ARTICLE DETAILS

**TITLE (PROVISIONAL)**
The effectiveness and utility of an electronic intervention for appropriate benzodiazepine and Z-drugs prescription in psychiatric clinics: Protocol for a multicentric, real-world randomized controlled trial in China

**AUTHORS**
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VERSION 1 – REVIEW

**REVIEWER**
Cathal Cadogan
Trinity College Dublin, Pharmacy

**REVIEW RETURNED**
02-Oct-2021

**GENERAL COMMENTS**
This is a protocol for a trial of an intervention targeting BZRA prescribing by psychiatrists in China. The manuscript would benefit from English language review. I hope the authors find my comments helpful.

Abstract: some points in introduction don’t align with the main text
- BZRAs “are the most prescribed drugs worldwide”; this is not mentioned/referenced in main text
- “As the main prescribers, psychiatrists…” same as above

Introduction: Overall, I don’t think that the introduction highlights the relevant gap that this research is trying to address. An educational intervention to improve BZRA prescribing does not seem particularly novel
- Benzodiazepines (BZDs) and Z-drugs (non-BZDs); suggest using the term benzodiazepine receptor agonists (BZRAs) to encompass both groups of drugs
- “cognitive failures” suggest using the term cognitive impairment instead
- “hip fractures or car accidents due to falls” this doesn’t read correctly
- “inappropriate prescription of BZDs and Z-drugs” should this refer to inappropriate prescribing? Also, how is this defined/measured long-term duration; what constitutes long term?
- “only a third of patients with BZDs utilization considered appropriate prescription without exceeded guidelines in terms of indication or contraindications” I don’t understand this sentence
- “In a recent multi-center, retrospective patient-link prescription database study in Chinese psychiatric clinics by our research team, we found approximately 3.03% outpatients were in hazardous use of BZDs and Z-drugs, and hazardous use here is defined as overdose (>40mg Diazepam Milligram Equivalence (DME)), long-term use (>consecutive 90 days), or both” – long sentence and difficult to follow; I think the word approximately is meant to be used instead of
appropriately
“Current research about the related interventions targeted at clinicians is rather little, and primarily by legislation restriction, education or providing resources for medication substitution among general practitioners” – I don’t think this is accurate; see other systematic reviews e.g.
Darker et al. Cochrane Database Syst Rev 2015; 5: CD009652.
Lynch et al. Addiction. 2020 ;115(9):1618-1639. doi: 10.1111/add.14981
Pollman et al. BMC Pharmacol Toxicol 2015; 16: 19.

“partial clinicians” not sure what this means
“It is difficult for psychiatrists to spare a complete period of time for systematic learning on the latest knowledge about the appropriate use of BZDs and Z-drugs” not sure what evidence this point is based on?
“New technologies such as web-based and mobile based health services show potential effects and flexibility in health care services 20 21 , making it possible for psychiatrists to receive electronic intervention to update related knowledge.” This is very broad/vague; I don’t see how this is a unique solution to addressing inappropriate BZRA prescribing

The description of the intervention’s development and its associated content is vague and lacks sufficient detail to enable replication; recommend using a reporting guideline such as TIDIER to ensure comprehensive reporting (BMJ 2014; 348 doi: https://doi.org/10.1136/bmj.g1687). I also don’t see how it will translate into changes at a patient level

Methods
It would be good to see the use of a reporting checklist (e.g. CONSORT) for the protocol; there are some issues with ordering/sequence where aspects such as randomisation are mentioned early on in this section but not elaborated on until the end

I would also encourage the authors to look at the Cochrane risk of bias tool; at present details is lacking across various domains. For example, the authors report “be randomly assigned to the standardized electronic intervention group, or to a waiting list (control group) in a ratio of 1:1” – this lacks detail of the how the randomisation sequence was generated and how participants were subsequently allocated. Having read the rest of the methods I see that further detail is provided at the end, but this goes back to point above about ordering

Given the fact that the study was conducted across five sites, does clustering need to be considered? It is not clear if psychiatrists within each site were randomly assigned to intervention and control groups which also raises issues regarding potential for contamination bias

Figure 2; suggest that individual participants details be removed

Primary outcomes: the wording of the definition of this is not clear (”The inappropriate prescription is defined as overdose use (>40mg DME according to the maximum dose of drug instruction), long-term use (>90 days) or over-indications use.”)
The time period for assessing this outcome is quite short given that gradual dosage reduction can take several months

Do patient participants have to consent to their prescribing data being included in the study?
Sample size: it is not clear if these numbers are based on psychiatrists or patients?
Results

“The research started October 2020. The intervention has been completed and the follow-up assessment is expected to be completed at the end of 2021.” It seems very late to be publishing the protocol.

