




BMJ Open Effectiveness and utility of an electronic intervention for appropriate benzodiazepine and Z-drugs prescription in psychiatric clinics: protocol for a multicentric, real-world randomised controlled trial in China

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ABSTRACT

Introduction Benzodiazepine receptor agonists (BZRAs), which include benzodiazepines and Z-drugs, are the most commonly prescribed psychotropic drugs worldwide, and their inappropriate use places a significant burden on public health. Given the widespread use of BZRAs in psychiatric settings, this condition may result from doctors' improper prescribing. Researchers have developed an electronic intervention system to assist psychiatrists in prescribing BZRAs appropriately. This study aims to determine the efficacy and utility of electronic intervention in reducing improper BZRAs prescriptions in real-world psychiatric outpatient settings.

Methods and analysis A multicentre randomised controlled research study will be conducted in real-world settings with licensed psychiatrists with prescription qualifications from five of Chinese most significant regional hospitals that provide high-quality mental healthcare. Participants will be 1:1 randomly assigned to receive a 3-month electronic intervention (11 related information pushing and 3 online lectures) or be placed on a waiting list. The primary outcome is the change in the proportion of inappropriate BZRAs prescriptions between the baseline period (3 months before the intervention) and 3 months after the intervention. Secondary outcomes will be examined at baseline, the third month and the sixth month. The secondary outcomes include psychiatrists' knowledge and attitudes about appropriate BZRAs prescription, the associated side effects of BZRAs among patients and self-efficacy. To measure the utility, intervention assessment and system utilisation data from the intervention group were collected.

Ethics and dissemination The institutional review board and ethics committees of Shanghai Mental Health Center, Second Xiangya Hospital, West China Hospital, Guangji Hospital and Wuhan Mental Health Center approved the study. After the study is completed, the results will be published in peer-reviewed journals or presented at conferences. If the educational materials are effective, they are available to the general public.

Trial registration number NCT03724669; Pre-results.

Strengths and limitations of this study

- This will be the first study to evaluate the effectiveness of the psychiatrist-targeted electronic intervention on inappropriate BZRAs prescriptions in Chinese psychiatric outpatient clinics.
- This is a multicentre study, and five of the most influential hospitals in the east, central and western parts of China were chosen because they have the highest number of outpatient visits for mental health services and thus may be indicative of the country's current situations.
- Because this is an open-label, real-world study, it is difficult to blind participants and investigators to group allocation.

INTRODUCTION

Benzodiazepine receptor agonists (BZRAs), which include benzodiazepines (BZDs) and Z-drugs (eg, zopiclone, zaleplon and zolpidem), are one of the most common prescribed psychotropic drugs given in clinical practice throughout the world.¹ BZRAs bind to specific sites on γ -aminobutyric acid (GABA) type A (GABA_A) receptors, exerting sedative effects and promoting sleep by amplifying GABA's inhibitory effect.² As a result, they are mostly used in psychiatric settings to treat insomnia, anxiety and panic disorder.^{3–6} Although BZDs and Z-drugs have distinct receptor affinities for GABA_A subunits, their pharmacological profiles, efficacy and side effects are identical.⁷ BZRAs adverse medication reactions are connected to an increased risk of cognitive impairment, psychomotor abnormalities, falls, hip fractures and automobile accidents,^{7–10} which greatly burden patients and society. Additionally, prolonged

use of BZRAs may develop tolerance, requiring dose adjustment to obtain the desired effect; otherwise, withdrawal symptoms such as anxiety, sleeplessness and restlessness arise.^{11 12} As a result, clinical guidelines recommend that BZRAs are relatively safe for short-term use (generally no more than 4 weeks).¹³

However, despite growing awareness of the hazards associated with BZRAs, the problem of inappropriate prescription (long-term, overdose or over-indications) persists globally.^{14 15} For instance, a retrospective observational study found that approximately 5.2% of US individuals (aged 18–80) used BZDs in 2008, with one-quarter receiving them for an extended period (≥ 120 days).¹ In British research, only one-third of patients were assessed to be using BZRAs appropriately as per indication.¹⁶ According to a recent study conducted by our research team, approximately 3.0% of outpatients were using BZRAs in a hazardous manner (co-occurrence of overdose and long-term use) and 55.9% of patients were prescribed with an over-indication via prescriptions analysis in Chinese psychiatric outpatient settings (unpublished).

