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

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Introduction

Depression is one of the most serious mental diseases, bringing great burden to society and families.Currently, antidepressant drugs commonly used in clinic mainly are tricyclic and monoamine substance reuptake inhibitors discovered in the 1950s and 1960s, which are classic monoamine strategy drugs. They improve depressive symptoms by increasing the concentration of monoamine transmitter in the brain, but their onset time is slow and efficacy is low. These drugs are only effective for about 60 - 70% of patients with depression, while the remaining 30% may be patients with treatment-resistant depression[1]. In addition, the onset time is delayed and often takes weeks and months to begin. Some even cause side effects of drugs (such as anxiety) before taking effect, aggravating the suicidal tendency of depressive patients. 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 over 70% of patients with refractory depression[2]. However, ketamine is classified as a psychotropic drug due to its potential addiction, which limits its application in clinical anti-depression treatment.

Hu Hailan's research group applied a variety of research tools of neuroscience, such as behavioral pharmacology, electrophysiology and photogenetics, to elucidate 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.

At the same time, animal experiments had also confirmed that cluster discharges in the lateral habenular nucleus mediated the occurrence of depression, and the cluster discharges were dependent on NMDA receptors and T-VSCC. In vitro brain slice，electrophysiological studies showed that Mibefradil (10um), a T-VSCCs inhibitor, could significantly inhibit the spontaneous cluster discharges of lateral habenular nucleus neurons and cluster discharges induced by hyperpolarization. Meanwhile, Mibefradil (10 nmol, 1 μl, each side) was injected bilaterally into the lateral habenular nucleus to inhibit T-VSCCs-mediated cluster discharges in neurons, sufficiently producing antidepressant effects[3,4,5].This series of studies provides a new idea for the rapid development of antidepressant drugs, that is, inhibiting T-VSCCs to achieve rapid antidepressant.

Ethosuximide is a T-VSCCs inhibitor. The IC50 of T-VSCCs current suppression is 0.3-1 mM, and the IC50 of sodium channel current suppression on squid axon is 60 mM. Therefore, it has higher selectivity to T-VSCCs. Ethosuximide can enter cerebrospinal fluid through the blood-brain barrier, inhibit T-VSCCs on the lateral habenular nucleus neurons, and then inhibit the cluster discharge of neurons, resulting in a rapid antidepressant effect.

The antidepressant effect of ethosuximide has been confirmed in animal experiments.It showed significant antidepressant effects in chronic restraint stress(CRS)-induced depression mice, acute congenitally learned helpless(cLH) rats and epileptic seizures model animals with depressive symptoms(WAG/Rij rats).In the CRS-induced depression mice model, the behavioral despair phenotype of the depression mice was significantly improved after a single intraperitoneal injection of ethosuximide (200 mg/kg) for 1 hour, which showed that the immobility time in forced swimming was significantly reduced[3]. Meanwhile, the pleasure-deficiency behavior of mice was also significantly improved, showing a significant increase in preference for sugar[3]. In learned helpless congenital depression rats, the immobility time of congenital depression rats in forced swimming was significantly reduced after a single intraperitoneal injection of ethosuximide (200 mg/kg) for 1 hour (unpublished data). In the model animals of epilepsy seizures with depressive symptoms (WAG/Rij

rats), 300 mg/kg ethosuximide was given daily through drinking water for 17 consecutive days at the age of 5 months with obvious epileptic seizures, which resulted in significant antidepressant effect (the immobility time of forced swimming was significantly reduced)[6].

In conclusion, ethosuximide can inhibit the T-VSCCs on the lateral habenular nucleus neurons and then inhibit the cluster discharges of neurons, resulting in a rapid antidepressant effect. The purpose of this study was to explore the antidepressant efficacy of ethosuximide tablets in patients with refractory depressive disorders, to preliminarily evaluate the clinical efficacy and safety, and to explore the possible mechanism of its antidepressant effect.

Reference

1.   Sackeim, H.A., *The definition and meaning of treatment-resistant depression.* J Clin Psychiatry, 2001. 62 Suppl 16: p. 10-7.

2.   Berman, R.M., et al., *Antidepressant effects of ketamine in depressed patients.* Biol Psychiatry, 2000. 47(4): p. 351-4.

