breakfast, take it for 4 weeks without interruption. If you had taken escitalopram or was allergic to escitalopram in the past, the researchers would choose another appropriate antidepressant according to your condition. Medication cycle: The study drugs will be taken for 6 weeks.

Research process

Before participating in this study, you must sign the informed consent. You will go through three stages in the study, including screening/cleaning, baseline and treatment phases.

- Screening/cleaning period: Visit will be conducted on day -6 to 0 with the screening period ranging from 3 to 7 days. General data collection, scale evaluation and laboratory examination need to be completed.

- Baseline period: The first visit will be conducted on day 1. The research doctor will review the data of your laboratory examination and test your scores by the relevant scales again to further confirm your condition. If you pass all screening procedures, researchers will randomly assign you to either ethosuximide or placebo group.

- Treatment period: You will be treated with ethambutamine or placebo for 2 weeks and escitalopram for 4 weeks (If you had taken escitalopram or was allergic to escitalopram in the past, the researchers would choose another appropriate antidepressant according to your condition.). Ten follow-up evaluations including scale score, laboratory examination, vital signs and adverse events will be carried out on day 1, day 2, day 3, day 4, day 6, day 10, week 2, week 3, week 4 and week 6 after medication.

Matters needing attention

In order to get the right information about the efficacy of ethambutamine for depression, you will be expected to do the following.

1. You need to work with your doctor to complete all scheduled research visits and procedures.
2. No combinations of psychotropic drugs such as antipsychotics, antidepressants, mood stabilizers, antianxiety drugs, central stimulants and other psychotropic drugs are allowed to be taken during the study period.
3. Chinese medicines with antidepressant effects specified in the instructions are not allowed to be taken during the study period.
4. Zolpidem, zopiclone, right zopiclone and zaleplone are allowed to be taken for insomnia before bed during the study. But the dosages of these drugs should not exceed the upper limits specified in the instructions, and the cumulative use time of the study period after randomization should not exceed one week.
5. The drugs for the original somatic diseases are allowed to continue to be taken, and the types and doses of drugs should be kept unchanged as far as possible during the study period.
6. No combinations of treatments such as modified electroconvulsive therapy (MECT), transcranial magnetic stimulation (TMS), vagal nerve stimulation (VNS), light therapy, laser therapy, acupuncture and moxibustion, and biofeedback therapy are allowed during the study period.
7. Systematic psychotherapy is not allowed during the study period.
8. If you intend to stop participating in the research, you should inform the researchers and make the final visit to the center as far as possible.

Risk and discomfort

During the first two weeks of the first phase of treatment, you may experience various types of adverse reactions.

Common adverse reactions: symptoms of digestive system: loss of appetite, hiccup, nausea, vomiting, stomach discomfort, abdominal pain, etc. Symptoms of nervous system: headache, dizziness, lethargy, ataxia, fatigue, etc. Functional lesion of liver and kidney functional lesion.

Rare adverse reactions: diseases of skin and subcutaneous tissue: urticaria, lupus erythematosus-like allergic reaction; Hematological abnormalities: leukopenia, granulocytopenia, thrombocytopenic purpura, aplastic anemia, etc.

During the last four weeks of the second phase of treatment, you may experience various types of adverse reactions.

Common adverse reactions: symptoms of nervous system: insomnia, drowsiness, dizziness, sensory abnormality, tremor; symptoms of digestive system: diarrhea, constipation, dry mouth, vomiting; psychiatric disorders: anxiety, disturbance, abnormal dreams, loss of interest; diseases of skin and subcutaneous tissue: increased sweating; diseases of musculoskeletal and foot tissue: arthralgia, myalgia; reproductive system diseases: sexual dysfunction; systemic disorders: Fatigue and

fever.

Rare adverse reactions: weight loss, agitation, panic attacks, sleep disorders, syncope, visual impairment, tachycardia, gastrointestinal bleeding, etc.

The research doctor will monitor the side effects of drugs on you. If you have any side effects, you should tell the research doctor immediately and the doctor will treat side effects for you. If you or your doctor think you can't tolerate side effects, you should stop taking research drugs and withdraw from the study for your health.

