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Sequential Multiple-Assignment Randomized Trials to Compare Antipsychotic Treatments (SMART-CAT) in first-episode schizophrenia patients: Rationale and trial design

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ABSTRACT

Accumulated studies have investigated pharmacological interventions for first-episode schizophrenia (FES) patients. However, studies on subsequent treatment steps, which are essential to guide clinicians, are largely missing. This Sequential Multiple-Assignment Randomized Trials comparing Antipsychotic Treatments (SMART-CAT) program intends to evaluate the effectiveness of commonly used antipsychotic drugs in FES patients. The major goals of this study are to examine: 1) what would be the optimal subsequent sequential treatment if the first antipsychotic drug failed; 2) whether clozapine could be used in those first-trial failed and have superior efficacy compared to other atypical antipsychotics. In this article we will report the detail protocol of SMART-CAT.

The SMART-CAT is a randomized controlled clinical multicenter trial in which 9 institutions in China will participate. A total of 720 FES patients will be enrolled and followed up for 12 months in this study. The trial includes three treatment phases (each phase lasting for 8 weeks) and a naturalistic follow-up phase; participants who do well on an assigned treatment will remain on that treatment for the duration of the 12-month treatment period, while non-responders will move to the next phase of the study to receive a new treatment. Phase 1 is a randomized controlled trial; patients will be randomly assigned to one of the treatments with oral olanzapine, risperidone, amisulpride, aripiprazole or perphenazine. Subjects who fail to respond after 8 weeks will enter the phase 2 randomization. Phase 2 is an equipoise-stratified randomization trial, and patients will be randomly assigned to oral olanzapine, amisulpride or clozapine for 8 weeks. Subjects who fail to respond after phase 2 will enter an open label trial (phase 3); patients who receive clozapine in phase 2 and fail to respond will be

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assigned to an extended clozapine treatment or modified electroconvulsive therapy add-on therapy (Phase 3A). Patients who were not assigned to clozapine in phase 2 will be assigned to treatment with clozapine or another SGAs not previously used in phase 1 and 2 (Phase 3B). The primary outcome for the treatment phase is the treatment efficacy rate, which is defined as at least 40% reduction in Positive and Negative Syndrome Scale (PANSS) total score. We hypothesize that clozapine is more therapeutically effective than any other SGAs to patients who failed to meet efficacy criteria in Phase 1, and earlier treatment with clozapine can improve the functional outcomes of schizophrenia patients. As for the naturalistic follow-up phase, time to all-cause treatment failure, marked by its discontinuation is selected as the primary outcome, since it reflects both efficacy and side effects. The all-cause discontinuation is defined as discontinuing for any reasons, including poor efficacy, intolerance of adverse reactions, poor compliance and other reasons.

The results of the SMART-CAT trial will provide evidence for the selection of antipsychotics in FES patients who fail to respond to the first trial of an antipsychotic drug. It will also provide evidence for the efficacy and safety of using clozapine in the early phase of schizophrenia treatment by comparing with other SGAs. The study is based on the combination of sequential therapy and dynamic therapy, which can be more suitable to assess the effectiveness of treatment options in the real-world clinical setting. As a result, we hope that this study can provide guidance for an optimal treatment algorithm in first-episode schizophrenia patients.

Trial registration: ID NCT03510325 in ClinicalTrials.gov

1. Introduction

Schizophrenia is a severe mental illness that affects up to 1% of the world population. It is characterized by a combination of positive symptoms, negative symptoms and cognitive impairment (Marder and Cannon, 2019). In addition, schizophrenia is associated with social and occupational disability, and leads to heavy societal expenditure (Montgomery et al., 2013; Schultz and Andreasen, 1999). According to the recent Global Burden of Diseases Study, the disability-adjusted life-years (DALYs) of schizophrenia has increased by 17.7% since 2005 (Collaborators, 2017).

