Efficacy of brief dynamic interpersonal therapy in patients with major depressive disorder: a prospective, multicenter randomized controlled trial protocol

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Study protocol

Keywords: Depression, Dynamic Interpersonal Therapy, Multicenter randomized controlled trial

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Abstract

Background : Dynamic Interpersonal Psychotherapy (DIT) is a brief manualized depression-focused intervention. This paper describes a study protocol of a multi-site, three-arm randomized controlled trial comparing medication plus DIT to medication alone and medication plus an active control psychotherapy in the treatment of major depressive disorder (MDD).

Methods : 240 patients with MDD will be randomly allocated on a 1:1:1 basis to the treatment conditions, with 80 patients in each group. Patients will be assessed pre-and post-intervention and at 6- and 12-months follow-up with the 17-item Hamilton Depression Scale (HAMD-17) and Hamilton Anxiety Scale (HAMA-14) administered by blind evaluators, and the Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder-7-item scale(GAD-7), side effect reaction scale (TESS), and The Self-Assessment Scale of the Overall Efficacy and Satisfaction of Patients (SASE). The primary outcome is change from baseline in HAMD-17 scores. Secondary outcomes include rates of response, remission and relapse, change from baseline in self-report depression and measures of anxious symptomatology, and subjective satisfaction of patients.

Discussion: This will be the first multicentered RCT in China to assess the potential efficacy of psychotherapy for MDD. The study has the potential to inform clinical treatment guidelines for the treatment of MDD in China.

Trial registration : ChiCTR□ChiCTR1800016970□ Registered on July 5 th 2018 - Retrospectively registered, http://www.chictr.org.cn/showprojen.aspx?proj=28786 .

Key words : Depression; Dynamic Interpersonal Therapy; Multicenter randomized controlled trial,

Introduction

Background and rationale {6a}

Major depressive disorder (MDD) is a prevalent psychiatric disorders with an estimated point prevalence of 10% worldwide and a lifetime prevalence up to 16% [1]. In China, the point prevalence of MDD ranges from 6.1% to 7.5% [2], with prevalence rates increasing annually. MDD tends to be a chronic and recurring illness and is associated with significant impairment in multiple domains and high suicide rates [3]. It is projected that by 2020 MDD will rank second among diseases with the highest social and economic burden worldwide [4]. The pervasiveness and disabling nature of MDD make the development of effective treatment protocols a high priority for the Chinese health care system.

In China, the treatment for MDD includes pharmacotherapy and psychotherapy, alone or in combination. Among the psychotherapies, psychodynamic therapy is widely used. Unike other psychological interventions that resolve problems on a consciousness level, psychodynamic therapies focus on changing maladaptive personality structure and core schemas. While psychodynamic therapy is usually

offered as a long term intervention (i.e., 50 or more sessions) [5], this is costly and difficult to sustain within a public mental health system. To increase accssessibility and affordability of psychodynamic therapy, time-limited approaches have been developed in the last 30 years, with recent well-designed clinical trials demonstrating their efficacy in the treatment of depression [6,7, 8].

Among the short-term approaches, Dynamic Interpersonal Therapy (DIT) was recently developed as a specific depression-focused intervention that could be implemented within the context of a public health care system [9]. It is currently recommended as one of the psychotherapeutic approaches provided through the Improving Access to Psychological Therapies initiative in the UK. The core features of DIT are: it is manualized; brief (i.e., 16 sessions); formulates depression as a response to perceived threats to attachments (loss/separation) and impaired mentalization function; and incorporates evidence-based psychodynamic therapeutic strategies and techniques (e.g., expressive, supportive and mentalization) [10,11].

Since DIT and other psychodynamic therapies have been developed and evaluated in Western countries, findings cannot be readily generalized to China due to possible cultural effects. Thus, before promoting a new method of psychotherapy in Chinese culture, it is necessary to test its applicability and make corresponding modifications first. The DIT manual developed by Lemma et al [12] was recently translated into Chinese. The proposed study is the first in China to evaluate the efficacy of DIT for MDD in hospital settings, as well as the first multicentered RCT in China to assess the efficacy of psychotherapy for MDD. The results of this study will have important implications for the provision of evidence-based care for depression in China.