Because of the characteristics of depression, suicidal ideation or even suicidal behavior may occur in the course of the disease due to fluctuation of the condition whether or not patients with depression participate in this study. In this study, patients who have a history of attempted suicide, or currently have a high risk of suicide, or have committed or attempted suicide will definitely not be enrolled. Researchers will focus on assessment of suicide-related risk during each visit, but during the interval of the visit, guardians need to strengthen care for patients to prevent suicide-related accidents.

During the study period, if you have any other health problems or feel any discomfort, please inform the research doctor or other researchers immediately, whether or not you think these problems are related to the research drugs.

Benefit

The research results will be beneficial to the development of medical science and will be helpful to other patients who will suffer from the same disease in the future. During the study, you will get more systematic clinical assessment, more comprehensive clinical safety monitoring, more convenient medical consultation channels and more timely treatment and side effects treatment, so as to facilitate the rehabilitation of the disease.

Cost

During the study period, patients need to pay for routine medical expenses, examination fees and costs for escitalopram in the second phase by themselves. However, the cost of scale assessment of clinical symptoms, the cost of research doctor's work and the cost of medication for ethosuximide and placebo in the first phase will be waived for patients.

Privacy protection

In the course of this study, we will collect your personal health information from your original medical records and all the data obtained from participating in this study.

Your personal health information will be applied for clinical research, research reports or scientific presentations without identifying your name. And the information will be kept confidential unless it need to comply with laws and regulations.

In order to complete the research, the sponsor and/or the person or company cooperating with the sponsor, the research doctors and the staffs of the research center,

the ethics committee and the regulator responsible for overseeing research have the right to access your coded health information.

You have the right to request your personal data owned by any research physician or sponsor, and you also have the right to correct any inaccuracies in your personal data. If you wish to make a request, please contact the physician in charge of research, who can help you contact the sponsor if necessary.

If you revoke your authorization, the research physician will no longer use research data about you and/or share the data with others. However, the information you have shared with the applicant company before revoking the authorization may still be applied by the sponsor.

You will certify that you authorize the sponsor to apply the research data described in this informed consent by signing this informed consent.

The results of this study may be published in medical journals/conferences, but your identity will not be disclosed.

Voluntary participation/withdrawal

It is up to you to decide whether or not to participate in the study. If you decide to participate, you need to sign this informed consent, and you have the right to withdraw at any phase of the study. If you decide not to participate in or withdraw from this study, the quality of your medical care or any benefits you are entitled to receive will not be affected and you will not be punished in any way. Similarly, your doctor may withdraw you from this study based on the judgment that it is not in your best interest to continue this study. In addition, the sponsor of the study may propose to suspend or terminate the study based on adverse drug reactions, or terminate the study for administrative reasons unrelated to the purpose of the study.

When you withdraw from this study for any reason, you will be asked to return to the Research Centre for final assessment by the research doctor from your safety point of view, which may include physical examination and/or laboratory examination.

Others

If you have any questions about this study, or you think you have suffered research-related injuries or reacted to research drugs, or you have any concerns about participating in this study, please contact the research doctor with the phone number listed on the last page of the informed consent form.

If you have doubts about your rights as a research subject, or you can't solve your concerns through a research doctor or other researchers, or you have complaints, or you have questions about what clinical research means, and so on, you can call:

Contact of ethics committee, Name: _____ , Phone number: _____.
Address: _____.

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Signature Page

I have read and understood the content of the informed consent. My questions have been answered satisfactorily. I volunteered to participate in this study and I knew that I would receive a letter of consent signed by name and date. After signing this consent, it does not mean that I give up any legal rights. I understand that I can withdraw from the study at any time.

By signing this informed consent, I agreed to participate in a multi-center, randomized, double-blind, placebo-controlled, two-stage clinical study on the efficacy and safety of ethosuximide in patients with treatment-resistant depression. I agree that my information and data in this research will be applied. I know that my personal information will be protected and I am willing to cooperate with researchers to complete the research task.

Subject name: _____ Subject contact number: _____

Subject signature : _____ Date: _____