First-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) are the most commonly used treatment for schizophrenia (Galletly et al., 2016; Kane, 2010). Compared to the FGAs, most SGAs have a higher affinity for the 5-HT receptor and may be more selective on the mesolimbic system; these properties may be associated with improvement in negative symptoms and cognitive dysfunction (Zhang et al., 2013). However, some SGAs may cause significant weight gain and cardiometabolic adverse effects (Miyamoto et al., 2005). There have been a number of clinical trials assessing the efficacy and safety of FGAs and SGAs in first-episode schizophrenia (FES) patients (Kahn et al., 2008; McEvoy et al., 2007; Robinson et al., 2015; San et al., 2012; Zhang et al., 2013). The results indicated that the response and remission rates are greatly higher in first-episode patients than in chronic patients (Zhu et al., 2017b); however, little difference were found among SGAs for the acute treatment of patients with first-episode schizophrenia (Zhu et al., 2017a).

The treatment in the early phase of schizophrenia is of crucial importance, where optimal treatment could positively influence the long-term course of the illness (Jordan et al., 2014; Lieberman et al., 2001). However, some important questions remain unanswered. For example: How to perform the sequential treatment if the FES patients failed the first antipsychotic drug? And which drug will be the most optimal choice for patients who fail their first trial? Although an FGA, olanzapine, and risperidone are recommended by the Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS), the evidence for this recommendation was derived from studies of chronic patients (Osser et al., 2013). The prospective, sequential multiple assignment randomized trial design (SMART) studies of FES patients are largely missing. The SMART design is based on the combination of sequential therapy and dynamic therapy, which is more suitable to assess the effectiveness of treatment options in the real world setting and has been widely used in mental health studies (Liu et al., 2014). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial is a multi-center, open-label SMART design trial that has been undertaken to examine the treatment of major depressive disorder. In the 4 levels of STAR*D, patients were randomized to various treatment options including monotherapies, combinations, or augmentation strategies. The results indicated that there was no difference in effectiveness between any treatments at any treatment level and have shed important light on the effectiveness of current treatment strategies for patients with depression (Rush et al., 2006a; Rush et al., 2006b; Trivedi et al., 2006; Sinyor et al., 2010).

Another important question is about clozapine, the most commonly used treatment for refractory schizophrenia patients (Galletly et al., 2016; Remington et al., 2017). Recently a three-phase switching trial was carried out in FES patients in the Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) trials (Kahn et al., 2018; Leucht et al., 2016), which included phase 1(amisulpride for 4 weeks in an open-label design), phase 2 (amisulpride or olanzapine for 6 weeks in a double-blind trial) and phase 3 (clozapine for 12 weeks in an open-label trial). The results indicated that clozapine can be effective in early treatment (for example less than 3 months) in nonresponding FES patients (Kahn et al., 2018). However, it is still not clear whether clozapine could be used for first-trial failed schizophrenia, and prescribing clozapine earlier (such as 8 weeks) after the first treatment failed.

This study intends to compare the effectiveness of commonly used antipsychotic drugs in FES patients using a SMART design, which is based on the combination of sequential therapy and dynamic therapy. In particular, we will compare clozapine with other SGAs in the early phase of trial. Clozapine is often recommended for treatment resistant schizophrenia and the last option of schizophrenia treatment. Although it is widely used in the early phase of schizophrenia treatment in China, few studies compared the overall efficacy and safety among clozapine and other SGAs in first-episode schizophrenia. As a result, we hope that our study will provide guidance for the optimal treatment algorithm for FES patients.

2. Rationale for trial design

The SMART-CAT trial is performed by a consortium of nine institutions including seven psychiatric institutions in China. A draft study design was first developed by the Shanghai Clinical Research Center for Mental Health (SCRC-MH) at Shanghai Mental Health Center (SMHC) in December of 2017 which was updated and finalized in 2018 for Institutional Review Board review and recommendations.

2.1. Our specific aims and hypotheses

- To define the appropriate treatment strategies for first-episode schizophrenia patients who fail their first antipsychotic trial,

especially the value of the early use of clozapine. We hypothesize that clozapine is more effective than other SGAs for the first-trial failed patients. Earlier treatment with clozapine can improve the functional outcomes of schizophrenia patients.

