Selection and measurement of control antidepressants in clinical tests for Chinese
A systematic review
Hao Liu, MDᵃ, Zhi-Min Yang, MDᵇ,∗, Ying Geng, MDᵇ, Huan Yang, MDᵇ, De-Heng Zhao, MDᵇ, Wei-Dong Xiao, MDᵃ, Gao-Hua Wang, MDᵃ,∗

Abstract
Objective: The study aims to help domestic application units and research institutions improve their research quality of antidepressant clinical tests by studying and analyzing the current status and problems in selecting control drugs during domestic antidepressant clinical tests and illustrating some key problems that should be noted when selecting the control drug in such researches.

Methods: Considering the current domestic and overseas status of control drug selection in antidepressant clinical tests, various considerations, and misunderstandings on control drug selection in domestic antidepressant clinical tests were clarified and described, and possible factors that may influence the absolute effect of antidepressants were analyzed. Furthermore, problems that should be noted in selecting control drugs for the antidepressant clinical test, especially the placebo control, were stated.

Results: During the antidepressant clinical research, selecting placebo controls conform to moral philosophy and safety requirements. To verify the absolute effect of a test drug, a placebo control should be set or 3-arm tests should be conducted as far as possible. Possible factors that may affect the absolute effect of the test drug, including illness severity of the subject at baseline and research scale, should be given consideration.

Conclusions: Application units and research institutions should consider the selection of subjects, control the failure rate, strengthen safety risks, and control and intensify quality control to further improve the overall quality and research level of domestic antidepressant clinical tests.

Abbreviations: FDA = Food and Drug Administration, WHO = World Health Organization.
Keywords: antidepressant drugs, clinical trials, control, placebo

1. Introduction
Depressive disorder is also called tristimania, which is clinically featured with a significant and lasting low mood. As reported by the World Health Organization (WHO), approximately 350 million people suffer from depression all over the world.[1–4] Because of the high incidence of depressive disorders and its severe consequences such as suicide, antidepressants have gradually attracted attention and have been extensively applied in China. In addition, antidepressant clinical tests have become an active field in new drug applications in recent years.[5] Depressive disorder is special, compared with other diseases to the body; and many factors influence the absolute effect of antidepressants.[3,6–8] Till date, the selection of control drugs in domestically applied antidepressant clinical tests has mainly involved positive drug control and/or placebo control, and these 2 controls have their own advantages and disadvantages.[3,9] In domestic antidepressant clinical tests, there are many worries and misunderstandings on the selection of control drugs, especially placebo controls. In most cases, positive drug control is more generally accepted and considered as a priority selection, whereas placebo control is less used in antidepressant clinical tests.[1,5–6] This article clarified and stated the above worries and misunderstandings. In addition, we analyzed possible factors that may influence the absolute effect of antidepressants, with emphasis on issues that should be noted during the selection of the control drug, especially placebo controls, in antidepressant clinical tests; which can be used as reference of pharmaceutical enterprises and clinical researchers.

2. Selection and general measurement of control drugs in antidepressant clinical tests
Randomized controlled tests have been deemed as the golden standard of clinical research, whereas the selection of control drugs is the key to a randomized controlled test. Except for the
general rules for drug clinical tests, antidepressant clinical tests should also consider the influence of the characteristics of the disease and drug on the clinical tests.\(^{[3]}\) Depressive disorder patients with different severity or types may have a large curative effect difference to the antidepressant therapy. This means that the research on patient heterogeneity has a significant influence on the effect of the test drug. In addition, the personal differences of subjects, the subjective expectations of these subjects to the researchers, the absence of objective biological indicators to therapeutic evaluation, and other factors are confounding factors that influence judgment on the effectiveness of the test drug in antidepressant clinical tests.\(^{[6-8,10]}\)

We know that the positive drug control and placebo control in clinical tests have their respective advantages and disadvantages. For example, positive drug control is easier to be accepted, whereas placebo control is more effective in verify the absolute effect of the test drugs. Therefore, to verify the absolute effect of antidepressants, at least one phase II or III clinical tests, taking placebo as control group with sufficient samples, should be carried out in antidepressant clinical tests for Chinese populations, especially for innovative drugs. In addition, optimal efficiency should be designed to obtain the absolute effect of the test drug relative to placebo, and it is required to judge whether the difference in its curative effect has any clinical meaning.\(^{[3]}\)

When selecting positive drug control in these antidepressant tests, the positive control drug that has similar clinical pharmacological characteristics with the test drug is generally selected, and the selection basis of the positive control drug should be determined in the test plan to provide the referenced clinical therapy guidance and literature.