Objectives {7}

The objective of this trial is to determine whether medication plus DIT is a more efficacious treatment for MDD than medication alone and medication plus a control psychotherapy. Medication treatment will consist of standard medication management for depression and our control psychotherapy, general supportive therapy (GSP), will be used to determine if DIT has benefits over and beyond non-specific therapeutic factors that contribute to therapy outcome, such as therapist attention and expectation of improvement. We hypothesize that DIT will be superior to the other treatment groups in improving symptoms of depression and anxiety at post intervention and at 6 and 12 months follow-up.

Trial design {8}

This study is a multicenter, parallel, superiority, three-arm, randomized controlled trial with recruitment planned in five hospitals. Two-hundred and forty outpatients will be randomly assigned on a 1:1:1 basis to one of the three treatment conditions, with 80 patients assigned to each group. Participants will be blind to the purpose of the study and our primary efficacy measure will be administerd by independent raters who are blind to treatment allocation.

Methods: Participants, Interventions And Outcomes

Setting and recruitment {9}{26a}{15}

Participants recruitment was planned in five hospitals in China, which are Shangai Mental Health Center, Beijin Anding Hospital, Anhui Mental Health Center, Wuhan Mental Health Center, and Shanghai Hongkou District Mental Health Center. New outpatients at each of the five sites will be pre-screened individually for 15–20 minutes by a research assistant (a senior psychiatric nurse working in the triage station) and those who are potentially eligible will be invited to participate in the study.

Written informed consent will be obtained by trained research assistants from all participants prior to entering the trial. Patients will be informed that their participation is voluntary and that they can withdraw from the study at any time without any negative consequences to their care. All efforts will be made to protect the privacy of the participants. Possible adverse reactions will be monitored throughout the trial. The trial will be implemented base on the principles of good clinical practice and reported according to the CONSORT statement [13,14]. The trial flow diagram is illustrated in Fig. 1. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [15] Checklist is shown in Additional file 1. This study has been registered at ChiCTR (ChiCTR1800016970).

After provision of informed consent, patients will be assessed with the Mini International Neuropsychiatry Interview (MINI)[16] to confirm the diagnosis of MDD and other eligibility criteria. The MINI will be administered by qualified raters who have been trained to high levels of inter-rater reliability (Kappa = 0.85). Training in the MINI included viewing teaching videos of an expert administering the MINI and as well as assessment of patients.

Participants and eligibility {10}

To be eligible, patients need to be between the ages of 18–65 years; meet DSM–5 criteria for MDD based on the MINI, with a score ≥18 on the 17-item Hamilton Depression Rating Scale (HAMD–17); have completed at least primary school education (i.e., ≥6 years of education); be antidepressant drug naïve or discontinued antidepressant medications at least 8 weeks prior to the screen visit; have not received psychotherapy in the last 6 months; and provide written informed consent.

Exclusion criteria include a severe concurrent medical condition; significant visual and auditory deficits; lifetime history of psychosis or bipolar disorder; history of substance use disorders in the last 24 months; history of psychotic features of affective disorder; high suicide risk; severe personality disorders (such as: Cluster A personalities and antisocial personality disorder); and intellectual disability. Other psychiatric comorbidities will be allowed so long as the MDD is the primary and predominant disorder.

Randomisation and blinding {16}{17}

Patients will be assigned to one of the three treatment groups via remote access to the central randomisation procedure that is hosted by the Clinical Trial Center of the Shanghai Mental Health Center. Permuted blocks of randomly varying lengths will be used to ensure there is an equal number of participants in the 3 treatment groups at all times. Once a participant is deemed eligible, a researcher

assistant at each site who is not involved in patient recruitment will log into a web-based interface to obtain the next allocation. This is restricted access and users other than the system owner do not have access to future allocations. Sequence generation is therefore concealed from the study investigators, participants, and assessors.

Allocation of each participant to each of three groups wil be recorded in a separate assessment log used only by the research assistant. As blinding of participants, providers and research assistants is not possible in psychotherapy trials, our primary outcome will be administered by blind evaluators who are unaware of the treatment participants are allocated to. The success of the blind will be ascertained by asking the evaluators to document whether patients revealed which group they were assigned to. In addition, patients will be asked not to reveal their assigned treatment during the blind assessments. The principal researchers and statisticians will also be blind to group allocation.