- To determine the long-term clinical effectiveness and tolerability of the SGAs, relative to perphenazine, in FES patients. We hypothesize that SGAs are associated with better treatment compliance and functional outcomes than perphenazine in FES patients. We also hypothesize that different kinds of SGAs are similarly effective in treating psychotic symptoms, but have different side effects, tolerability, compliance and functional outcomes in FES patients.
- To verify the efficacy of clozapine in refractory, first-episode schizophrenia. We hypothesize that clozapine is more effective than any other SGAs in refractory schizophrenia. And MECT add-on therapy is more effective than clozapine extended treatment in clozapine treatment-resistant schizophrenia.

3. Methods

3.1. Patient sample

7 psychiatric institutions from China will participate in this trial. The study will enroll 720 patients with a first episode of schizophrenia, schizophreniform or schizoaffective disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and verified with the Mini International Neuropsychiatric Interview (M.I.N.I. 7.0) (Sheehan et al., 1998).

3.1.1. Inclusion criteria

(1) meet the DSM-5 diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder, (2) inpatients or outpatients, (3) age between 16 and45 years old, (4) be first episode, and the course less than 3 years, (5) drug-naïve, or taking the same antipsychotic medication no longer than 2 weeks, and the cumulative antipsychotic drug exposure time no more than 6 weeks, (6) the severity of psychotic symptoms is moderate or above, which is defined as: at least one of the following items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, or suspiciousness/persecution) score ≥ 4, and the PANSS total score > 70, (7) has an adequate decisional capacity and informed consent is provided.

3.1.2. Exclusion criteria

Patients with chronic, recurrent schizophrenia or treat-resistant schizophrenia are excluded. Patients with medical or psychiatric comorbidities and those who require concomitant other medications are excluded. Patients with contraindications to even one of the proposed treatment arms are excluded. Patients with risks such as extreme agitation, stupor or suicide are excluded. Female patients with pregnancy or breast-feeding are also excluded.

The sample size was estimated primarily based on phase 2, but not phase 1. The reason for focusing on sample size and power of phase 2 is that our primary objective is to define the appropriate treatment strategies for first episode schizophrenia patients who fail the first antipsychotic trial, especially the value of the early use of clozapine. According to the previous studies, we hypothesized that the response rate of clozapine and other SGAs in phase 2 was 52% and 37% separately (Agid et al., 2011; Edwards et al., 2011; Kahn et al., 2018; Suzuki et al., 2007). The α was 0.05 (one-tailed), the test efficiency (1-β) (power) was set to 0.8,the allocation proportion of clozapine and other SGAs in phase 2 was set to be 1:2. At the same time, the response rate of first episode schizophrenia in phase 1 is 51.9% (Zhu et al., 2017b), and the withdrawal rate in phase 1 is about 10%. As a result, the total estimated patient sample size is about 720.

3.1.3. Ethics and dissemination

The SMART-CAT study is conducted in accordance with the Declaration of Helsinki. The study was approved by SMHC Institutional Review Board. And written informed consent was obtained from all participants.

3.2. Study design

Fig. 1 contains a schematic diagram of the trial design. This study is a multi-phase RCT of antipsychotic medication treatment in schizophrenia patients. It includes three treatment phases (each phase lasts for 8 weeks) and a naturalistic follow-up phase. Participants who respond well on an assigned treatment will remain on that treatment for the duration of the 12- month treatment period. If an assigned treatment is deemed a failure, the patients will move to the next phase of the study to receive a new treatment. The study is single-blinded, with the evaluators blinded to the treatment assignment; In order to replicate the real-world clinical setting, the medications are open-label and flexible, and the drug dosages are adjusted based on clinical judgment.

Phase 1 of the trial is a randomized controlled trial (RCT) for 8 weeks; patients will be randomly assigned to one of the treatments with oral olanzapine, risperidone, amisulpride, aripiprazole or perphenazine. Non-responders or patients with intolerable side effects in phase 1 will be switch to phase 2.