3.   Yang, Y., et al., *Ketamine blocks bursting in the lateral habenula to rapidly relieve depression.* Nature, 2018. 554(7692): p. 317-322.

4.   Cui, Y., et al., *Astroglial Kir4.1 in the lateral habenula drives neuronal bursts in depression.* Nature, 2018. 554(7692): p. 323-327.

5.   Cui, Y., et al., *Lateral Habenular Burst Firing as a Target of the Rapid Antidepressant Effects of Ketamine.* Trends in Neurosciences, 2019. 42(3): p. 179-191.

6.   Sarkisova, K.Y., et al., *Spike-wave discharges are necessary for the expression of behavioral depression-like symptoms.* Epilepsia, 2010. 51(1): p. 146-60.

Research Purpose

To evaluate the clinical efficacy and safety of ethosuximide in patients with treatment-resistant depression, and to explore its underlying mechanism.

Research Contents

Subject selection criteria

Diagnostic criteria

Diagnosis of major depressive disorder(single or recurrent episodes) is made according to The fifth Edition of Diagnostic and Statistical Manual of Mental Disorders(DSM-V)criteria. All patients with previous or current episodes are ineffective after treatment with two different recommended doses of antidepressants for a full course of treatment (maximum treatment dose of at least 6 weeks).

Inclusion criteria

1.　Inpatient of both sexes are aged from 18 to 65 years;

2.　Diagnosis of major depressive disorder(single or recurrent episodes) is made according to DSM-V criteria;

3.　Subjects with previous or current depressive episodes did not response to two different antidepressants with recommended doses and adequate duration (maximum treatment dose of at least 6 weeks);

4.　The subjects who will score more than or equal to 22 points on the MADRS scale at screening and baseline period;

5.　The subjects who will score more than or equal to 3 points on the first clause of MADRS scale at screening and baseline period;

6.　Subjects who will sign written informed consent and volunteer to participate in the clinical study.

Exclusion criteria

1.　Diagnoses of other mental disorders (such as organic mental disorders, schizophrenia, bipolar and related disorders, anxiety disorders, obsessive-compulsive disorders and so on) are made according to DSM-V criteria;

2.　Depressive episodes, such as depression caused by hypothyroidism, secondary to a systemic disease or an organic mental disorder caused by a neurological disease;

3.   Subjects with a history of attempted suicide, or currently at high suicide risk, or with suicide behavior/attempt, or scoring more than or equal to 3 points on the 10th clause of MADRS scale;

4.   Subject whose score of MADRS scale in baseline period will be 25% lower than that in screening period;

5.   Subjects with a history of severe or poorly controlled cardiovascular, liver, kidney, blood, endocrine, respiratory diseases, etc;

6.   Subjects with a history of epileptic seizures, except for a single febrile convulsion in children;

7.   Researchers believe that the results of subjects' physical and laboratory examinations are clinically significant abnormalities in screening or baseline period. The following indicators exceed the following criteria: 1)ALT or AST levels are 1.5 times higher than the upper limit of laboratory normal values. 2)Thyroid Function are 1.1 times higher than the upper or lower limit of normal values. 3) Serum creatinine values are 1.1 times higher than the upper limit of normal values. 4)The levels of blood urea nitrogen are higher than the upper limit of normal values;

8.   The result of electrocardiogram (ECG) is abnormal in screening or baseline period, such as male subjects with QTc interval (> 450 ms) and female subjects with QTc interval (> 470 ms) , and the researchers thought it is not suitable for selection;

9.   Subjects could not swallow oral medicines or have a history of gastrointestinal surgery or any other diseases that may interfere with drug absorption, distribution, metabolism or excretion;

10.   Monoamine oxidase inhibitors (MAOIs) are taken by subjects now or within 2 weeks before screening. Subjects who took antipsychotics, antidepressants or mood stabilizers before randomization and these drugs' cleaning phase had less than five half-lives. Subjects who took fluoxetine within 1 month before screening. Subjects who continue to take Chinese medicines with antidepressant effects specified in the instructions after signing informed consent.