Nowadays, the interventions for BZRAs use are primarily patient-oriented, and may include self-managed or monitored gradual dose reduction, educational literature, minimal interventions or physician-administered cognitive behavioural therapy, to increase patients' knowledge of the possible dangers of BZRAs.^{17–20} While some physicians are aware of the potentially detrimental effects of long-term BZRA usage, they assert that it is difficult to convince patients to cease the medications. They lack suitable non-pharmacological therapeutic approaches and information to prevent improper BZRAs use.²¹ Interventions for service providers, such as prescribing doctors, generally include legislation restriction to limit prescriptions, education and providing resources for medication replacement among general practitioners.¹⁷ Moore *et al*²² suggested that BZDs be rigorously regulated and prescribed only by medical experts such as psychiatrists. This, however, is not the case. According to a recent cohort study, prescription by psychiatrists is one of the clinical correlates of long-term BZDs use.²³

To the best of our knowledge, there is no associated evidence about intervention for psychiatrists to reduce the inappropriate prescribing of BZRAs. Due to the vast population in China²⁴ and the nature of their professions in dealing with troubled people,²⁵ it is difficult for psychiatrists to devote a full length of time to systematic studies on the most recent BZRAs-related knowledge. Furthermore, non-specific BZRAs knowledge, inadequate information of the evidence-based alternative treatment and difficulties implementing medicine according to recommendations in clinical practice contributed to this situation.¹⁸

New technologies, such as web-based and mobile-based health services, demonstrate potential effects and flexibility in healthcare services,^{26 27} also providing a powerful and easy platform for distant education. Our research

team created an intervention system based on WeChat, China's most popular social media application, to perform various functions such as educational intervention, assessment, feedback, notification and data management.

The electronic intervention system for appropriate BZRAs use by prescribing psychiatrists was developed using the most recent evidence-based guidelines and expert consensus. It was created after extensive debate and approval by Chinese addiction experts. The intervention content consists of four modules: the rational use of BZRAs, their rational use in common mental disorders, the quick identification and brief intervention for BZRAs use disorders and their use for special groups, which are delivered in the form of 11 related information pushing and 3 online lectures through the electronic intervention system.

The major goal of this study is to determine whether the electronic intervention is beneficial in reducing psychiatrists' inappropriate prescription habits. The secondary goal is to evaluate the intervention's impact on their knowledge and attitudes about appropriate BZRAs prescription, self-efficacy, common side effects in prescribing patients and whether the electronic intervention has good therapeutic utility in the real world.

METHODS AND ANALYSIS

Trial design

This is a real-world, multicentre, open-label, randomised and controlled clinical trial involving two parallel groups.

Study setting and recruitment

Participants will be recruited from five of China's most significant regional tertiary hospitals that provide the highest-quality mental health treatments in the east, central and western regions (three psychiatric hospitals and two general hospitals). All hospitals (Shanghai Mental Health Center, Second Xiangya Hospital of Central South University, West China Hospital of Sichuan University, Affiliated Guangji Hospital of Soochow University and Wuhan Mental Health Center) have the highest number of outpatient visits for mental health services in their respective areas. The study's advertisement is sent to these five hospitals and given to potential volunteers. Interested psychiatrists who match the eligibility criteria will be recruited in these hospitals.

Eligibility criteria

The study will recruit licensed psychiatrists with prescription qualifications. The inclusion criteria are as follows: (1) at least 3 years working experience as a psychiatrist; (2) providing outpatient services for at least 1 year with a frequency of more than once per week; and (3) willingness to accept electronic interventions for the appropriate BZRAs prescription. The exclusion criteria are as follows: (1) they will retire within 6 months; and (2) they refuse to retrieve their prescription information from the outpatient database.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Description of the electronic intervention system (TiDieR checklist)

Brief name

The Intelligent Addiction Intervention System is an electronic intervention system that uses WeChat to educate psychiatrists about BZRAs and to promote self-monitoring.

Why: intervention theory

Self-monitoring activities such as assessment and education according to social cognitive theory,²⁸ can boost self-efficacy beliefs, hence facilitating motivation and behaviour.