Intervention description {11}

Medication

Patients in all three treatment groups will be prescribed a selective serotonin reuptake inhibitor (SSRI) approved by the Chinese food and Drug Administration (CFDA) for the treatment of MDD (e.g. paroxetine, sertraline, citalopram). The type of SSRI will be based on clinician recommendation and the dose will be titrated according to usual practice. The dosage could be adjusted on a weekly basis over the 16 weeks of acute treatment if needed, with the maximum dose not exceeding dosage guideline. Patients with sleep disorders will be prescribed benzazem if needed, but not for more than two weeks. Other psychotropic drugs and herbal remedes for depression are proscribed.

Dynamic Interpersonal Psychotherapy

Patients assigned to the medication + DIT group will receive 16 weekly sessions of DIT, with each session lasting 45 minutes. A Chinese version of the DIT protocol developed by Lemma, Target and Fonagy [12] will be used. The therapy is divided into three stages. The task of the initial stage (sessions 1 to 4) is to identify one dominant and recurring unconscious interpersonal pattern, the interpersonal affective focus (IPAF), which is assumed to be central to the onset and/or maintenance of the depressive symptoms. The task of the middle stage (sessions 5 to 12) is to help the patient work through the IPAF. This phase involves maintaining a systematic focus on the agreed IPAF by prioritizing work on current significant relationships that demonstrate the activation of the IPAF, focusing on the therapeutic relationship as a live example of the IPAF in action, and helping the patient practice the skill of recognizing internal states (e.g., feelings, thoughts, wishes) and connecting them to the week's events and to the identified IPAF. The final sessions (sessions 13–16) are devoted to helping the patient explore the affective experience and conscious and unconscious meaning of ending the therapy, reviewing treatment gains, and helping them anticipate future difficulties and vulnerabilities.

General supportive psychotherapy

Patients assigned to the medication + GST group will receive 16 weekly sessions of GST, with each session lasting 45 minutes. As a control psychotherapy, supportive therapy is an active but less specific intervention that is intended to control for common factors that account for positive outcomes with all psychotherapies. GST is unstructured and no specific psychotherapeutic techniques are used other than those common to all approaches (e.g., reflective listening, offering support, helping patients feel understood). GST is procedurally distinct from DIT, thus avoiding contamination between the study treatments. A manual for GST developed by our own research team will be followed in this trial and is available on request.

Therapist selection and supervision

The therapies will be delivered by licensed psychotherapist with at least three years of psychotherapy experience, with at least Master degree on psychology, or psychiatrist. For DIT, we will select therapists who have at least three years experience conducting psychodynamic therapy. The therapists will deliver only one treatment to avoid treatment contamination and they will be specifically trained in their respective treatment approach. Prior to the study, our therapists received training from expert DIT trainers. After training, only those who demonstrate competence for DIT and GST respectively, will be invited as therapists in the study. To maintain treatment integrity throughout the trial, therapists at each site will receive 90-minutes of group supervision on a biweekly basis. Supervision will be conducted by experienced supervisors in the respective therapies.

Treatment integrity

All therapy sessions will be videotaped and for each therapist-patient dyad three tapes will be randomly selected from the early, middle, and late phase of therapy to examine therapist adherence and competence. Treatment adherence and competence will be assessed by two raters who are experts in the respective therapy. Adherence and competence to DIT will be evaluated with a Chinese-version of a therapist competence scale developed by Lemma et al [12]. Adherence and competence of GSP will be evaluated with an scale developed by the authors for this study.

Treatment discontinuation

Patients will be withdrawn form the study for the following reasons: 1) uncontrolled concurrent medical disease 2) exacerbation of a concurrent medical condition; 3) treatment-emergent serious adverse events; 4) the patient requests to be withdrawn; 5) poor treatment compliance; and 6) the researchers believes it is in the best interest of the patient to discontinue treatment (e.g.,increased suicide risk; participation in the study presents a significant burden to the patient; patient requires hospitalization or day treatment).

Outcomes measures {12}

Primary efficacy measure

Our primary efficacy measure is the HAMD–17 administered by blind assessor. The scale will be administered at baseline, at weeks 2, 4, 8, 12 and 16, and at 3-, 6- and 12- months post treatment.

Secondary efficacy measures

Rates of response, remission and relapse will be explored based on the score of the HAMD–17. Remission is defined as a score ≤7 on the HAMD–17 and response is defined by a 50% reduction (or more) in total HAMD–17 scores. Relapse is defined as as an episode meeting DSM–5 criteria for MDD. Other secondary measures include the Hamilton Anxiety Scale (HAMA–14), which will be administered by blind evaluators, and the self-report Patient Health Quetionnaire (PHQ–9), Generalized Anxiety Disorder–7-item scale (GAD–7) and self-assessment scales of the overall efficacy and satisfaction of the patients. These measures will be administed at the same time points as the HAMD–17.

