

# BMJ Open Effect of esketamine on perioperative depressive symptoms in major surgery patients (PASSION II): study protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** Depressive symptoms are common for patients undergoing major surgery and may worsen their mental health and lead to poor clinical outcomes. It is essential to seek a safe rapid-acting treatment for relieving moderate-to-severe depressive symptoms in patients undergoing major surgery.

**Methods and analysis** This study is a randomised, placebo-controlled and double-blinded trial aiming to determine the effect of esketamine on moderate-to-severe depressive symptoms in patients undergoing major surgery. Five hundred and sixty-four participants, aged 18–65 years old, undergoing major surgery will be randomly allocated into the esketamine and placebo groups at a 1:1 ratio. Esketamine or placebo will be given intravenously at the same speed on suturing the incision by anaesthesiologists in charge who are blinded to the randomisation. In the esketamine group, the total dosage of esketamine will be 0.2 mg/kg body weight. To estimate the efficacy and safety endpoints, blinded evaluation by trained researchers will be completed at 3 days, 5 days, 1 month, 3 months and 6 months after surgery. The primary outcome is the remission rate at the third postoperative day. The secondary outcomes include depression-related scores, severe pain events and safety-related endpoints such as psychotic symptoms, manic symptoms and dissociative symptoms.

**Ethics and dissemination** This study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China on 30 October 2020 (KY-2020-058-02). This trial is designed to explore whether the administration of esketamine could improve the mental health of patients with depressive symptoms undergoing major surgery. The conclusions of this study will be published in peer-reviewed journals.

**Trial registration number** NCT04425473.

## INTRODUCTION

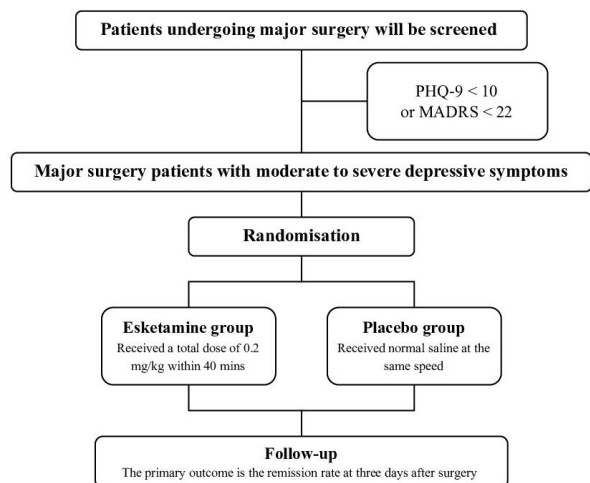
Depression is a common mental disorder that has been the primary risk of disability and is an important risk factor associated with a high burden of disease; it is estimated that more than 300 million people suffer worldwide.<sup>1 2</sup> Patients undergoing major surgery may have depressive symptoms induced by

## Strengths and limitations of this study

- This study is a double-blinded, randomised, placebo-controlled study that focuses on depressive symptoms in major surgery patients.
- This study will target a pragmatic endpoint, and the conclusion may provide high-quality evidence for clinical practice.
- This study compares esketamine and placebo, and further studies could evaluate the difference between esketamine and ketamine or other antidepressants.

stress reactions, which could affect mental health in the surgery population. Depressive symptoms are characterised by loss of interest and low mood, during the perioperative period. Although depressive symptoms are different from depression disorder, they could also lead to worse clinical outcomes after surgery, such as cognitive dysfunction, delirium, pain and even shortened survival time.<sup>3–6</sup> It has been reported that more than 24% of patients have depressive symptoms during the perioperative period, and this figure is nearly 44% in patients undergoing cardiac surgery or neurosurgery.<sup>6–9</sup> However, few interventions resolve the depressive symptoms that occur during the perioperative period, and the influence of antidepressant effects in the early stage on prognosis in the future remains controversial.

Ketamine, a classic anaesthetic for sedation and analgesia, has been reported that could take rapid antidepressant effects in depression patients.<sup>10</sup> However, the benefit of ketamine administration in patients with depressive symptoms undergoing major surgery is inconsistent.<sup>11–13</sup> To address this problem, our research team developed the PerioperAtive depressive Symptoms in patients undergoing Intracranial tumOur resectioN (PASSION)



**Figure 1** Flow diagram for PASSION II. MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-9, Patient Health Questionnaire 9.

study to explore the effect of ketamine on depressive symptoms in the neurosurgery population.<sup>14</sup> In the 84 participants that were enrolled, we found that ketamine improved depressive symptoms at the third postoperative day, and the response rate was higher in the ketamine group than in the placebo group (41.5% vs 16.3%), and no adverse events occurred. However, there were several limitations in the PASSION study; for example, the degree of remission did not reach desired levels chiefly because of the relatively small sample size, a single type of surgery was involved in the trial and esketamine has been gradually substituted for ketamine in clinical practice.