Phase 2 of the trial is an equipoise-stratified randomization (ESR) trial for 8 weeks; patients will be randomly assigned to treatment with oral olanzapine, amisulpride or clozapine. Non-responders or patients with intolerable side effects in phase 2 will switch to phase 3.

Phase 3 of the trial is an 8-week open label trial where patients and psychiatrists will be involved in shared decision making. If a patient received clozapine in phase 2 failed to response, the individual will be assigned to the clozapine extended treatment or modified electroconvulsive therapy (MECT) add-on therapy (**Phase 3A**); alternatively, non- clozapine users in phase 2 will be assigned to clozapine or another SGAs not previously used in phase 1 and 2 (**Phase 3B**).

The follow-up phase is for patients who respond well among the three treatment phases or non-responders experiencing the treatment phases. Refractory patients will not be provided with study medication and will be followed naturalistically with their choice of treatment. For patients who relapse after meeting one of the phase response criteria will be defined as discontinued. The interval from response to relapse and the potential causes for recurrence will be recorded.

3.2.1. Rationale of antipsychotic medications included in phases 1 and 2

In phase 1, olanzapine, risperidone, amisulpride, aripiprazole and perphenazine are selected. Several researches have assessed the efficacy and safety of SGAs in FES patients (Kahn et al., 2008; McEvoy et al., 2007; Robinson et al., 2015; San et al., 2012). A comparative review indicated that there was little difference in therapeutic efficacy among SGAs in FES patients (Salimi et al., 2009). Currently, olanzapine and risperidone are the most widely used SGAs in China (Duggan et al., 2005; Edwards, 1994). Amisulpride and aripiprazole are selected for their unique receptor-affinity properties (El-Sayeh and Morganti, 2006; Mota et al., 2002); Amisulpride has a selective and high affinity for dopamine (D3/D2) receptors (Mota et al., 2002), and aripiprazole is a partial D2 receptor agonist and an 5-HT2 receptor antagonist (El-Sayeh and Morganti, 2006). Perphenazine, a midpotency drug, was selected as the representative of FGAs for the following reasons: first, its clinical values in schizophrenia have been proved by the CATIE study (Lieberman et al., 2005); second, perphenazine is inexpensive and is broadly used in China, which is still a developing country.

In phase 2, olanzapine, amisulpride and clozapine are selected. For the first-trial failed patients, we place greater emphasis on the efficacy (Osser et al., 2013), while still heightening awareness of the toxicities of some of these agents. The reason why we selected olanzapine and amisulpride in phase 2 is that two meta-analyses showed that