11. Subjects who received modified electroconvulsive therapy (MECT) , transcranial magnetic stimulation (TMS), vagal nerve stimulation (VNS), or systematic psychotherapy within 3 months before screening;

12. Subjects with a history of allergies to two or more foods or drugs;

13. Subjects who addicted to alcohol or substances within 6 months before screening;

14. Prenatal, lactating, or reproductive women who had positive results of HCG tests before participating in the study; Male and female subjects will not take effective contraceptive measures or plan to be pregnant within 3 months after the study;

15. Subjects who participated in clinical research within 30 days before signing the informed consent form for this study;

16. According to the judgement of the researchers, other situations are not suitable for clinical research.

Withdrawal criteria

Subjects withdrawing from the study: subjects who quit voluntarily and who need to withdraw after medical assessment of researchers.

1. Subjects who break off informed consents at any time;

2. Subjects who are lost to follow-up;

3. Severe adverse events, or intolerable adverse events happen, and are identified by the researchers that subjects need to quit;

4. Subjects who violate the protocol severely that affect the assessment of safety and efficacy of the research definitely;

5. Subjects who get psychiatric symptoms, mania, suicidal or self-injurious behaviors during the study;

6. Subjects who are pregnant during the study;

7. Subjects need to withdraw from the study in other situations after assessment of researchers.

Suspension criteria

Research suspension means that clinical research has not been completed according to the plan, and has been stopped halfway. The main purpose of research suspension is to protect the rights and interests of subjects, ensure the quality of research and avoid unnecessary economic losses.

1. If serious security problems happen, the study will be stopped in time.

2. If we find the drugs have no clinical value, the study will be discontinued to avoid delaying treatment of the subjects and unnecessarily economic losses.

3. If we find that the clinical study has major errors which make us difficult to evaluate drug effects, or a well-designed study, which has significant deviations in the implementation process, is difficult to evaluate drug effects for us, it will be discontinued.

Prohibited drug and prohibited treatment

Prohibited drug:

1. Antipsychotics, antidepressants, mood stabilizers, antianxiety drugs, central stimulants and any other psychotropic drugs (except those permitted for combination);

2. Chinese medicines with antidepressant effects specified in the instructions.

Prohibited treatment:

1. Antipsychotics, antidepressants, mood stabilizers, antianxiety drugs, central stimulants and any other psychotropic drugs (except those permitted for combination).

2. Chinese medicines with antidepressant effects specified in the instructions.

Combined medication and treatment

1. In the study, zolpidem, zopiclone, Eszopiclone and zaleplone are allowed to be combined for the treatment of insomnia and taken before retiring. The dosage should not exceed the upper limit specified in the instructions, and the cumulative use time of the study period after randomization should not exceed one week.

2. Drugs for the treatment of original somatic diseases are permitted to take. But the types and doses of drugs should be kept as constant as possible in the study.

Research protocol

Research medication

1. Ethosuximide, Drug specification: 250mg/capsule, Pfizer Inc.

2. Escitalopram, Drug specification: 10mg/pill, Xian Janssen Pharmaceutical Ltd.

Number of subjects

The subjects are divided into two groups, 20 in each group.

Methods of drug administration

Subjects with treatment-resistant depression who meet the inclusion criteria and do not meet the exclusion criteria are randomly assigned to the following two study groups:

Group 1: A (2 weeks) + C (4 weeks)

Group 2: B (2 weeks) + C (4 weeks)

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.

The time of the first administration should be after the next day's breakfast randomly. If the patient had taken escitalopram or was allergic to escitalopram in the past, the researchers would choose another appropriate antidepressant according to the patient's condition. Medication cycle: The study drugs will be taken for 6 weeks.

Random double-blind method

Random method

Random tables and random codes are generated by SAS software. Each subject would get a unique random code according to the random tables, and every random code corresponds to the corresponding study group and drug number. Each participant has the same opportunity to be assigned to the study or the control group.(the ratio of the number of cases between the study group and the control group is 1:1)

Double-blind method

It is a double-blind and double-simulation study. All subjects, researchers and evaluators are blind to grouping information in the course of the clinical study. The results of the study are audited by blind state data. The placebos are administered in capsules with no difference in appearance, color, weight or odor from the positive drugs. Both subjects and drugs are coded blindly.

In the study, the coding system for research drugs have an emergency blindness detection procedure, so as to quickly identify the drugs in emergency medical condition, without destroying the blind design of clinical research.