Note that the comparison between test drugs and positive control drugs should be conducted under the same conditions. The dosage and dosage regimen of the positive control drug must be optimal. One of the main defects of positive drug control is that the researchers may artificially lessen the curative effect difference of the 2 drugs in the noninferiority or equivalency test. From the sensitivity of the test design, once the 2 drugs have the equivalent effect, it is not enough to indicate the efficiency of the test drug. Therefore, it is suggested to add one placebo control to determine the efficiency of the test drug, which is called 3-arm test design.

In a word, in domestic antidepressant clinical tests, whether placebo or the positive drug is chosen as the control group, it should depend on the purpose of the clinical test, the target population, the clinical research stage, related rules and regulations, and so on.\(^{[3]}\) To verify the absolute effect of the test drug, placebo control should be set or 3-arm tests should be conducted as far as possible.

3. Moral philosophy and safety risk measurement of placebo controls in antidepressant clinical tests

As described above, positive drug control appears to be a more generally accepted and preferred choice in domestic antidepressant clinical tests. To find the reasons, the most common explanation from the application units is the consideration of the moral philosophy of safety. In antidepressant clinical tests, positive drugs have less or even no curative effect on some subjects, but the placebo may have a better effect on them. It can be expected that in comparing patient taking placebo and patients taking the positive drug, the former may delay the relief of symptoms or have decreased alleviation amplitudes. However, in practice, global clinical research data in recent years has indicated that the curative effect difference between positive drug and placebo is increasingly narrowed,\(^{[3]}\) and the treatment of depressive disorder itself has a high placebo effect. Therefore, in most cases, the decrease of such alleviation amplitude only has limited influence on the benefit and risk ratio of these subjects. In the meantime, if the temporary delay of the symptom alleviation (not more than several weeks) is the only problem concerned, the moral philosophy will not refuse to set placebo control in antidepressant clinical tests.\(^{[9]}\)

The safety disputes generated by placebo controls are that the researchers become concerned about the increase of suicide risk, and such risk is uncontrollable. In fact, Temple R et al.\(^{[9]}\) analyzed that clinical tests of antidepressants approved to hit the market from 1981 to 1997, in which the terminal data include suicide and the suicidal attempt data; and nearly 20,000 cases were included. These results revealed that the suicide and suicidal attempt between the placebo group and active drug group have no difference at all. Given that suicide in clinical trials is rarely seen, if we exclude patients with a high-risk tendency of suicide during the subjects selection (eg, the score of the second item of HAMD is ≥3), and the verified scoring scale is used to closely monitor the suicide intention of the subjects during the whole research, the suicide risk generated by placebo therapy can be actually controlled.

4. Domestic and overseas present status of control drug selection in antidepressant clinical tests

The Food and Drug Administration (FDA) requires that the application units of NDA should prove that the curative effect of antidepressants is more obvious than the placebo at least in 2 clinical control tests. Indeed, this regulation has loopholes, because the FDA does not regulate the number of clinical tests with the same research purpose that the application unit can carry out.\(^{[11]}\) It can be observed from Table 1 that a common antidepressant selects the placebo control in a critical phase III research, which supports its arrival in the market; and the critical research of most antidepressants includes the 3-arm tests. Thus, existing antidepressants in the market have proven their effectiveness by more than 2 tests in critical research, which supports its arrival in the market. This is of great referential meaning for domestic antidepressant clinical research.

5. Measurement of factors that influence the absolute effect of the test drug in domestic and overseas antidepressant clinical tests

This retrospective research found that approximately 50% of antidepressant clinical tests reported to the FDA did not obtain
optimal efficiency.\textsuperscript{12} Other studies have also concluded the same results.\textsuperscript{13–14} Affected by other factors such as commercial factors, successful research results (i.e., antidepressant is superior compared with placebo) are easier or more reported or published. Nevertheless, a systematic analysis on published antidepressant clinical tests in recent several decades found that the curative effect difference between antidepressants and placebo is just at the medium level, whereas such difference is increasingly lessened in recent years. This means that the absolute effect of antidepressant decreases and that of placebo increases. Even for teenager depressive disorder patients, the curative effect of some antidepressants is not as good as the placebo.\textsuperscript{14–16} This has been gradually proven and accepted in more and more retrospective researches.\textsuperscript{17–19}

Many factors that may influence the curative effect difference of antidepressants, including depression severity of baseline, research period, drug dosage, research scale, research time and regions, and so on.\textsuperscript{7} For example, in comparing researches with a fixed dosage, antidepressants in clinical tests with variable dosages can realize optimal efficiency. Relative to long-term research, antidepressants in short-term research can realize optimal efficiency. The antidepressant research carried out in regions with more research experience and higher research level may have more superior efficiency. In all these factors, depression severity at baseline and the research scale are generally considered as the most factors that influences the absolute effect of antidepressants.\textsuperscript{11,14–19}