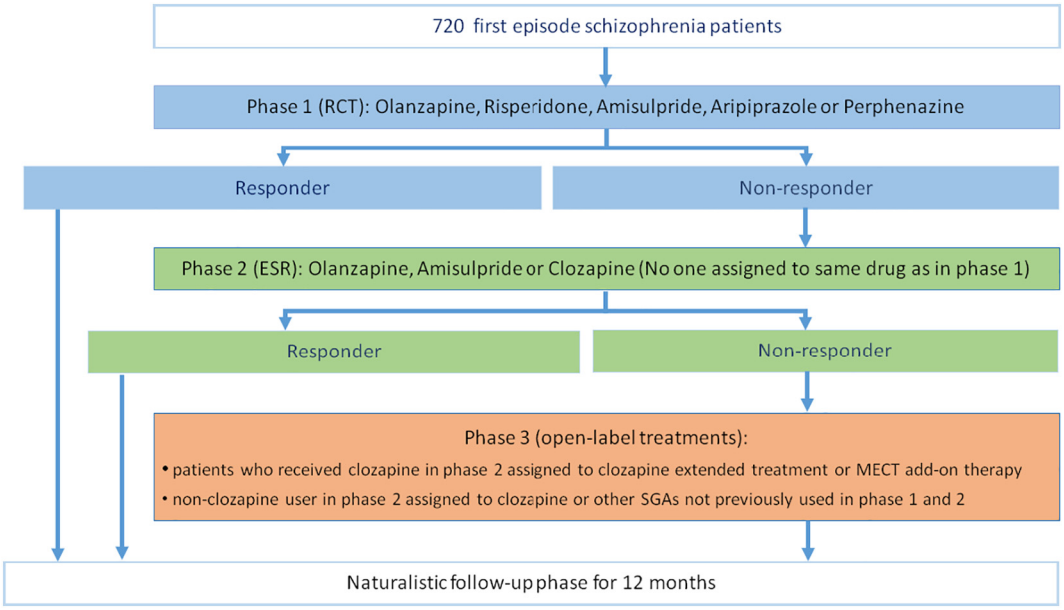

Fig. 1. The SMART-CAT trial design. Responders stay on assigned medication for duration of 12-month treatment period, and non-responders move to the next phase to receive a new treatment. RCT = randomized controlled trial, ESR = Equipoise-Stratified randomization.

amisulpride and olanzapine were more effective than any other SGAs (except for clozapine) in improving the overall symptoms in schizophrenia patients (Huhn et al., 2019; Leucht et al., 2013).The results from the European First-Episode Schizophrenia Trial (EUFEST) also indicated that amisulpride and olanzapine were more effective than other antipsychotics in FES patients (Boter et al., 2009; Kahn et al., 2008). As for clozapine, some studies have revealed that clozapine is superior for treatment-resistant schizophrenia and is the current recommendation for treatment-resistant patients (Galletly et al., 2016; Remington et al., 2017). Recent studies showed benefit of early clozapine treatment initiation in schizophrenia patients (Agid et al., 2007; Remington et al., 2013),and some indicated that clozapine treatment delay could lead to negative outcomes (Shah et al., 2018; Tang et al., 2017; Ucok et al., 2015); Moreover, the results of OPTiMiSE suggested that clozapine could be started early in non-responding first-episode patients (Kahn et al., 2018).

3.2.2. Patient and clinician involvement in decision making in phases 2 and 3

In phase 2, the Equipoise-Stratified Randomization is designed to allow patients or their psychiatrists to exclude inappropriate treatment based on previous experience or anticipated risk (Jin et al., 2013; Lavori et al., 2001). Such design will be able to improve enrollment and retention rates. In phase 3, shared decision making is essential for treatment-refractory patients who failed twice in this trial. In addition, clozapine is involved in phases 2 and 3. Treatment with clozapine is open-label and regular blood monitoring is required for its possible risk of granulocytopenia.

3.3. Treatment

3.3.1. Pharmacological treatments

Initial dosage and recommended dosing for pharmacological treatments are listed in Table 1. The drug dosages will be adjusted based on the clinicians' judgment, combining patients' therapeutic response and potential side-effects.

The initial titration period is one week for all treatments, and later the antipsychotics dosages can be adjusted by clinicians based on the patients' response and side-effects. If an assigned treatment failed, the patients will move to the next phase to receive a new treatment with a recommended cross-titration interval for no more than 2 weeks (usually one week).

Clinicians can prescribe adjunctive and concomitant medications according to the patients' conditions; and clinicians are strongly instructed to record the reasons for these prescriptions. Antipsychotics other than the assigned study medicines are not allowed. The antipsychotic cannot be discontinued or changed without considering the treatment a failure.

3.3.2. Modified electroconvulsive therapy

Combined clozapine-MECT therapy in phase 3 is recommended as a safe and effective treatment for clozapine-resistant schizophrenia patients (Petrides et al., 2015). Participants will sign a separate informed consent for MECT before the standard institutional MECT procedures. MECT will be administered three times per week for the first 2 weeks, then twice a week for the next 2 weeks. The total treatment duration is about one month.

3.4. Outcomes

3.4.1. Primary outcome

Subjects will attend several follow-up visits for clinical examinations and assessments by the following Schedule of Events (Table 2).