Intervention providers

The distant intervention is offered indirectly through text or video by mental health or addiction professionals. Five hundred ninety-five physicians were surveyed regarding their attitudes and knowledge of BZRAs. The initial teaching content was based on the surveys above, the most recent evidence-based guidelines and experts' consensus^{5 12 29-32} regarding the appropriate use of BZRAs. Then, a focus group of eight mental health or addiction experts with at least 10 years of experience was convened to discuss in detail the four topics, which included the basis for BZRAs use, their rational use in common mental disorders, the rapid identification and brief intervention for BZRAs use disorders and their use in special groups. Transcripts of the recordings were created, and thematic analysis was performed to confirm the important components. Additionally, the intervention content was presented to two Chinese addiction experts for review and consensus on the final form of educational materials (table 1).

Where: intervention location

The intervention is handled online and in personal private time via the WeChat official account platform, which comprises three parts: the users' WeChat page on mobile devices, an administrator web page for investigators and a backend server for data storage. The platform contains a range of modules, including intervention, assessment, feedback and notification.

Participants who follow the research team's WeChat official account platform have access to two primary menu buttons on the individual chat platform: User centre and Intervention & Assessment (figure 1A,B). The User centre presents the participant with tabs of Accumulate points, Previous message and Feedback. The accumulate points page allows participants to check their points from the Intervention. The Previous message tab allows them to review the intervention content repeatedly. If users encounter any technical difficulties, they can submit a note via the Feedback tab. The Intervention & Assessment option allows users to view a list of tasks (intervention or

Table 1 The educational contents for the standardised use of BZRAs

| No. | Content |
|--|---|
| Module 1: The basis for rational use of BZRAs | |
| 1 | Pharmacological effects and rational use of BZDs |
| 2 | Pharmacological effects and rational use of Z-drugs |
| 3 | The current situation of BZRAs abuse* |
| Module 2: Rational use of BZRAs in mental disorders | |
| 4 | Sleep physiology and rational use of BZRAs in insomnia |
| 5 | Non-pharmacological interventions for insomnia |
| 6 | Clinical practice of diagnosis and treatment for insomnia* |
| 7 | Rational use of BZRAs in other mental disorders |
| Module 3: Abuse, dependence and brief intervention of BZRAs | |
| 8 | Rapid identification for BZRAs use disorders |
| 9 | Management for long-term use of BZRAs |
| 10 | Management and regulations of BZRAs prescription |
| 11 | The brief intervention for BZRAs use disorder* |
| Module 4: Other | |
| 12 | Physician-patient communication skills among hazardous use population |
| 13 | Situations that BZRAs should be banned or used with caution (case reports) |
| 14 | Rational use of BZRAs in special populations (including the elderly, drug abusers, pregnant and lactating women, patients with physical diseases, children and adolescents) |

*The educational contents are delivered in the form of online lectures.
BZDs, benzodiazepines; BZRAs, benzodiazepine receptor agonists.

assessment content) that are either pending completion or have been completed. Each intervention comprises an article that may include visual, video or audio elements and two to four matching exercises (figure 1C,D). To encourage users, they can receive six points for reading the materials and four points for completing the tasks. The assessment module incorporated participant-completed online surveys. Additionally, if users do not complete the intervention or evaluation on time, the system immediately sends them a reminder. After three alerts, the centre investigator contacted the participants personally by phone when the task is not completed.

The administrator web page (figure 2) enables investigators to control group assignments, configure intervention and assessment content, track implementation progress and send necessary alerts to participants to encourage adherence. Additionally, they can obtain feedback from users regarding any technical or other issues encountered during use. Each centre has its name and password to access the administrator's web page and a