Participant timeline {13}

The intervention cycle will be 16 weeks. After the research commences, assessment will occur at week 2, 4, 8, 12, 16 during the study period. And the follow-up assessments occur at month 5, 7, 10 and 16. An overview of specific masurements and time points for data collection is presented in Figure 2.

Sample size {14}

A power analysis was conducted by the program “G*Power”. Twenty-six studies of the effectiveness of short-term dynamic therapy (STDT) were subjected to two meta-analyses. Effect sizes (ES) obtained by each method were similar. STDT attained average ESs of 0.71 and 0.34, relative to waitlist and minimal treatment groups, respectively, with a slight superiority at long-term follow up assessment. [17]. Based on these former theoretical considerations and results of comparable studies[18,19], we assume a medium effect size of 0.50. An a priori power analysis (with two-tailed alpha set at.05 and a power of.80 indicates that 64 subjects in each group will be adequate to detect the effect through a t-test at $p < 0.05$ level of significance. Assuming about 20% the dropout rate, the targeted total sample size will be 240.

Data collection and management {18}{19}{27}

The project team at the Clinical Psychological department of Shanghai Mental Health Center will serve as the data coordinating center responsible for data collection forms, coordination of data transfer and data analysis. Health of participants will be monitored through the whole study process in the five sites. If any adverse events do take place, and in the unlikely event that harm is suffered, the research management team will liaise with the responsible clinician. All adverse events will be documented in the final written report of this study. All study data will be stored securely in Shanghai Mental Health Center. All paper-based documents and data will be stored in a secure filing cabinet. All electronic data will be secured on a password-protected computer. All documents that contain names or personal identifying information will be stored separately from other study data and identified by code number. Access to files will be limited to research staff involved in the study. The statistician for the final analysis will receive depersonalized

data where the participants' identifying information will be replaced by an unrelated sequence of numbers.

Statistical analysis {20}{21}

The principal analyses will be conducted using the intention-to-treat sample. Two-sided 5% significance level will be adopted and corresponding 95% CIs will be calculated whenever possible. Primary and secondary continuous outcomes from baseline to week 16 will be analyzed using analysis of variance and general linear mixed models. Treatment group, time and interaction between treatment and time will be the main predictors of interest, with gender, age, education level and baseline score entered as covariates and treatment site as a random effect in the model. The mixed models will be estimated using Restricted Maximum Likelihood.For the main analysis, the least square mean difference between the groups at 16 weeks will be tested at the 5% level of significance; additional analyses will include comparisons at weeks 2, 4, 8 and 12, with adjustment for multiple testing. Multiple comparison issues of post hoc analysis will be handled using Bonferroni adjustment. Dichotomous outcomes will be compared between groups using Chi-square test, Fisher's exact test or generalized estimating equation. To assess maintenance of treatment gains, the above analyses will be repeated with the addition of 6- and 12-months follow-up scores.

Trial oversight {5d}{21a}{22}{23}

The day-to-day management of the trial will be the responsibility of the project management team, based at Shanghai Mental Health Center. The team will meet monthly to assess progress. The project manager will also be responsible for training of the research assistants at each of the trial center. The trial statistician will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

A Trial Steering Committee (TSC) and a Data & Safety Monitoring Committee(DSMC) will be set up to guarantee the quality of study. The Committee will adopt a charter, which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, see copies of data accrued to date or summaries of that data by treatment group, and they will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the TSC at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least annually during the recruitment phase of the study.

Treatment emergent adverse events will be monitored at each visit. Adverse events are defined as any significant unfavorable change in the patient's pretreatment mental condition regardless of its relationship to treatment. Serious adverse events include mortality, hospitalization, suicide, or attempted suicide. All adverse events will be recorded in the case report form. The assessment of adverse events

includes classification, grading, identifying the relationship with treatment, and formulating coping methods.

The study will also be monitored or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures by the study sponsor. A monitoring plan will be developed according to standard operating procedures, which involve a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

Dissemination plan {31}

Participants who are interested in the trial results will be informed. The primary outcomes and secondary outcomes will be reported and submitted for publication. Presentations will be held within the organization and at national and international conferences. No professional writers will be employed for publications associated with this protocol. The authors are intended to participate in future publications associated with this protocol.