The primary outcome for the treatment phase is the treatment efficacy rate, which is defined as a 40% reduction or more of the total score in the Positive and Negative Syndrome Scale (PANSS) (Leucht et al., 2005; Samara et al., 2015). This level of improvement is associated with the level of “much improved” in the Clinical Global impressions-

Table 1
Initial dosage and recommended dosing for pharmacological treatments.

Medications	Initial dosage	Recommended dosing
Olanzapine	5–10 mg	5–20 mg/day
Risperidone	1–2 mg	2–6 mg/day
Amisulpride	200–400 mg	400–1200 mg/day
Aripiprazole	5–10 mg	10–30 mg/day
Perphenazine	2–4 mg	6–36 mg/day
Clozapine in phase 2	25–50 mg	200–400 mg/day
Clozapine in phase 3	25–50 mg[a]	200–600 mg/day

[a] This initial dosage is for patients who first used clozapine in phase 3.

Table 2
Schedule of events.

Items	V0	V1	V2	V3	V4[a]	V5	V6[a]	V7	V8[a]	V9	V10	V11
	Screening	Baseline	W2	W4	W8/M2	W12	W16/M4	W20	W24/M6	M8	M10	M12
Informed consent	√											
Screening, diagnosis and laboratory tests												
Clinical diagnosis	√	√										
Physical examination	√	√										
Demographic information	√	√										
Uremic screening for drug abuses (if necessary)	√											
Urine pregnancy test(if necessary)	√											
MRI scan or CT scan(if necessary)	√											
Clinical monitoring and lab tests[b]		√		√	√	√	√	√	√	√	√	√
Measures and assessment												
Clinical and functional assessments												
CRDPS[c]		√	√	√	√	√	√	√	√	√	√	√
Positive and Negative Syndrome Scale (PANSS)		√	√	√	√	√	√	√	√	√	√	√
Calgary Depression Scale for Schizophrenia (CDSS)		√	√	√	√	√	√	√	√	√	√	√
Clinical Global Impression Scale-Severity (CGI-S)		√	√	√	√	√	√	√	√	√	√	√
UPSA-B[d]		√			√		√		√			√
Heinirich Quality of life Scale (HRQOL)		√			√		√		√			√
Medication Satisfaction Questionnaire (MSN)		√			√		√		√			√
Subjective Well-being under Neuroleptics (SWN)		√			√		√		√			√
Side effects and adverse events measures												
The Barnes Akathisia Scale (BAS)		√	√	√	√	√	√	√	√	√	√	√
Simpson-Angus Extrapyramidal Side Effects Scale (SAS)		√	√	√	√	√	√	√	√	√	√	√
Abnormal Involuntary Movement Scale (AIMS)		√	√	√	√	√	√	√	√	√	√	√
Arizona Sexual Experiences Scale (ASEX)		√	√	√	√	√	√	√	√	√	√	√
Three Factor for Eating Question-21(TFEQ-21)		√			√		√		√			√
Visual Analogue Scale (VAS)		√			√		√		√			√
Physical Activity Evaluation		√			√		√		√			√
Neurocognitive assessments												
The MATRICS consensus cognitive battery (MCCB)		√			√		√		√			√
NBSC[e]		√			√		√		√			√
Neuroimaging(optional)		√			√		√					
Pharmacoeconomics assessments		√			√		√		√	√	√	√
Blood sample[f]		√			√		√					
Treatment record table												
Medication record table		√	√	√	√	√	√	√	√	√	√	√
Adverse events (AEs)		√	√	√	√	√	√	√	√	√	√	√
Study enclosure table												√

[a] V4, V6 and V8 refer to the end of phase 1, phase 2 and phase 3 respectively; responders in phase 1, 2 or 3 will be naturalistic followed-up bimonthly for the duration of 12-month treatment period, non-responders will move to the next phase to receive a new treatment and be followed-up monthly, whatever the response at the end of phase 3, the subjects will be followed-up bimonthly.
[b] Clinical monitoring and lab tests include vital signs, blood count, liver function, renal function, thyroid function, serum prolactin level and QTc interval, furthermore, body weight, waist circumstance, glucose, insulin and lipids profiles are also examined regularly.
[c] CRDPS=Clinician-Rated Dimensions of Psychosis Symptom severity.
[d] UPSA-B=UCSD Performance-based Skills Assessment-Brief.
[e] NBSC=New cognitive battery for patients with schizophrenia in China.
[f] Blood samples are collected for later pharmacogenomics studies.