Research visit

Participants must read and sign the informed consents that are approved by the Ethics Committee(EC) before starting the study. Checks and research procedures are carried out according to the research flow chat.

Screening/Cleaning Period (Day-6 - 0) - Visit 0

Visit will be conducted on day -6 to 0 (at least day -2 to 0) with the screening period ranging from 3 to 7 days. It will need to be re-screened if screening dates are more than 7 days from the date of administration. If antipsychotics, antidepressants and mood stabilizers were used before randomization, the cleaning time of these drugs should be more than 5 half-lives. Contents of visit:

1. Sign informed consents;
2. Collect demographic data: name, sex, birth date, nationality, height etc;
3. Inquiry about previous history;
4. Vital signs: at least including blood pressure (sitting position), heart rate,

respiratory rate, body temperature and weight;

5. Physical examination: at least including head face, skin system, lymph node, eye, ear, nose, throat, mouth, respiratory system, abdomen, cardiovascular system, musculoskeletal system and nervous system;

6. Diagnosis of major depressive disorder(single or recurrent episodes) is made according to DSM-V criteria;

7. Subjects with previous or current depressive episodes do not response to two different antidepressants with recommended doses and adequate duration (maximum treatment dose of at least 6 weeks);

8. Scale score: MADRS;

9. Laboratory tests:

complete blood count: hemoglobin (HGB), red blood cell count (RBC), white blood cell count (WBC), neutrophil count (NEUT), lymphocyte count (LY), platelet count (PLT);

routine urine: PH, white blood cells, erythrocyte (ERY), nitrite (NIT), protein, glucose (GLU), ketone body (KET), urinary cholanogen (UBG), bilirubin;

blood biochemical examination: aspartate aminotransferase (AST), glutamate aminotransferase, alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), lactate dehydrogenase (LD), total protein, albumin (ALB), urea nitrogen (BUN), creatinine, creatine kinase (CK), total bilirubin (TBIL), direct bilirubin (DBIL), uric acid, blood sugar (Glu), triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL) ,low density lipoprotein (LDL), sodium (Na), potassium (K), chlorine, phosphorus (P), calcium (Ca), prolactin (PRL);

pregnancy test: detection of HCG in blood or urine of women with childbearing age;

thyroid function examination: FT3, FT4, TT3, TT4, TSH;

10. ECG: 12 leads cardiogram;

11. Inclusion and exclusion criteria;

12. Records of combined medication.

Baseline period (day 1) - Visit 1

The baseline period is day1.

Contents of visit:

1. Inclusion and exclusion criteria;

2. Diagnosis of major depressive disorder(single or recurrent episodes) is made according to DSM-V criteria;

3. Subjects with previous or current depressive episodes do not response to two different antidepressants with recommended doses and adequate duration (maximum treatment dose of at least 6 weeks);

4. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

5. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

6. Physical examination: including head face, skin system, lymph node, eye, ear, nose, throat, mouth, respiratory system, abdomen, cardiovascular system, musculoskeletal system and nervous system;

7. Records of adverse events;

8. Records of combined medication;

9. Randomization;

10. Drugs dispensing.

Treatment Period (Day 2) - Visit 2

Visit will be conducted on day2 after randomization(24 hours after taking medicine).

Contents of visit:

1. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

2. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

3. Records of adverse event;

4. Records of combined medication;

5. Drugs recovery and dispensing.

Treatment Period (Day 3) - Visit 3

Visit will be conducted on day3 after randomization(48 hours after taking medicine).

Contents of visit:

1. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

2. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

3. Records of adverse event;

4. Records of combined medication;

5. Drugs recovery and dispensing.

Treatment Period (Day 4) - Visit 4

Visit will be conducted on day4 after randomization(72 hours after taking medicine).

Contents of visit:

1. Laboratory tests: blood concentration of ethambutamine;

2. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

3. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

4. Records of adverse events;

5. Records of combined medication;

6. Drug recovery and dispensing;

Treatment Period (Day 6) - Visit 5

Visit will be conducted on day6 after randomization.

Contents of visit:

1. Laboratory tests: blood concentration of ethambutamine;

2. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

3. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

4. Records of adverse events;

5. Records of combined medication;

6. Drugs recovery and dispensing.

Treatment Period (Day 10) - Visit 6

Visit will be conducted on day10 after randomization.