### GENERAL COMMENTS

This is great research and one of a kind to look at this problem of Benzodiazepine prescriptions. As we know research shows short-term use of Benzodiapiens but clinically it is very hard for patients to get off Benzodiazepines once they have taken them for some period of time. I believe Psychiatrists as well as other Primary care physicians and allied health providers continued education is important on this topic as well as an increase in community resources for psychotherapy.

### VERSION 1 – AUTHOR RESPONSE

**Response to Reviewer 1**

**Abstract**

- some points in introduction don’t align with the main text; BZRAs “are the most prescribed drugs worldwide”; this is not mentioned/referenced in main text

"As the main prescribers, psychiatrists…” same as above

**Reply:** We are very sorry for our negligence of reference in main text. We added related evidence in main text as follows:

“Benzodiazepine receptor agonists (BZRAs), including benzodiazepines (BZDs) and Z-drugs (e.g., zopiclone, zaleplon and zolpidem), are one of the most commonly prescribed psychotropic drugs worldwide in clinical practice (Olfson, M.et al., 2015).”

Second, “As the main prescribers, psychiatrists…”, we modified the statement in the abstract section as follows: “As BZRAs are commonly used in psychiatric settings,” and listed related evidence in the main text as follows: “Therefore, they are mainly used for treatment of insomnia, anxiety, and panic disorder in psychiatric settings.3-6.”

**Introduction**

- Overall, I don’t think that the introduction highlights the relevant gap that this research is trying to address. An educational intervention to improve BZRA prescribing does not seem particularly novel.

**Reply:** It is true that educational intervention to improve BZRAs prescribing does not seem particularly novel. However, to our knowledge, evidence of WeChat-based BZRAs interventions for prescribing psychiatrists is not available at present. Our designed system can realize multi-functions including intervention, assessment, feedback, notification, and data management.
- Benzodiazepines (BZDs) and Z-drugs (non-BZDs); suggest using the term benzodiazepine receptor agonists (BZRAs) to encompass both groups of drugs.

Reply: Thanks for your suggestion. We replace all the terms of “Benzodiazepines (BZDs) and Z-drugs (non-BZDs)” by “benzodiazepine receptor agonists (BZRAs)”.

- “cognitive failures” suggest using the term cognitive impairment instead

“hip fractures or car accidents due to falls” this doesn’t read correctly

Reply: We rewrote the sentence as follows: “Adverse drug reactions of BZDs and Z-drugs are associated with the risks of cognitive impairment, psychomotor abnormalities, falls, hip fractures and car accidents …”

- “Inappropriate prescription of BZDs and Z-drugs” should this refer to inappropriate prescribing? Also, how is this defined/measured

Reply: Yes. We added the detailed definition of inappropriate prescribing in the main text as follows:

“The problem of inappropriate prescription (long-term, overdose and over-indications) of BZRAs is prominent worldwide…”

- long-term duration; what constitutes long term?

Reply: In this retrospective study of benzodiazepine prescriptions in the US (Olfson, M. et al., 2015), the definition of long-term duration was more than a total of 120 days of BZDs supply.

- “only a third of patients with BZDs utilization considered appropriate prescription without exceeded guidelines in terms of indication or contraindications” I don’t understand this sentence

Reply: We rewrote the sentence as follows: “only a third of patients were considered to use BZRAs within indication.”

- “In a recent multi-center, retrospective patient-link prescription database study in Chinese psychiatric clinics by our research team, we found approximately 3.03% outpatients were in hazardous use of BZDs and Z-drugs, and hazardous use here is defined as overdose [>40mg Diazepam Milligram Equivalence (DME)], long-term use (>consecutive 90 days), or both” – long sentence and difficult to follow; I think the word approximately is meant to be used instead of appropriately

Reply: We updated the definition and rewrote the sentence as follows: “In a recent study by our research team, we found approximately 3.0% outpatients were in hazardous use of BZRAs via analysis of prescriptions in Chinese psychiatric outpatient settings. To be specific, we defined the co-occurrence of overdose [>40mg Diazepam Milligram Equivalence (DME)] and long-term use (>consecutive 90 days) as hazardous BZRAs use (unpublished).”
“Current research about the related interventions targeted at clinicians is rather little, and primarily by legislation restriction, education or providing resources for medication substitution among general practitioners” – I don’t think this is accurate; see other systematic reviews e.g. Darker et al. Cochrane Database Syst Rev 2015; 5: CD009652.
Lynch et al. Addiction. 2020;115(9):1618-1639. doi: 10.1111/add.14981
Pollman et al. BMC Pharmacol Toxicol 2015; 16: 19.