Improvement (CGI-I) (Leucht, 2014). As for the naturalistic follow-up phase, time to all-cause treatment failure, marked by its discontinuation is selected as the primary outcome, for it reflects both efficacy and side effects (Fleischhacker et al., 2005; Stroup et al., 2003), and all-cause discontinuation is defined as discontinuing for any reasons (including poor efficacy, intolerance of adverse reactions, poor compliance et al.). (Fleischhacker et al., 2005; McEvoy et al., 2007; San et al., 2012; Stroup et al., 2003).

3.4.2. Other outcome measures

3.4.2.1. Clinical and functional assessments. In addition to PANSS (Kay et al., 1987), Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPS) (Barch et al., 2013; Regier et al., 2013), Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992) and Clinical Global Impression Scale-Severity (CGI-S) (Padhi and Fineberg, 2010) are selected for clinical assessment of patients with schizophrenia. The University of California, San Diego (UCSD) Performance- based Skills Assessment-Brief (UPSA-B) (Mausbach et al., 2011) will be used to evaluate the social function; The Heinirich Quality of life Scale (HRQOL) (Heinrichs et al., 1984) is adopted for the evaluation of life quality. Medication Satisfaction Questionnaire (MSN) (Kalali, 1999) and the Subjective Well-being under Neuroleptics (SWN) (Naber et al., 2001; Naber et al., 1994) will be used to assess whether participants were satisfied with their assigned treatments.

3.4.2.2. Side effects, adverse events and clinical monitoring. Given the substantial clinical experience, we will use the following scales to evaluate the potential side effects of antipsychotics. The Barnes Akathisia Scale (BAS) (Barnes, 2003), Simpson-Angus Extrapyramidal Side Effects Scale (SAS) (Simpson and Angus, 1970) and Abnormal Involuntary Movement Scale (AIMS) (Listed, 1988) are used to assess extrapyramidal adverse effects; the Arizona Sexual Experiences Scale (ASEX) (McGahuey, 2000) will be employed to assess sexual dysfunction. Each participant's vital signs, blood count, liver function, renal function, thyroid function, serum prolactin level and QTc interval will be examined routinely. Metabolic side effects of antipsychotics, especially body weight, waist circumstance, glucose, insulin and lipids profiles, will be monitored regularly. The Three-Factor Eating Questionnaire (TFEQ-R21) (Rosnah et al., 2013), Visual Analogue Scale (VAS) and Physical Activity Evaluation will be used to assess the participants' eating and movement status at regular intervals.

3.4.2.3. Neurocognitive assessments. The MATRICS consensus cognitive battery (MCCB) has been widely used for cognitive function assessment in schizophrenia patients (Kern et al., 2008; Nuechterlein et al., 2008), and it has been validated in China (Shi et al., 2015). Recently, Shi et al. introduced the "new" cognitive battery for patients with schizophrenia in China (NBSC), which includes 4 tests from the MCCB and 5 new tests (Trial making A, BACS, HVLT-R learning and recall, CPTIP, dominant hand Grooved Pegboard, Color Trails I and II, PASAT). It was proved to be more sensitive in detecting cognitive impairment of schizophrenia in China (Shi et al., 2019); As a result, the 5 additional tests are also selected in this study, and the NBSC will be further verified in first-episode patients.

3.4.2.4. Neuroimaging. About 200 participants will undergo multimodel MRI examinaitons (structural MRI, functional MRI and Magnetic Resonance Spectroscopy). Baseline and two follow-up scans (two and four months after baseline) will be conducted. We hypothesize that therapeutic response in phases 1 and 2 could be identified by structural, functional and metabolic differences in brain in schizophrenia patients.