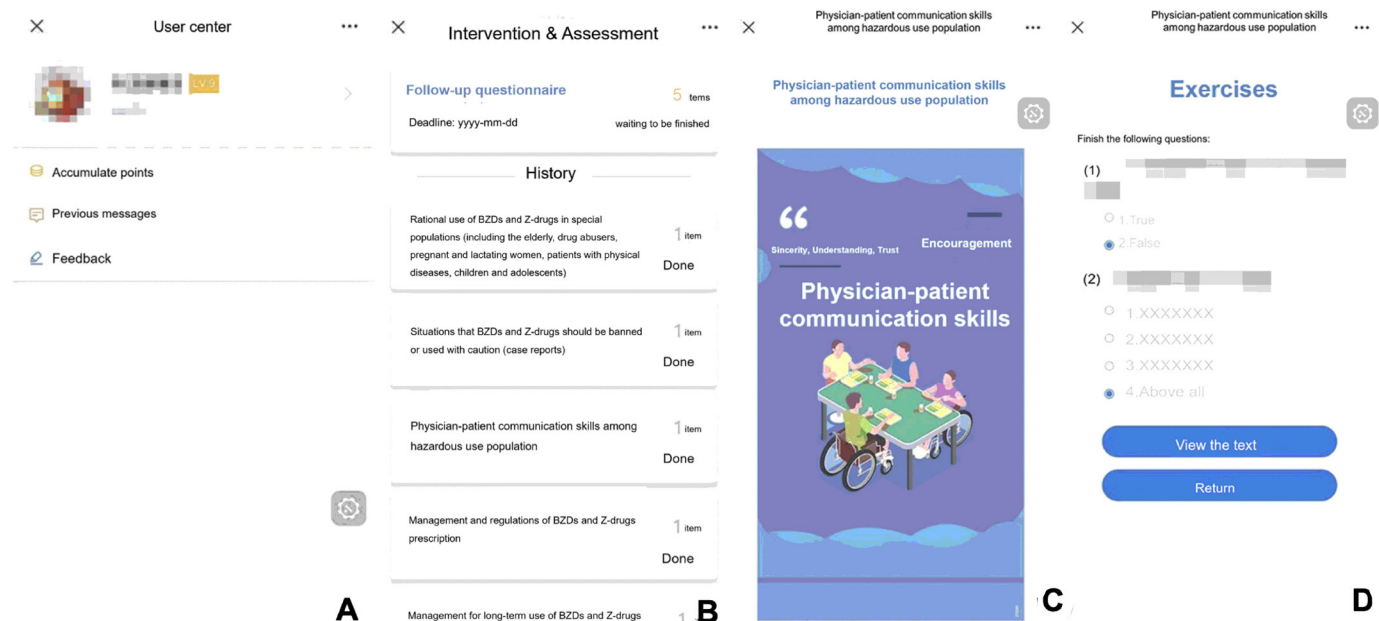


Figure 1 The screenshot of the WeChat official account platform for users in the mobile devices: (A) User centre interface, (B) Intervention & Assessment interface, (C) educational article of the Intervention module, (D) corresponding exercise after text reading. The page which is actually in Chinese is translated into English. BZDs, benzodiazepines.

principal investigator to supervise the participants at their hospital.

Procedures and materials

Psychiatrists who match the eligibility criteria will be enrolled in the study after signing electronic informed consent and gaining access to the WeChat official account platform on their cellphones. Demographic data and baseline assessments of secondary outcomes (table 2) will be obtained before group assignment. After that, participants will be randomised

to receive electronic interventions or be placed on a waiting list for 3 months. Participants were required to complete online questionnaires after the third and sixth month regarding their knowledge and attitudes towards BZRAs prescription, common side effects in prescribing patients and self-efficacy. At the end of the third month, the utility of electronic intervention will be evaluated online. Meanwhile, the outpatient clinics' prescription database collected their consecutive monthly prescription data for BZRAs (3 months