Contents of visit:

1. Laboratory tests: blood concentration of ethambutamine;

2. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

3. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

4. Records of adverse events;

5. Records of combined medication;

6. Drugs recovery and dispensing.

Treatment Period (Day 14) - Visit 7

Visit will be conducted on day14 after randomization.

Contents of visit:

1. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

2. Laboratory tests:

blood concentration of ethambutamine.

complete blood count: hemoglobin (HGB), red blood cell count (RBC), white blood cell count (WBC), neutrophil count (NEUT), lymphocyte count (LY), platelet count (PLT);

routine urine: PH, white blood cells, erythrocyte (ERY), nitrite (NIT), protein, glucose (GLU), ketone body (KET), urinary cholanogen (UBG), bilirubin;

blood biochemical examination: aspartate aminotransferase (AST), glutamate aminotransferase, alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), lactate dehydrogenase (LD), total protein, albumin (ALB), urea nitrogen (BUN), creatinine, creatine kinase (CK), total bilirubin (TBIL), direct bilirubin (DBIL), uric acid, blood sugar (Glu), triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL) ,low density lipoprotein (LDL), sodium (Na), potassium (K), chlorine, phosphorus (P), calcium (Ca), prolactin (PRL);

3. ECG: 12 leads cardiogram;

4. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

5. Records of adverse events;

6. Records of combined medication;

7. Drugs recovery and dispensing;

Treatment Period (Day 22±1) - Visit 8

Visit will be conducted on day22±1 after randomization.

Contents of visit:

1. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

2. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

3. Records of adverse events;

4. Records of combined medication;

5. Drugs recovery and dispensing.

Treatment Period (Day 29±1) - Visit 9

Visit will be conducted on day29±1 after randomization.

Contents of visit:

1. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

2. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

3. Records of adverse events;

4. Records of combined medication;

5. Drugs recovery and dispensing.

Treatment Period (Day 42±1) - Visit 10

Visit will be conducted on day42±1 after randomization.

Contents of visit:

1. Scale score: MADRS、QIDS-SR、HAMA、YMRS;

2. Laboratory tests:

   blood concentration of ethambutamine.

complete blood count: hemoglobin (HGB), red blood cell count (RBC), white blood cell count (WBC), neutrophil count (NEUT), lymphocyte count (LY), platelet count (PLT);

routine urine: PH, white blood cells, erythrocyte (ERY), nitrite (NIT), protein, glucose (GLU), ketone body (KET), urinary cholanogen (UBG), bilirubin;

blood biochemical examination: aspartate aminotransferase (AST), glutamate aminotransferase, alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), lactate dehydrogenase (LD), total protein, albumin (ALB), urea nitrogen (BUN), creatinine, creatine kinase (CK), total bilirubin (TBIL), direct bilirubin (DBIL), uric acid, blood sugar (Glu), triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL) ,low density lipoprotein (LDL), sodium (Na), potassium (K), chlorine, phosphorus (P), calcium (Ca), prolactin (PRL);

3. ECG: 12 leads cardiogram;

4. Vital signs: including blood pressure (sitting position), heart rate, respiratory rate, body temperature and weight;

5. Records of adverse events;

6. Records of combined medication.

Observation measures

Validity Index

Main efficacy measures

Changes of MADRS score at therapeutic visit point compare with baseline.

Secondary efficacy measures

1. Changes of QIDS-SR score at therapeutic visit point compare with baseline.

2. Changes of HAMA score at therapeutic visit point compare with baseline.

3. Changes of individual score of MADRS at therapeutic visit point compare with baseline.

4. Changes of YMRS score at therapeutic visit point compare with baseline.

5. Efficacy after 2 and 4 weeks of treatment.(Efficacy means that the score of MADRS decreasing by more than or equal to 50% compares with its baseline score)