Discussion

Despite the large number of studies on treatment of depression, there is a clear lack of controlled research on psychotherapy especially in China. Psychodynamic psychotherapy has shown some promising signs of efficacy but more controlled studies are strongly needed in order to be empirically validated. This will be the first multicentered RCT in China to compare the clinical efficacy of DIT plus medication versus medication alone and medication plus a control psychotherapy in patients with MDD. The study will provide valuable information about the relative efficacy of these three different interventions for depression, and has the potential to inform clinical treatment guidelines for MDD in China.

Trial Status

The trial is in the ongoing recruitment phase. The protocol version number is 2019–03 (20191125). The recruitment began since April 8th, 2019. Approximately, the recruitment will be completed until April in 2021.

Abbreviations

DIT: Dynamic Interpersonal Therapy

MDD: Major Depressive Disorder

HAMD-17: 17-item Hamilton Depression Scale

HAMA-14: 14-item Hamilton Anxiety Scale

PHQ-9: Patient Health Questionnaire

GAD-7: Generalized Anxiety Disorder-7-item scale

TESS : The Side Effect Reaction Scale

SASE: The Self-Assessment Scale of the Overall Efficacy and Satisfaction of Patients

RCT: Randomized Controlled Trial

GSP: General Supportive Therapy

MINI : The Mini International Neuropsychiatry Interview

SSRI : Selective Serotonin Reuptake Inhibitor

CFDA : Chinese Food and Drug Administration

IPAF : The Interpersonal Affective Focus

STPP: Short Term Psychodynamic Psychotherapy

TSC : Trial Steering Committee

DSMC: Data & Safety Monitoring Committee

SAEs: Serious Adverse Events

ICMJE: International Committee of Medical Journal Editors

Declarations

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Funding {4}

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Trial Sponsor

Sponsor: Shanghai Mental Health Center Clinical Research Center

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Authors' contributions: {31b}

Jianyin Qiu contributed to the conception of the study and obtained funding for the trial as the primary investigator. Jianyin Qiu, Lanlan Wang and Diana Koszycki collaboratively developed the study design and prepared the manuscript. Jianfeng Luo made sure about the statistic method. Qian Wang, Jun Tong, Xiaosi Li, and Fang Fang are the primary investigator at each site and will assure the strategic coordination of the project. Wenhui Jiang drafted the treatment manual for the study. Hongyan Wang and Wenqing Zhao are research coordinators. All authors read and approved the final manuscript.

Ethics approval and consent to participate {24}

The protocol of this study has been approved by the ethics committee at each site and finally approved by the ethics committee of Shanghai Mental Health Center (registration number 2018-13). The ethics approval applies to all participating centres. And the trial is registered with ClinicalTrial.gov (number: ChiCTR1800016970). The study will be conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent to participate in the study will be obtained from all the participants.

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests.

Availability of data and materials {29}

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All authors will have access to the complete dataset.

