



## Letter to the editor: Methodological comments to “Electroacupuncture for tapering off long-term benzodiazepine use: A randomized controlled trial”



Dear Editor,

We recently read the paper "Electroacupuncture for tapering off long-term benzodiazepine use: A randomized controlled trial" by Wing-Fai Yeung et al. (2019). This is the first randomized, placebo-controlled trial to examine the benefits of electroacupuncture as an adjunct treatment of gradual benzodiazepine withdrawal in chronic benzodiazepine users. The article is rigorous in design, explicit in the inclusion and exclusion criteria, elaborate in trial methodology, reasonable in sample size, and complete in various aspects. It is an outstanding article among randomized controlled trials.

However, we have some doubts in the process of reading, and we hope to discuss them with the author.

- (1) About the placebo acupuncture. We note that the researchers used Streitberger placebo needles. As a non-invasive placebo, which are widely used worldwide and has been proven to be sufficiently credible to be used in investigations of the effects of acupuncture (Streitberger and Kleinhenz, 1998). However, as far as we understand from the trial, it uses a usual acupuncture needle (Dong Bang, Korea, 0.25 × 30 mm) for the treatment group and Streitberger placebo needles for the placebo acupuncture group. This may cause inconsistencies in the appearance of the two needles. This is not conducive to the realization of the blinding. By consulting the relevant literature (White et al., 2001), we believe that the treatment group and the placebo acupuncture group should use acupuncture instruments with the same appearance. For example, the Streitberger needle has two devices with the same appearance: the real acupuncture needles and the placebo acupuncture needles. We don't understand why the author chose Streitberger placebo needles, but did not the corresponding Streitberger real acupuncture needles. In addition, both of the two Streitberger needles have a plastic ring covered with plastic sheet. So we think that it is not suitable for use in the hair-intensive area such as head, But the researchers chose many acupuncture points on the head. We don't understand whether the author has a special way to deal with this contradiction.
- (2) About benzodiazepines. Almost all benzodiazepines, such as benzodiazepine derivatives and benzodiazepine related drugs (e.g.,

zolpidem and zaleplon), are covered in the inclusion criteria for this trial. However, as far as we know, although the pharmacological profiles of these compounds have many features in common with those drugs, some differences have also been identified. Most benzodiazepines bind non-selectively to benzodiazepine receptor subtypes, which may account for their undesirable adverse effects. The newer BZ<sub>1</sub>-receptor selective non-benzodiazepines such as zolpidem and zaleplon were developed in an attempt to overcome some of the adverse effects (such as withdrawal symptoms) (Wagner and Wagner, 2000). Therefore, we believe that the subjects who have different benzodiazepines choices may have different degrees of difficulty in drug withdrawal. The trial included a large number of benzodiazepines that were too widespread and untargeted, which may be one of the reasons for the negative conclusion. We recommend more targeted drug inclusion criteria and disease inclusion criteria in the subsequent trials.

This experiment as an innovative and rigorous RCT published in an internationally influential magazine, has attracted much attention to its study design and implementation methods. Therefore, we hope that the author can respond to our doubts and this will promote future similar trials.

### Potential conflicts of interest

None.

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