Esketamine is a racemic compound of ketamine that has been reported to have rapid and marked antidepressant effects.<sup>15</sup> Based on studies with ketamine, esketamine was developed and has been used for major depression patients since the Food and Drug Administration approved its use in 2019. Compared with traditional antidepressants, which require more than 1 week to take effect in depression patients, esketamine shortens the reaction period to nearly 1 hour after administration with few adverse effects, and the use of esketamine nasal spray has become a novel antidepressant for treatment-resistant depression patients.<sup>16</sup> Compared with ketamine, esketamine shows similar pharmacological characteristics but less side-effect. However, the effects of esketamine administration on depressive symptoms are still unknown. Thus, we should make further efforts to determine the effect of esketamine on depressive symptoms in major surgery patients.

Safety issues associated with the administration of esketamine during surgery are also unclear. It is reported that ketamine could change the intracranial pressure and haemodynamics during drug administration, and increase the risk of psychotic symptoms, hallucinations, or nausea and vomiting after major surgery. For repeated application, ketamine was reported associated with drug abuse and may interact with bladder urothelial cells and

induce apoptosis.<sup>17</sup> Due to esketamine and ketamine having similar pharmacological effects, whether the harmful effect mentioned above for single administration of esketamine in major surgery patients is not known for certain.

Based on the previous studies, the depressive symptoms may be a temporary state because of the stress by operation or diseases. Thus, we conducted this trial to explore the effectiveness of esketamine used in surgery patients with depressive symptoms. It is hypothesised that the administration of esketamine intravenously will improve the depressive symptoms in the major surgery population. The primary endpoint is the remission rate at postoperative day 3, and the secondary endpoints consist of other effectiveness and safety-related parameters.