3.4.2.5. Pharmacoeconomics and cost-effectiveness assessments. Traditional antipsychotic treatments were mainly evaluated by their efficacy and side effects, which is important but not enough. For example, the SGAs with high cost may not be superior to FGAs with a low cost in the real world settings (Hastrup et al., 2013; Park and Kuntz, 2014; Rosenheck et al., 2016). In this study, we evaluated the direct medical costs (for example, antipsychotics costs, medical examinations costs, health care and service costs and adverse events costs) and indirect costs (such as traffic, nursing, and losing of labor) of the treatments. At the same time, the quality of life parameters are collected, which will be combined with symptoms to generate quality-adjusted life years (QALYs) (Nemeth et al., 2018; Rabinowitz et al., 2013).

4. Statistical methods and analytic plan

Analyses will be conducted on the intent-to treat population and full analysis set. The demographic data of the three phases will be compared between groups by parametric test or non-parametric test according to whether they are normally distributed. We use means and standard deviations to describe the normal distribution data, median and percentile to describe the nonnormally distribution data. Further tests were stopped once a comparison was found not to be significant at a two-sided alpha level of 0.05.

4.1. Phase 1

The primary analysis will consist of a comparison of all-cause treatment discontinuation rates between the perphenazine treatment group and the pooled SGAs treatment groups (olanzapine, amisulpride, aripiprazole, risperidone) in phase 1 from the beginning of the trial to the following period (12 months), which will be compared between treatment arms with a log-rank test at a two-sided alpha level of 5%. The secondary analysis will consist of the comparison of treatment efficacy among 5 antipsychotics groups. Chi-square test will be used to test whether the response rate is significantly different among 5 groups. Besides, the mean score change in PANSS between groups will be analyzed using Kruskal Wallis test. To control for type I error due to multiple comparisons, a hierarchical testing procedure will be applied for the primary and key secondary end points.

4.2. Phase 2

The primary analysis will consist of a comparison of treatment efficacy rate in clozapine treatment group and the pooled SGAs treatment groups (olanzapine, amisulpride). Chi-square test will be used to test whether the response rate is significantly different between clozapine and other SGAs. Logistic regression analyses will be used to control for covariates such as the duration of untreated psychosis (DUP) and the severity of disease. The secondary analysis will consist of a comparison of all-cause treatment discontinuation rates between the clozapine group and the pooled SGAs groups (olanzapine, amisulpride) from the beginning of phase 2 to the planned following period, which will be compared between treatment arms with a log-rank test at a two-sided alpha level of 5%.The DUP and the severity of disease will be corrected with Cox regression. In the second step of the primary analysis and the secondary analysis, the two atypical treatment groups will be compared with clozapine group respectively. To control for type I error due to multiple comparisons, a hierarchical testing procedure was applied.

4.3. Phase 3

This is an exploratory phase. In Phase 3A, Chi-square test will be used to compare the response rate between clozapine extended group and MECT add-on therapy group. In Phase 3B, Chi-square test will be used to compare the response rate between clozapine group and the pooled SGAs groups (olanzapine, amisulpride, risperidone, aripiprazole). And all-cause treatment discontinuation rates will also be examined by a log-rank test at a two-sided alpha level of 5%.

5. Summary

This article described the rationale, aims and design of the SMART-CAT schizophrenia trial. The optimal treatment in the early phase of schizophrenia is of crucial importance. However, some critical questions remain unanswered and they still puzzle the clinicians. For example, how to perform the sequential treatment after the first antipsychotic drug fails? When should we initiate clozapine treatment? Is clozapine more effective than other SGAs for patients who fail their first antipsychotic trial? This study intends to compare the effectiveness of commonly used antipsychotic drugs in FES patients using a SMART design. Based on the combination of sequential therapy and dynamic therapy, the SMART design is more suitable to assess the effectiveness of treatment options in the real-world clinical setting. We hope that our study will provide guidance for the optimal treatment algorithm for FES patients.

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CRediT authorship contribution statement

All authors were responsible for the design of study and data acquisition, and the writing of the paper.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

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