5.1. Baseline illness severity of the subject

With the popularization of depressive disorder knowledge and the enhancement of the understanding level in China, increasingly more minor and medium level depressive disorder patients have joined in the clinical research of placebo controls. The change in baseline illness among these subjects can better explain the increase in placebo curative effect in recent years. Correspondingly, many studies revealed that the severer the baseline depression is, the more obvious the curative effect difference between the antidepressant and placebo will be, which means that the absolute effect of antidepressants will be better. On the contrary, the lighter the baseline depression is, the less obvious the curative effect difference between antidepressant and placebo will be; which means that the absolute effect of antidepressants would be worse.\textsuperscript{14,11,16,19–20} As a result, during the antidepressant clinical research of placebo controls, to better prove the absolute effect of antidepressants, application units and research institutions need to pay more attention to the baseline depression severity of these subjects. HAMD-17 and MARDs always be recommended to assessed the depression severity in these clinical tests.\textsuperscript{21–23}

5.2. Research scale

Although based on the statistical analysis, the placebo control research appears to be easier to obtain, and the optimal or positive research results have a larger quantity of samples, the increase of samples generally lead to the increase in research centers, group numbers of each research center, or research time, which will cause additional variable factors to the whole research. Thus, researches with larger scales are not always better. The research of Undurraga et al\textsuperscript{16} revealed that the number of research centers for one placebo control research is better if it does not exceed 10 in antidepressant clinical tests. The optimal number of subjects in each center is 30 to 75, and better shows the curative effect difference of antidepressants and placebos.\textsuperscript{16} With the enhancement of the entire research level and the accumulation of research experience, the research scale of domestic clinical tests is gradually expanding. However, in antidepressant clinical tests for placebo controls, researches with larger scales are not always better in effectively verifying the absolute effect of test drugs. Therefore, application units and research institutions should reduce interference from variable factors during the research as far as possible.

6. Precautions to control drug selection in domestic antidepressant clinical tests

6.1. Selection of the study population

In the antidepressant clinical tests of placebo control, in view of the possible influence of the subject’s baseline illness severity on the absolute effect of antidepressants, the application units should put emphasis on the reasonability of the different subgroup populations classified by baseline illness severity. When the application units and research institutions prepare and implement the clinical test scheme, they should ensure that the distribution of subgroup population involved conforms to clinical practice, and should select appropriate populations based on the characteristics of the research drug at the same time. If the involved subjects have too minor or severe conditions, this does not only fail to guarantee the representativeness of such research population and the generality of the research results, but may also cause fake positive or fake negative results for the absolute effect of the antidepressant, affecting research quality.

6.2. Strengthened safety risk controls

During the implementation of the domestic clinical tests for placebo control, research schemes and researchers tend to exclude patients with severe depressive order out of the placebo control tests. This would not only cause the nonrepresentativeness of the research population in the placebo controlled research, but may also affect the generality of the test results. In addition, reduction and baseline illness severity may further mitigate the curative effect difference between antidepressants and placebos, causing a failure to obtain an optimal result or even the failure of tests. Therefore, emphasis on the safety risk control of clinical tests should not be reflected by including more subjects with minor states of illness, but by scientific and reasonable design and risk control schemes. For example, limiting the duration of tests (generally 6–8 weeks), close follow up, regular special measurements, and risk assessment allow patients to exit from the test in case of severe deterioration of illness, acceptance of standard therapy, and so on.\textsuperscript{18}

6.3. Control of failure rate

During the research of domestic antidepressant clinical tests, the subjects and researchers worry too much about delayed treatment or safety risk. Hence, they are not willing to use placebo controls. Even if it is clear that the medical treatment would not be delayed, the subjects may also retreat from the test, because their state did not improved, which will influence the test quality. In fact, Schalkwijk et al\textsuperscript{15} believed that one of the main reasons that cause the enhancement of the placebo curative effect in the recent 30 years is that the failure rate generated through the insufficiency of the curative effect is reduced.\textsuperscript{15} In addition, the failure rate of antidepressant clinical tests for placebo control in
China basically does not exceed 20%. Consequently, in clinical tests of placebo control, application units and research institutions can consciously carry out popular science propaganda and introductions of related knowledge in various methods in the test initialization phase or patient screening phase, and note to intensify communication and contact between researchers and subjects. This would be of great help in reducing the failure rate and improving the test quality.