## METHODS AND ANALYSIS

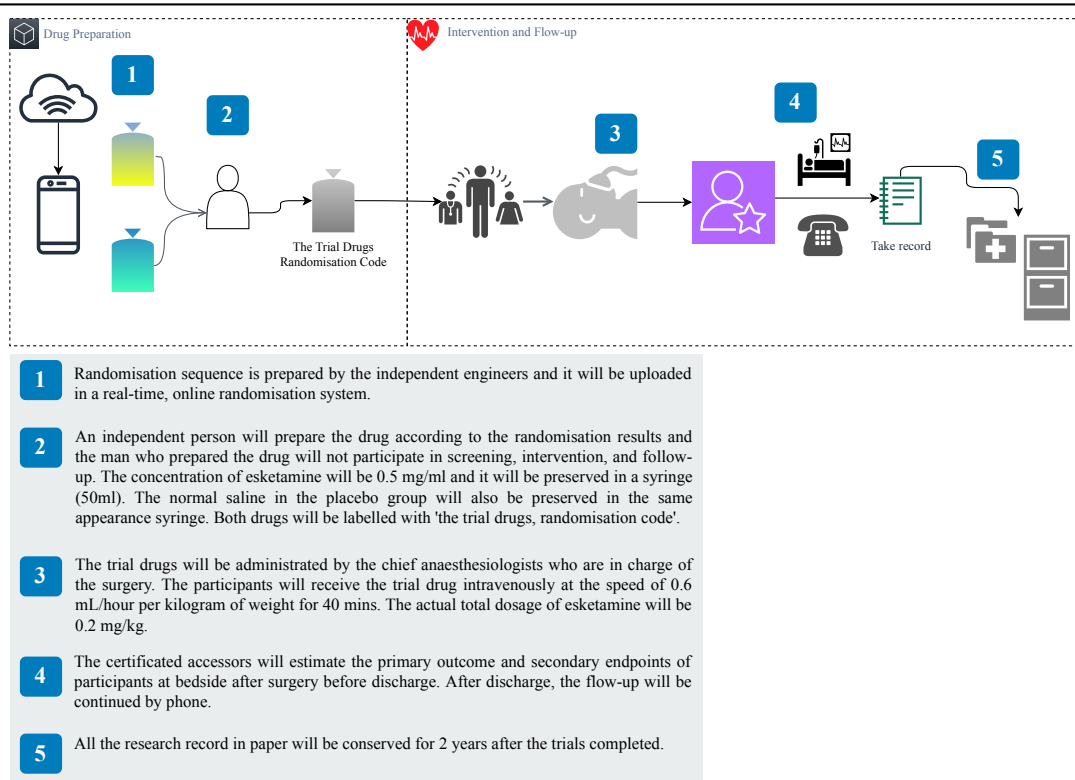
### Trial design

This study is a multicentre randomised controlled clinical trial to explore the effect of esketamine on depressive symptoms screened during the perioperative period (the flow chart see figure 1). It was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China (KY-2020-058-02). All participants or their legal representatives will provide written informed consent after screening and before randomisation. Registration information has been supplied on clinicaltrials.gov.

### Participants

The study will be conducted at medical centres in China, and training of the study protocol will be held regularly to guarantee the quality of the trial. Major surgery patients who are 18–65 years old with moderate-to-severe depressive symptoms will be included after informed consent is obtained from their legal representative. Moderate-to-severe depressive symptoms are defined as Patient Health Questionnaire 9 (PHQ-9)<sup>18 19</sup> scores equal to or more than 10 and Montgomery-Åsberg Depression Rating Scale (MADRS) scores equal to or more than 22.<sup>20</sup> Major surgery is defined as an elective operation with an estimate of more than 2 hours and includes neurosurgical tumour resection, coronary artery bypass grafting operation, total hip or knee arthroplasty surgery, breast cancer surgery, pneumonectomy or hepatectomy. Patients with any of the following will be excluded: aphasia or other conditions that may lead to the inability for mental assessments; diseases requiring maintenance of intubation after surgery; history of psychotic or bipolar disorder; primary diseases that could change hormone levels with laboratory evidence; body mass index more than 30 kg/m<sup>2</sup>; Child-Pugh grade B or C (defined as Child-Pugh scores more than six points); history of antidepressant therapy in the 2 weeks before screening; repeated suicide attempts (evaluated by a score equal to or more than 3 on the 12-item Quick Inventory of Depressive Symptomatology); history

## Blinding Process



**Figure 2** Schedule of blinding in drug preparation, intervention and follow-up.

of adverse events to ketamine or esketamine; history of drug use disorder or current pregnancy or breastfeeding.

### Randomisation and grouping

Participants will be randomly assigned to the esketamine group or placebo group at a 1:1 ratio. Randomisation results will be achieved via a real-time, online system before surgery. A randomised four-blocks design stratified patients by depressive severity (severe depressive symptoms are defined by MADRS scores equal to or more than 30). The randomisation sequence was created by independent engineers who will keep the allocation blind, and all study-related investigators will be blinded to the randomisation results.

### Intervention and anaesthesia management

All participants included in this study will receive trial drugs intravenously when the incision is being sutured. In the esketamine group, patients will be administered a total dose of 0.2mg/kg esketamine (Hengrui Induction, Jiangsu, China) over 40 min. Patients in the placebo group will receive an equivalent volume of normal saline at the same speed. Patients in this study will be under general anaesthesia for major surgery. Anaesthesia management will follow the standard procedure. Total intravenous anaesthesia or balanced anaesthesia will be implemented to maintain appropriate levels of sedation, analgesia and muscle relaxation. Anaesthetics are

administered at appropriate dosages based on consideration of the clinical anaesthetists and will include sedatives (propofol or etomidate), analgesics (sufentanil or remifentanil), muscle relaxants (rocuronium or cisatracurium) or inhaled anaesthetics (sevoflurane). Patient-controlled analgesia devices will be applied after surgery by using sufentanil and ondansetron to maintain numerical rating scale scores equal to or less than 4. Other analgesics could be used with the occurrence of severe pain (numerical rating scale score more than 7) during the postoperative period.

### Blinding

The trial drugs will be prepared by an independent person who is not participating in screening, intervention and follow-up procedures (see figure 2). Esketamine will be diluted to a concentration of 0.5mg/mL with normal saline. Both esketamine and normal saline will be kept in syringes (50mL) with the same appearance and labelled with 'the trial drugs, randomisation code'. The participants will receive the trial drug at a speed of 0.6mL/hour per kilogram of weight for 40 min. The intervention will be completed by the anaesthesiologists in charge of the surgery. The anaesthesiologists, accessors and patients will be blinded to the type of drug administered during surgery. The administered drug will be unmasked, with the agreement of the primary investigator, when

esketamine-related severe adverse events occur (such as an allergy to the study drug) after the intervention and before the termination of surgery.