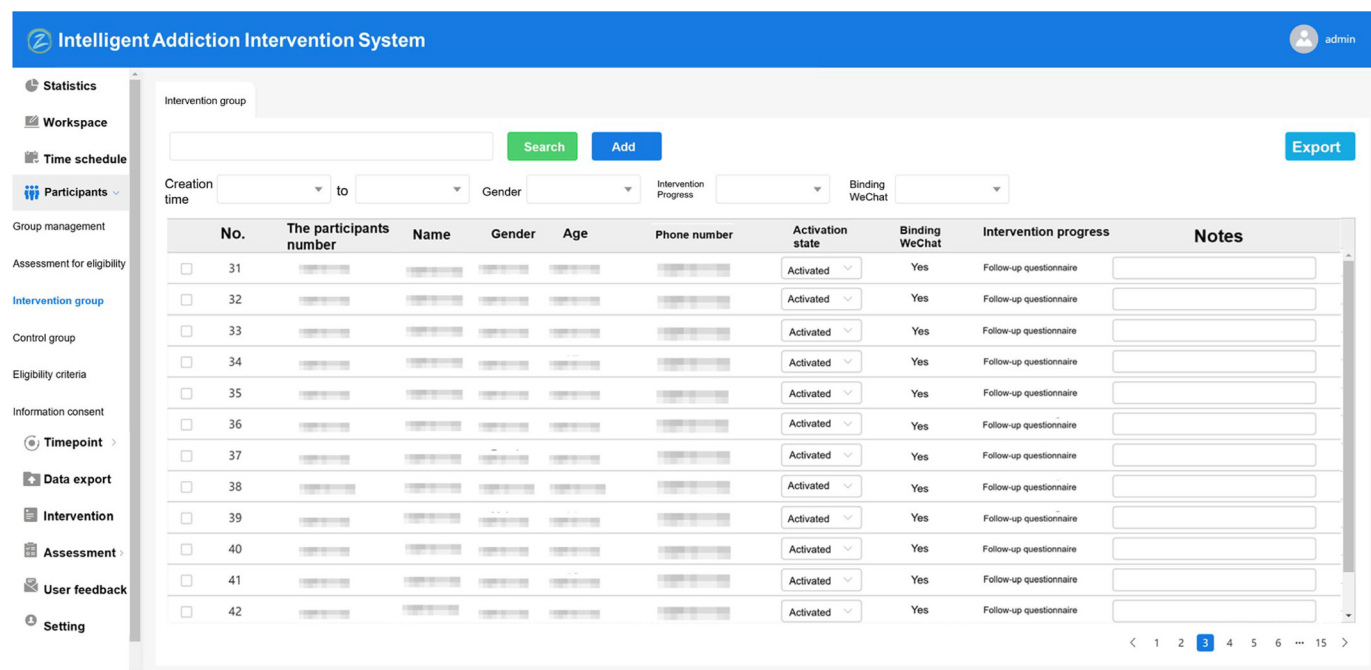


Figure 2 The screenshot of the administrator web page for investigators. The web page which is actually in Chinese is translated into English.

Table 2 Time point for the schedule of assessments

| Time point | Assessment period | | | |
|--|-------------------|----------|---------|---------|
| | -3 month | Baseline | 3 month | 6 month |
| Primary outcome | | | | |
| Proportion of inappropriate BZRAs prescription | ● | ●● | ●● | ● |
| Secondary outcomes | | | | |
| BZRAs-related knowledge | | x | x | x |
| Attitude towards BZRAs prescription | | x | x | x |
| Common adverse effects in prescribing patients | | x | x | x |
| Self-efficacy | | x | x | x |
| Utility of the electronic intervention | | | x | |
| Utilisation of the electronic intervention | | ● | ● | |

BZRAs, benzodiazepine receptor agonists.

before and after the intervention period). The study's flow chart is depicted in [figure 3](#). The following are the primary and secondary outcomes.

Primary outcome: proportion of inappropriate BZRAs prescription

The prescription data for BZRAs for each psychiatrist was retrieved from the outpatient prescription database at each institution during the baseline period (3 months before the intervention) and the intervention period (0–3 months) and the follow-up period (3–6 months). The database includes anonymous prescription information such as (1) the patient's unique code and demographic information; (2) the doctors' unique code; and (3) diagnosis and prescription information on medicine kind, dose, duration, usage and so on. The amounts of various BZRAs will be first converted

to DME, and the cumulative daily DME usage for a patient with each prescription.³³ Then, based on the collected daily DME usage, the average daily dosage and continuous days of use per prescription were computed. Prescriptions written in compliance with any of the following conditions are deemed inappropriate: overdose, long-term usage or use for contra-indications. If the daily DME dose exceeds 40mg/day, the prescription is an overdose. For the prescription length restrictions of no more than 30 days in China, we conservatively chose a 90-day cut-off as long-term use. Over-indication use is defined as the use, not by any indications approved by the Chinese FDA.