6.4. Strengthened research quality control

In view of various confounding factors that may influence the curative effect of antidepressants, to prove the absolute effect of antidepressants, application units and research institutions should reduce or eliminate the variable factors of the test by quality. Such variable factors include research experience and level of research institutions, quality control of the researcher, research consistency of the centers, research period, number of research centers, and number of samples in each center. Other quality control measures include strengthening training, communication and experience summary, finding and rectifying problems in research in time; paying attention to the process management of the research, and establishing a management model with multi-level quality control; and intensifying the application of electronic and information management in quality control. In a word, good quality control is the basis and precondition to ensure a successful test. [23]

7. Summary

For randomized clinical tests of domestic antidepressants, especially innovative antidepressants, placebo control or 3-arm tests should be carried out to prove the absolute effect of the test drug. In addition, considering the enhancement of the placebo effect in antidepressant clinical tests in recent years to obtain a better absolute effect of the test drug, application units and research institutions should focus on the selection of the research population, control the failure rate, strengthen safety risk control, and intensify quality control to further improve the overall quality and research level of domestic antidepressant clinical tests.

References

[1] Smith K. Mental health: a world of depression. Nature 2014;515:181.
[2] Sheikhman MB. The burden of depression. Nature 2014;515:163.
[3] EMEA: Guideline on clinical investigation of medicinal products in the treatment of depression [EB/OL]. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143770.pdf. Accessed on May 30, 2013.
[4] Dong B, Chen Z, Yin X, et al. The efficacy of acupuncture for treating depression-related insomnia compared with a control group: a systematic review and meta-analysis. Biomed Res Int 2017;2017:9614810.
[5] Zhang Y, Becker T, Ma Y, et al. A systematic review of Chinese randomized clinical trials of SSRI treatment of depression. BMC Psychiatry 2014;27:245.
[6] Ren Y, Zhu C, Wu J, et al. Comparison between herbal medicine and fluoxetine for depression: a systematic review of randomized controlled trials. Complement Ther Med 2015;23:674–84.
[7] Prasko J, Osikowa M, Grimaldi A, et al. Personality features, dissociation, self-stigma, hope, and the complex treatment of depressive disorder. Neuropsychiatr Dis Treat 2016;12:2539–52.
[8] Nurt D. Help luck along to find psychiatric medicines. Nature 2014;515:165.
[9] Temple B, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Ann Intern Med 2000;133:464–70.
[10] Furukawa TA, Cipriani A, Atkinson LZ, et al. Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. Lancet Psychiatry 2016;3:1059–66.
[11] Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med 2008;5:e45.
[12] Kirsch I. Antidepressants and the placebo effect. Z Psychol 2014;222:128–34.
[13] Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008;358:252–60.
[14] Khin NA, Chen YF, Yang Y, et al. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry 2011;72:464–72.
[15] Schalkwijk S, Undurraga J, Tondo L, et al. Declining efficacy in controlled trials of antidepressants: effects of placebo dropout. Int J Neuropsychopharmacol 2014;17:1343–52.
[16] Undurraga J, Baldessarini RJ, Randomizad . Placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. Neuropsychopharmacology 2012;37:851–64.
[17] Cipriani A, Geddes JR, Furukawa TA, et al. Metaanalysis on short-term effectiveness and safety of antidepressants for depression: evidence-based approach to inform clinical practice. Can J Psychiatry 2007;52:553–62.
[18] Khan A, Leventhal RM, Khan SR, et al. Severity of depression and response to antidepressants and placebo: analysis of the Food and Drug Administration database. J Clin Psychopharmacol 2002;22:40–5.
[19] Angst J. Severity of depression and benzodiazepine co-medication in relationship to efficacy of antidepressants in acute trials: a meta-analysis of moclobemide trials. Hum Psychopharmacol 1993;8:401–7.
[20] National Institute for Health and Clinical Excellence. Depression in adults: The treatment and management of depression in adults. NICE clinical guideline 90 [EB/OL]. 2009. Available at: http://www.nice.org.uk/guidance/cg90/resources/guidance-depression-in-adults-pdf. Accessed on October 2009.
[21] Liu H, Zhang H, Xiao W, et al. Scales for evaluating depressive symptoms of the Chinese patients of schizophrenia. J Nerv Ment Dis 2009;197:140–2.
[22] Liu H, Zhang HY, Xiao WD, et al. Comparison of 5 assessment tools for evaluating depressive symptom in patients with schizophrenia. Chinese Ment Health J 2015;29:570–5.
[23] Yang H, Zheng DR, Zhao DH, Yang ZM. CFDA: General consideration on clinical trial design in the treatment of depression [EB/OL]. 2013. Available at: http://www.cde.org.cn/dzkw.do?method=largePage&id=312903. Accessed on January 5, 2013.