### Outcomes

The primary outcome is the proportion of participants attaining remission (defined as a MADRS score less than or equal to 10) 3 days after surgery, based on an evaluation by blinded assessors at the bedside.

Secondary outcomes, including the differences in MADRS scores at 3 days and 5 days (or discharge) after surgery and the rates of patients achieving a response (MADRS scores reduced to or lower than half of the baseline MADRS score), the rate of severe pain within 72-hour postoperative period (severe pain is defined by the numeric rating scale pain scores equal to or more than 7).<sup>21</sup>

Safety outcomes include manic symptoms evaluated by the 11-item Young Mania Rating Scale (defined by YMRS scores more than or equal to 5) within the 3-day postoperative period,<sup>22</sup> psychotic symptoms measured by a non-zero score on four particular items of the Brief Psychiatric Rating Scale (unusual thought content, suspiciousness, hallucinations and conceptual disorganisation) during the 3 days after surgery,<sup>23,24</sup> dissociative symptoms assessed by a non-zero score on the Clinician-Administered Dissociative States Scale within 3 days after the operation,<sup>25</sup> and all drug-related adverse events during surgery or before discharge.

### Data management

The clinical data will be recorded and managed with the electronic database. The paper version materials including the protocol, the case reported forms, informed consent forms and electronic version database will be preserved by the primary investigator and stored in the independently locked strong box in Beijing Tiantan Hospital.

### Sample size calculation

It has been reported that the remission rate difference in the antidepressant effects between esketamine and ketamine was 3.8% in treatment-resistant depression patients.<sup>26</sup> In the perioperative population with depressive symptoms, the remission rate was reported to be 23.1% in the ketamine group and 9.3% in the placebo group based on the PASSION study at our research site. We assumed that the remission rate in the esketamine group will be 19.3% and that in the placebo group will be 10%. A sample size of 506 participants will provide 80% power to show the difference between the esketamine group and the placebo group (with a ratio of 1:1), including 1 interim analysis by using a two-sided significance level of 0.05.<sup>27</sup> With the consideration of a 10% attrition rate, the total sample size is planned to be 564.

### Interim analysis

The planned interim analysis will be performed after 424 patients (75% of the total sample size) completed the follow-up. This interim analysis will be based on

the intention-to-treat principle, and the p value will be set at 0.019 following adjustment by O'Brien-Fleming methods.<sup>28</sup>

### Statistical analysis

Continuous variables will be reported as the mean (standard deviation) for normally distributed data and the median (IQ ranges) for skewed distributions. Categorical variables will be reported as the number (proportion), and the relative risk with its 95% CI will be calculated. The difference between groups will be reported with 95% CI of absolute differences calculated by independent t-tests for continuous variables and using the Hodges–Lehmann method for skewed variables. The primary endpoint of remission rate at 3 days after surgery will be analysed by using the  $\chi^2$  test or Fisher's exact test. The secondary outcomes will be analysed using t-tests, Mann–Whitney U tests and  $\chi^2$  or Fisher's exact tests as appropriate. The adjusted ORs will be estimated by using a logistic regression model by taking into account the unbalanced baseline variables, age, sex, the severity of depressive symptoms and pain severity after surgery.

For missing values, both imputations with the mean or median or the last observed assessment and multiple imputations will be applied. Sensitivity analysis for different imputation plans will be used to explore the statistical nature of the missing data. All statistical tests will be two-sided at a significance level of 0.05 and the effect sizes will also be reported. Because of the potential for type I errors due to the lack of adjustment for multiple comparisons, the findings for secondary outcomes or sensitivity analysed should be interpreted as exploratory. All analyses will be performed by using Stata V.14.0.

### Safety consideration

Once adverse events occurred during drug intervention, the principal investigator will be informed immediately. Based on the severity of the adverse events and the relation to esketamine, the unmasking process will be considered by the principal investigator. All the adverse events that occurred during the trial will be recorded in detail and closely monitored until stabilisation or the time of the study intervention is not the cause for adverse events. All the adverse events will be reported to the Institutional Review Board by the principal investigator.

### Patient and public involvement

Patients and the public were not involved in the trial design. Participants will have access to the findings of the study on request.