6. Remission rate after 2 and 4 weeks of treatment.(Remission means that the total score of MADRS is less than 10.)

Safety Index

1. Adverse events;

2. Vital signs;

3. Physical examination;

4. Laboratory tests(Including complete blood count, routine urine, blood biochemical examination, prolactin);

5. ECG: 12 leads cardiogram;

6. Scale evaluation(SAFTEE).

Flow chart of experiment
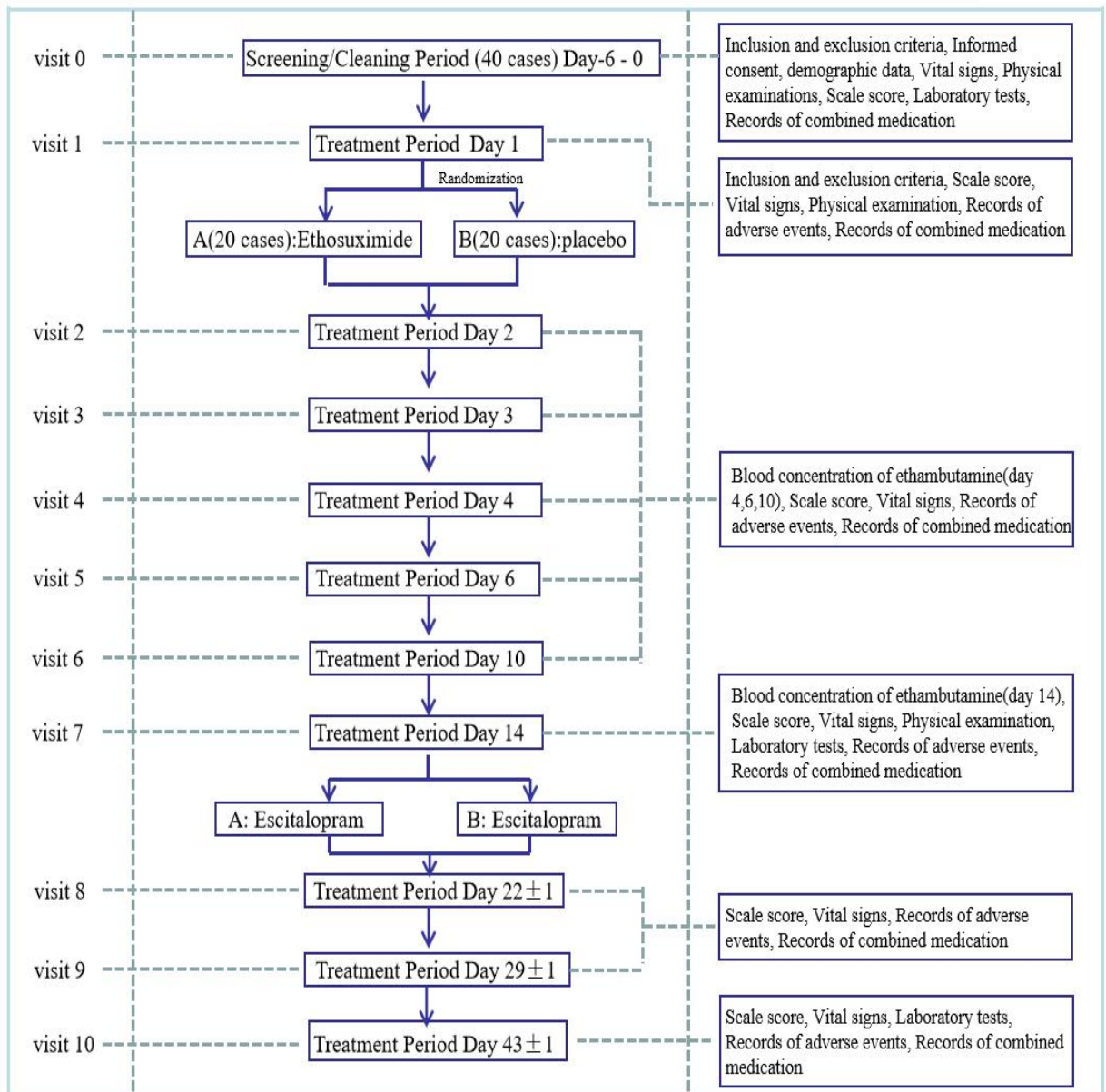
Dealing with Adverse Event

In the study, doctors will monitor the side effects of drugs. If subjects have side effects, the doctor will treat them accordingly. If the subjects could not tolerate side effects, they will be stopped to take research drugs and withdraw from the study.