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Figures

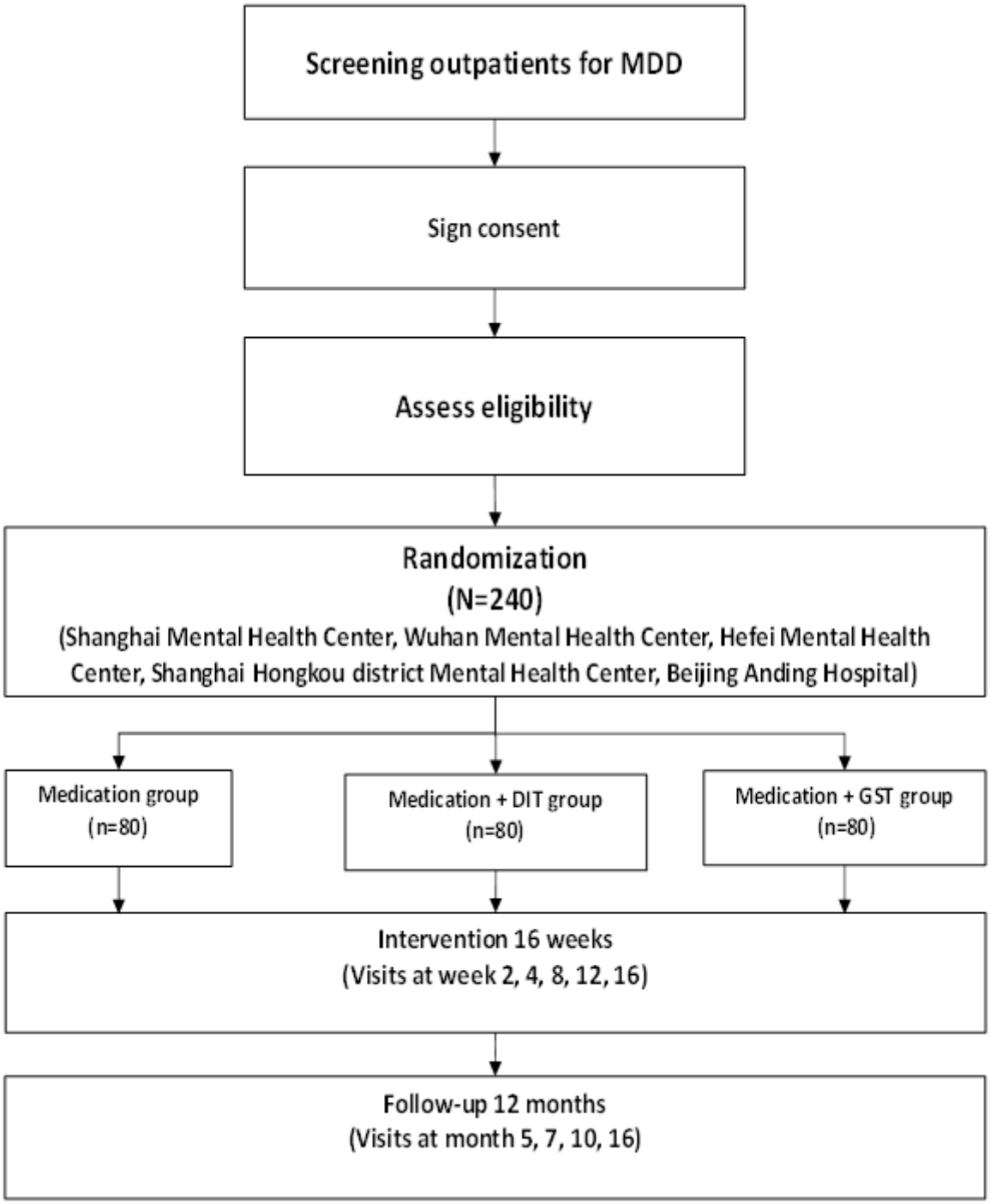

Figure 1

Flow diagram of enrollment, intervention and assessments.

	Study period										
	Enrollment	Randomisation	Post randomization								Close
TIMEPOINT	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9
		0	2 w	4 w	8 w	12 w	16 w	5 m	7 m	10 m	16m
ENROLMENT:											
Eligibility screen	X										
Informed consent	X										
Allocation		X									
INTERVENTIONS:											
Medication only		X					X				
Medication +DIT		←	—	—	—	—	→				
Medication +GST		←	—	—	—	—	→				
ASSESSMENTS:											
Primary outcome measure:											
HAMD-17	X	X	X	X	X	X	X	X	X	X	X
Secondary outcome measures:											
PHQ-9		X	X	X	X	X	X	X	X	X	X
HAMA-14	X	X	X	X	X	X	X	X	X	X	X
GAD-7		X	X	X	X	X	X	X	X	X	X
Other measures:											
MINI	X										
Demographic information	X										
TESS		X	X	X	X	X	X	X	X	X	X
SASE		X	X	X	X	X	X	X	X	X	X

DIT: Dynamic Interpersonal Therapy

GSP: General Supportive Therapy

HAMD-17: 17-item Hamilton Depression Scale

PHQ-9: Patient Health Questionnaire

HAMA-14: 14-item Hamilton Anxiety Scale

GAD-7: Generalized Anxiety Disorder-7-item scale

MINI : The Mini International Neuropsychiatry Interview

TESS : The Side Effect Reaction Scale

SASE: The Self-Assessment Scale of the Overall Efficacy and Satisfaction of Patients

Figure 2

Study design and measurement time points

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- grantcertificate20180828.pdf
- SPIRITchecklist.doc
- ethicsapproval.pdf