### Ethics and dissemination

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China on 30 October 2020 (KY-2020-058-02). It has been registered on clinicaltrials.gov on 11 June 2020. The first participant was recruited on 19 February 2021. The conclusions of this study will be published in peer-reviewed journals.

## DISCUSSION

This study is a randomised placebo-controlled double-blinded clinical trial that aims to explore the effect of esketamine on depressive symptoms in the major surgery population. The participants will be administered 0.2 mg/kg esketamine intravenously within 40 min with the suturing of the incision. The efficacy and safety endpoints will be observed during the perioperative period and in the long term after major surgery.

In this study, the patients in the control group will receive normal saline rather than other antidepressants. To the best of our knowledge, traditional antidepressants need to be administered continuously for more than 1 week before taking effect, which is not suitable for short hospital stays in surgery patients. Besides, traditional antidepressants, such as selective serotonin reuptake inhibitors and tricyclic antidepressants, may lead to a potential risk for bleeding, arrhythmia and anaesthetic metabolism dysfunction during surgery.<sup>29</sup> For ethical concerns, the participants enrolled in this study will be provided with a professional consultation from the psychiatrist as necessary.

Although the PASSION study found that ketamine could alleviate the depressive symptoms assessed by clinician-rating scales to some extent in neurosurgery patients, there are still several concerns about the evidence of clinical trials regarding the resolution for depressive symptoms in the surgery population. First, screening standards for depressive symptoms during the perioperative period are lacking, and assessments in different depressive populations may affect the results of studies. Minor depressive symptoms may induce few adverse outcomes and disappear spontaneously after surgery. However, moderate-to-severe depressive symptoms could lead to worsening moods, enhanced postoperative pain or suicidal ideation, and there is an urgent need to resolve these symptoms. Second, the rating scale tools are subjective. Self-rating scales have commonly been used in previous studies, which also require clinician-rating scales to verify the antidepressant effects. Third, small sample size may have led to false-positive or false-negative results in previously reported studies. Fourth, the long-term effects of ketamine or esketamine on depressive symptoms in patients undergoing major surgery remain unclear. Meanwhile, whether the analgesic effect of esketamine is the key factor considering the antidepressant effects needs to be investigated.

The safety of esketamine as an antidepressant in the context of surgery is unknown. Esketamine, as a novel drug for replacing ketamine, is not approved for intravenous use as an antidepressant. The plasma concentration for the antidepressant dosage of ketamine was reported to be approximately 70–200 ng/mL, which is far lower than the anaesthetic concentration (2000–3000 ng/mL).<sup>10</sup> It is essential to explore an appropriate and safe dosage of esketamine for antidepressant treatment during surgery. Esketamine used in patients undergoing general anaesthesia is theoretically safer than the administration in awake patients. However, different

anaesthetics administered during general anaesthesia may induce synergic effects with esketamine or attenuate treatment effectiveness. Thus, it is important to monitor the quality of recovery from general anaesthesia. Similar to ketamine, which could lead to psychotic symptoms, hallucinations, manic symptoms or dissociative symptoms, esketamine given at an antidepressant dosage may also increase these risks after surgery. Determining the safe dosage will also be important for the popularisation of esketamine used as an antidepressant during the perioperative period. Based on the previous study, both 0.2 mg/kg and 0.4 mg/kg of esketamine administered intravenously were reported with remarkable antidepressant effects and low-dose of esketamine (0.2 mg/kg) with fewer side-effects rate than high-dose of esketamine after drug administration.<sup>15</sup> Thus, we selected 0.2 mg/kg of esketamine as the intervention dosage in this study.

In summary, this study is a randomised controlled trial focusing on the mental health of perioperative patients. The expected result is that esketamine could markedly improve the remission rate after surgery without obvious adverse events, and long-term outcomes may also benefit from the administration of esketamine.

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**Contributors** YZ and BM were involved in the preparation of the manuscript, and contributed equally to this work. YZ, GW and RH were involved in the study concept and trial design. WS, JW and YF were involved in the data collecting and trial design. AW was involved in the sample size calculation and statistical analysis plan. All authors have read and approved the manuscript.

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**Competing interests** None declared.