**Reply:** The systematic reviews you mentioned above is mainly patient-oriented. Previous interventions targeting at reducing benzodiazepine and Z-drug use were mainly for patients, rather than for prescribing doctors. Interventions for prescribing doctors include legislation restriction, education or providing resources for medication substitution among general practitioners (Ng BJ et al. Drugs & aging 2018). Our study aimed to test the effectiveness and utility of our designed WeChat-based intervention which provided guidance of appropriate BZRAs prescription for psychiatrists. Our designed system can realize multi-functions including intervention, assessment, feedback, notification, and data management. To our best knowledge, related evidence is not available. For better understanding, we rewrote this sentence as follows:

“Nowadays, the interventions for BZRAs abuse are mainly patient-oriented, including self-managed or supervised gradual dose reduction, educational books, minimal interventions, or cognitive behavioral therapy provided by physicians, to raise patients’ awareness of potential risks of BZRAs.17-20 Though some clinicians realize the possible adverse consequences of long-term use of BZRAs, they claim that it is difficult to persuade patients to discontinue using the drugs and themselves also lack corresponding non-pharmacological therapy techniques and knowledge to reduce the inappropriate use of BZRAs.21 Interventions for service provider, the prescribing doctors, primarily include legislation restriction to limit prescription, education or providing resources for medication substitution among general practitioners.17 Moore et al. 22 recommended that BZDs should be strictly controlled and only prescribed by medical experts, such as psychiatrists, however, this is not the case. A recent cohort study indicated that prescription by psychiatrists is one of the clinical correlates of long-term BZDs use.23

To our knowledge, related evidence about intervention for psychiatrists is not available to reduce the inappropriate prescription of BZRAs……..”

- “partial clinicians” not sure what this means

**Reply:** we replace “partial” with “some”.

- “It is difficult for psychiatrists to spare a complete period of time for systematic learning on the latest knowledge about the appropriate use of BZDs and Z-drugs” not sure what evidence this point is based on?

**Reply:** Doctor’s work is busy and they have to spend lots of time dealing with patients, especially among psychiatrists due to the nature of their professions in dealing with troubled persons often over extended periods of time (Moore KA et al. Int J Soc Psychiatry 1996). The situation is even worse in China due to its enormous population (Chuan Liu et al. BMC Health Serv Res. 2015). For better understanding, we rewrote this sentence to stress the importance of electronic intervention for psychiatrists as follows:
"It is difficult for psychiatrists in China to spare a complete period of time for systematic learning on the latest BZRAs-related knowledge due to the enormous population in China and the nature of their professions in dealing with trouble people which require plenty of time. Moreover, nonspecific BZRAs related knowledge, limited knowledge of evidence-based alternative treatment, and difficulties applying medication as per guidelines in clinical practice also contributed to this situation.

New technologies such as web-based and mobile based health services show potential effects and flexibility in health care services, providing a powerful and convenient platform for distant education. Our research team designed an intervention system which is based on WeChat, the most popular social media application in China, to realize multi-functions including educational intervention, assessment, feedback, notification, and data management. According to the social cognitive theory, self-monitoring such as assessment and education could increase self-efficacy beliefs to facilitate one’s motivation and behaviors."

The description of the intervention's development and its associated content is vague and lacks sufficient detail to enable replication; recommend using a reporting guideline such as TIDier to ensure comprehensive reporting (BMJ 2014; 348 doi: https://doi.org/10.1136/bmj.g1687). I also don’t see how it will translate into changes at a patient level

"Moreover, as the index of interest in this study is at psychiatrists' level, changes in BZRAs use at the patient level after intervention are unknown."

We first surveyed 595 doctors about their attitudes and knowledge of BZRAs. The initial educational contents were primarily based on the above surveys, latest evidence-based guidelines, and experts' consensus for the appropriate use of BZRAs. Then a focus group was conducted among 8 mental health or addiction experts with more than 10-year working experience to fully discuss around the 4 topics, including the basis for rational use of BZRAs, their rational use in common mental disorders, the quick identification and brief intervention for the BZRAs use disorders, and their use for the special groups. The recordings were converted into transcripts and thematic analysis was used to confirm the key components. The intervention content was further submitted to 2 Chinese addiction experts to review and reach a consensus for the final version of educational contents (See details in Table 1)."
Methods

- It would be good to see the use of a reporting checklist (e.g. CONSORT) for the protocol; there are some issues with ordering/sequence where aspects such as randomisation are mentioned early on in this section but not elaborated on until the end.

Reply: In this study, we used SPIRIT checklist (doi: 10.1136/bmj.e7586.) for the protocol of clinical trials. A completed copy of the SPIRIT checklist has been uploaded as a supplementary file. And we restructured the ordering/sequence and moved the details about randomization to the “Allocation and blinding” section.