Secondary outcomes

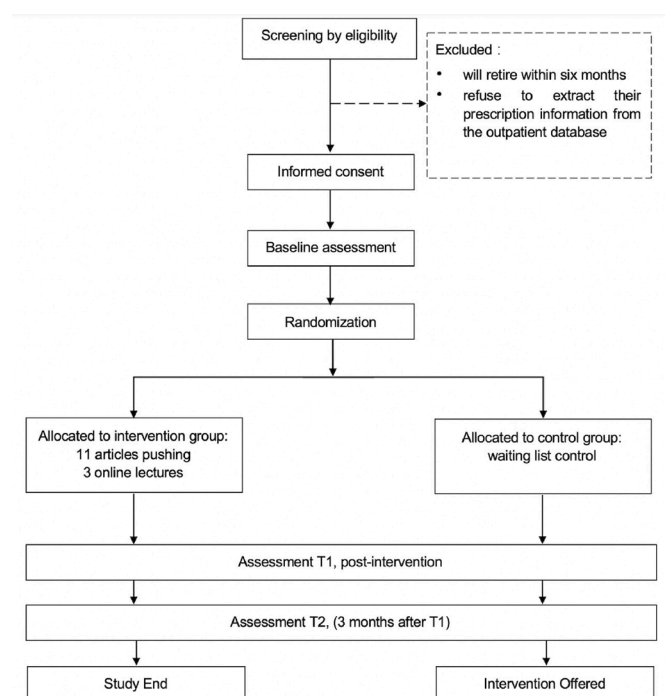
BZRAs-related knowledge: BZRAs-related knowledge is tested using 22 true or false self-created questions about the pharmacological effects, an indication of use, identification and treatment of addiction and adverse effects.

Attitude towards BZRAs prescription: A 14-item self-created questionnaire with a 4-point Likert format is used to assess participants' attitudes toward various aspects of BZRAs prescription, such as an indication of use, adverse effects, related guidelines, drug regulations, identification and treatment of BZRAs use disorders, use among special populations and BZRAs training.

Common adverse effects in prescribing patients: The psychiatrists are asked to rate how frequently the common side effects of BZRAs occur in their prescribing patients on a scale of 'Never' to 'Always'. The questionnaire contains eight items and is scored on a 4-point Likert scale, with one signifying the lowest frequency.

Self-efficacy: To assess participants' self-efficacy, an adapted 10-item version of the General Self-Efficacy Scale (GSES) was used. Self-efficacy, refers to one's overall confidence in dealing with various difficult situations.³⁴ Each question is graded on a 4-point Likert scale. The Chinese version of the GSES is reliable and valid.³⁵

Electronic intervention utility and utilisation: Participants in the intervention group will be asked to complete

**Figure 3** Flow chart of participants.

an online 17-item questionnaire to evaluate the intervention's forms, contents, efficacy and clinical generalisation. Furthermore, utilisation data, such as accumulated scores, mean number and length of time reading or watching, were automatically stored in the administrator's WeChat and DingTalk backend systems.

Randomisation and blinding

Participants will be randomised in a 1:1 ratio using block randomisation tables prepared by SPSS Statistics V.24 (IBM Corp) and assigned to receive either 3-month electronic interventions or be placed on a waiting list. This is an open-label real world study, and it is obvious that blinding participants and investigators to group allocation is difficult. The intervention group was instructed not to discuss the educational content or lecture videos with the control group.

Intervention

Intervention group: Psychiatrists in the intervention group will receive a 3-month electronic educational intervention covering information on standardised use of BZRAs, consisting of two main components: (1) educational articles delivered once a week (11 times total) via the WeChat official account platform, and (2) three additional online lectures from addiction specialists via the DingTalk platform, an intelligent working platform created by Alibaba Group. The comprehensive information about the online lectures will be given to the WeChat individual messaging platform twice, one a day and once an hour before the event. On the DingTalk platform, participants can attend live lectures or examine the videos at any time with arbitrary intensity.

Control group: Participants in the control group will complete the assessment modules without any educational information regarding the online lectures. They acquired educational texts and view online lectures after completing their study.

Tailoring and fidelity

Participants assigned to the intervention group receive the identical intervention material and the duration and intensity of the voluntary intervention. The participants will be observed and reminded by the lead investigator in each centre to ensure that the intervention is carried out according to protocol. If users do not complete the intervention or evaluation on time, they send them an automatic reminder. After three notifications, the investigator contacts the participants directly via phone when the task has not been completed. The electronic intervention's utilisation data is also used to assess adherence.

Discontinuation

The study's endpoint is after the sixth month, and participants may withdraw at any moment for any reason during the study term. If possible, the reasons for leaving the study will be documented.