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## REFERENCES

- 1 GBD 2015 Disease and injury incidence and prevalence collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-



- 2015: a systematic analysis for the global burden of disease study 2015. *Lancet* 2016;388:1545–602.
- 2 GBD 2016 Disease and injury incidence and prevalence collaborator. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet* 2017;390:1211–59.
  - 3 Vasudev A, Saxby BK, O'Brien JT, et al. Relationship between cognition, magnetic resonance white matter hyperintensities, and cardiovascular autonomic changes in late-life depression. *Am J Geriatr Psychiatry* 2012;20:691–9.
  - 4 Kazmierski J, Kowman M, Banach M, et al. Incidence and predictors of delirium after cardiac surgery: results from the IPDACS study. *J Psychosom Res* 2010;69:179–85.
  - 5 De Cosmo G, Congedo E, Lai C, et al. Preoperative psychological and demographic predictors of pain perception and tramadol consumption using intravenous patient-controlled analgesia. *Clin J Pain* 2008;24:399–405.
  - 6 Arnold SD, Forman LM, Brigidi BD, et al. Evaluation and characterization of generalized anxiety and depression in patients with primary brain tumors. *Neuro Oncol* 2008;10:171–81.
  - 7 Orri M, Boleslawski E, Regimbeau JM, et al. Influence of depression on recovery after major noncardiac surgery: a prospective cohort study. *Ann Surg* 2015;262:882–9. discussion 89–90.
  - 8 Connerney I, Shapiro PA, McLaughlin JS, et al. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. *Lancet* 2001;358:1766–71.
  - 9 Mainio A, Hakko H, Niemelä A, et al. Depression in relation to anxiety, obsessiveness and phobia among neurosurgical patients with a primary brain tumor: a 1-year follow-up study. *Clin Neurol Neurosurg* 2011;113:649–53.
  - 10 Sanacora G, Frye MA, McDonald W, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* 2017;74:399–405.
  - 11 Kudoh A, Takahira Y, Katagai H, et al. Small-dose ketamine improves the postoperative state of depressed patients. *Anesth Analg* 2002;95:114–8. table of contents.
  - 12 Jiang M, Wang M-H, Wang X-B, et al. Effect of intraoperative application of ketamine on postoperative depressed mood in patients undergoing elective orthopedic surgery. *J Anesth* 2016;30:232–7.
  - 13 Mashour GA, Ben Abdallah A, Pryor KO, et al. Intraoperative ketamine for prevention of depressive symptoms after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Br J Anaesth* 2018;121:1075–83.
  - 14 Zhou Y, Peng Y, Fang J, et al. Effect of low-dose ketamine on perioperative depressive symptoms in patients undergoing intracranial tumor resection (passion): study protocol for a randomized controlled trial. *Trials* 2018;19:463.
  - 15 Singh JB, Fedgchin M, Daly E, et al. Intravenous Esketamine in adult treatment-resistant depression: a double-blind, Double-Blind-Randomization, placebo-controlled study. *Biol Psychiatry* 2016;80:424–31.
  - 16 Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal Esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* 2018;75:139–48.
  - 17 Short B, Fong J, Galvez V, et al. Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry* 2018;5:65–78.
  - 18 Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. primary care evaluation of mental disorders. patient health questionnaire. *JAMA* 1999;282:1737–44.
  - 19 Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
  - 20 Bech P, Andersen HF, Wade A. Effective dose of escitalopram in moderate versus severe DSM-IV major depression. *Pharmacopsychiatry* 2006;39:128–34.
  - 21 Karcioğlu O, Topacoglu H, Dikme O, et al. A systematic review of the pain scales in adults: which to use? *Am J Emerg Med* 2018;36:707–14.
  - 22 Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978;133:429–35.
  - 23 Hu Y-D, Xiang Y-T, Fang J-X, et al. Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. *Psychol Med* 2016;46:623–35.
  - 24 Brousse G, Meary A, Blanc O, et al. Clinical predictors of response to olanzapine or risperidone during acute episode of schizophrenia. *Psychiatry Res* 2010;179:12–18.
  - 25 Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered dissociative states scale (CADSS). *J Trauma Stress* 1998;11:125–36.
  - 26 Correia-Melo FS, Leal GC, Vieira F, et al. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: a randomized, double-blind, non-inferiority study. *J Affect Disord* 2020;264:527–34.
  - 27 Wu MC, Lan KK. Sequential monitoring for comparison of changes in a response variable in clinical studies. *Biometrics* 1992;48:765–79.
  - 28 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549–56.
  - 29 Roose SP, Rutherford BR. Selective serotonin reuptake inhibitors and operative bleeding risk: a review of the literature. *J Clin Psychopharmacol* 2016;36:704–9.