- I would also encourage the authors to look at the Cochrane risk of bias tool; at present details is lacking across various domains. For example, the authors report “be randomly assigned to the standardized electronic intervention group, or to a waiting list (control group) in a ratio of 1:1” – this lacks detail of the how the randomisation sequence was generated and how participants were subsequently allocated. Having read the rest of the methods I see that further detail is provided at the end, but this goes back to point above about ordering.

Reply: We restructured the ordering/sequence and added more detail about randomization in the “Allocation and blinding” section.

- Given the fact that the study was conducted across five sites, does clustering need to be considered? It is not clear if psychiatrists within each site were randomly assigned to intervention and control groups which also raises issues regarding potential for contamination bias.

Reply: Thanks for your suggestion. In this study, we want to conduct a pilot study first to see the effectiveness of this intervention in tertiary hospitals (highest level in China). Different levels of hospitals (such as local community hospitals or clinics) had different amounts and characteristics of patients. The use status of BZRAs is different accordingly. So, we chose 5 of the most influential regional tertiary hospitals with the highest-quality mental services, and the types of these hospitals are relatively similar, so we did not consider clustering.

It is true that there is a potential for contamination bias. Including the intervention group and the control group in the same hospital at the same time cannot avoid the possibility of contamination like mutual communication. However, the intervention is an online intervention and conducted in personal private time, and there are a large number of psychiatrists in the selected hospital, which could minimize the contamination in subsequent analysis. We added this point in the “Allocation and Blinding” section as follows: “This is an open-label real world study, and it is clearly hard to blind the participants and investigators to group allocation. However, the intervention is an online intervention and conducted in personal private time. Participants in the intervention group will be informed not to discuss the educational content or lecture videos with those in the control group.”

- Figure 2; suggest that individual participants details be removed.

Reply: We had removed the details of individual participants.
Primary outcomes: the wording of the definition of this is not clear (“The inappropriate prescription is defined as overdose use (>40mg DME according to the maximum dose of drug instruction), long-term use (>90 days) or over-indications use.”)

Reply: We added more details as follows:

“The prescription in accordance with any of the following conditions is considered to be inappropriate: overdose use, long-term use or over-indications use. If the average daily DME usage is more than 40mg/day according to the maximum dose of drug instruction, the prescription is defined as 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 use not in accordance with any of the indications approved by the Chinese FDA.”

The time period for assessing this outcome is quite short given that gradual dosage reduction can take several months

Reply: Thanks for your suggestions. It needs long-time professional treatment and rehabilitation for patients with substance abuse or even substance use disorder. The intervention in this study targets psychiatrists’ inappropriate BZRAs prescription. We think that it can preliminarily observe changes in doctors’ prescribing behaviors within 6 months. However, we will prolong our follow-up period with sufficient funding.

Do patient participants have to consent to their prescribing data being included in the study?

Sample size; it is not clear if these numbers are based on psychiatrists or patients?

Reply: The requirement for informed consent was exempted from patients due to the anonymity and psychiatrists who participated in this study signed the written informed consent. We added a statement in the methods section under the sub-heading ‘Patient and Public Involvement as follows: “No patients are involved in this study. For the patients whose prescribing data being included in the study, the requirement for informed consent was exempted from patients due to anonymity.”

Sample size: These numbers are based on dispensing data of BZDs from service providers after multi-strategic approach, including provision of treatment guidelines, provision of consumer information, a local media campaign and education and training of health professionals (Dollman WB et al., 2005). We added more details in the “Sample size” section as follows:

“Previous study reported that intervention could result in a 19% reduction in BZDs prescriptions after multi-strategic intervention, including local media involvement, provision of treatment guidelines and consumer information, and education and training from medical professionals.36”

Results

- “The research started October 2020. The intervention has been completed and the follow-up assessment is expected to be completed at the end of 2021.” It seems very late to be publishing the protocol
Reply: Thanks for pointing out this problem. It is true that it is late to publish this paper. In fact, we started writing and submitting the protocol very early, but it was late due to the COVID-19 epidemic, rejections by other journals and our own delay. However, to better guide the development of clinical research, we still want to publish the protocol.

Response to Reviewer 2

- This is great research and one of a kind to look at this problem of Benzodiazepine prescriptions. As we know research shows short-term use of Benzodiazepines but clinically it is very hard for patients to get off Benzodiazepines once they have taken them for some period of time. I believe Psychiatrists as well as other Primary care physicians and allied health providers continued education is important on this topic as well as an increase in community resources for psychotherapy.

Reply: Thank you very much for your careful review and precious comment.