Sample size

A previous study found that a multistrategic intervention, involving local media involvement, treatment guidelines and consumer information, and education and training from medical professionals might result in a 19% reduction in BZDs prescriptions.³⁶ Assuming a 95% confidence level, 90% statistical power and a dropout rate of 20%, a sample size of N=54 individuals per group was needed.

Statistical methods

All analyses based on the intention-to-treat principle will be carried out using IBM SPSS Statistics V.24.0 and a significant level of $p < 0.05$ (two-sided). To compare the base-lines of the two groups, the Student t-test for continuous variables and the χ^2 for categorical variables will be used. The proportion of inappropriate BZRAs prescriptions between the two groups is calculated 3 months before baseline, during the intervention period and 3 months following the intervention, and the reduction of the variable will be compared using the Wilcoxon signed-rank test. In terms of secondary outcomes, the Fisher's exact test will be used for dichotomous variables, and mixed-effects models will be used for rating scales with fixed factors (intervention group vs control group) and time (0, 3 and 6 months). Descriptive data will be employed to describe the utility and utilisation of the electronic intervention.

ETHICS AND DISSEMINATION

Research ethics approval

The trial was filed at ClinicalTrials.gov and was designed in compliance with the Helsinki Declaration principles. Because the study collects data from five cities, the entire study would be monitored and approved by five institutional review boards and ethics committees: Shanghai Mental Health Center (2019–22), Second Xiangya Hospital of Central South University (2019–190), West China Hospital of Sichuan University (2019–686), Affiliated Guangji Hospital of Soochow University (2019–033) and Wuhan Mental Health Center (ky2019.03.01).

Consent or assent

Before recruiting, participants received electronic consent files outlining the study's goal, methods, potential risks and benefits via the WeChat platform. After thoroughly understanding the study's subject, all volunteers must sign an electronic informed consent form to participate.

Confidentiality

After receiving informed consent from all participants, the investigators will develop a unique user identifier for each participant in the administrator end. All participant-specific data will be gathered and stored on a server at the Shanghai Mental Health Center with password-protected access to protect participant privacy and data security and

supplied to designated researchers who undertake data analysis with consent.

Ancillary and post-trial care

After the trial, each participant in the intervention and control groups will receive a gift (about 300 Chinese Yuan). Meanwhile, control group members have accessed educational resources.

Dissemination policy

The study's findings will be published in peer-reviewed publications or presented at professional meetings. If electronic intervention reduces physicians' inappropriate prescribing habits in mental facilities, teaching materials will be available to the general public.

RESULTS

The research is scheduled to begin in October 2020. The intervention has concluded, and a follow-up assessment is scheduled for the end of 2021.

DISCUSSION

To the best of our knowledge, no psychiatrist-centred intervention has been done in Chinese psychiatric clinics to reduce improper BZRA prescriptions. The study will confirm the effectiveness and value of the electronic intervention on psychiatrists' prescription of appropriate BZRAs. Suppose this WeChat-based intervention is shown to be effective and useful. In that case, it significantly impacted addressing the existing situation of inappropriate BZRAs prescription and associated drug control regulations.

There are various limitations of the study. It should be highlighted that the findings could not be applied to psychiatrists in rural areas or other small-scale hospitals in China because the selected psychiatrists are from tertiary institutions in urban areas. Furthermore, because the trial was conducted across five sites, it is unclear if psychiatrists at each site were randomly assigned to intervention and control groups, which raises concerns about contamination bias. We did not consider clustering in our analysis since we want to undertake a pilot study first to see how beneficial this intervention is in tertiary hospitals. The types are generally similar. Second, considering that steady dosage reduction can take many months, the time frame for evaluating this effect is relatively short. We believe that it is possible to notice improvements in doctors' prescribing patterns within 6 months. However, we will extend our follow-up period if adequate funds are available. Third, because the indicator of interest in this study is at the level of psychiatrists, changes in BZRAs use at the patient level after intervention are unknown.

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Contributors NZ and HJ conceived the original concept of the protocol for the study. XW, JX, CL, GW and YZ were responsible for the research implementation and data collection. XX, YY, NZ and HJ analysed data and interpreted the results. XX and YY are co-first authors and drafted the manuscript. All authors critically reviewed the content and approved the final version for publication.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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