



## Research paper

# Attitudes toward placebo-controlled clinical trials among depressed patients in Japan



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## ABSTRACT

**Background:** Placebo-controlled clinical trials are the standard in the design of clinical studies for the licensing of new drugs. Medical and ethical concerns regarding placebo use still exist in clinical trials of depressed patients. The aim of this study was to investigate the attitudes toward placebo-controlled clinical trials and to assess factors related to the willingness to participate in such trials among depressed patients in Japan.

**Methods:** A total of 206 depressed patients aged  $49.5 \pm 15.7$  years (mean  $\pm$  SD) who were admitted to three psychiatric hospitals were recruited for a cross-sectional study from June 2015 to March 2016. After a thorough explanation of the placebo, the study participants completed a brief 14-item questionnaire developed to evaluate patients' attitudes regarding possible participation in placebo-controlled clinical trials. The Quick Inventory of Depressive Symptomatology was also administered to assess depressive symptoms.

**Results:** The results indicated that 47% of the patients would be willing to participate in a placebo-controlled clinical trial. Expectations for the improvement of disease, desire to receive more medical care, encouragement by family or friends, and desire to support the development of new drugs were associated with the willingness to participate in such trials, whereas a belief that additional time would be required for medical examinations and fear of exacerbation of symptoms due to placebo use were associated with non-participation.

**Limitations:** Patients were asked about possible participation in placebo-controlled clinical trials.

**Conclusions:** Less than half of the respondents were willing to participate in placebo-controlled clinical trials. Attitudes toward participation in a placebo-controlled clinical trial need to be considered when deciding whether to conduct such a trial.

## 1. Introduction

Depression is a serious affective illness with heterogeneous symptomatology expressed as a combination of emotional, physical, cognitive, and social aspects. The age at onset of depression is typically young adulthood, and the prevalence of depression remains elevated throughout the entire lifespan (Kessler et al., 2007). The World Health Organization has projected that major depressive disorder will rank second in worldwide disability-adjusted life-years (DALYs) by the year 2020 (World Health Organization, 2001). However, the results of depression treatment with currently available antidepressants are still

unsatisfactory. To achieve more effective and safe pharmacotherapy, new anti-depressive agents should be developed that are based not only on serotonin but also on other biochemical mechanisms (Su, 2009). As the social and economic costs of depression continue to increase, research is needed to compare the efficacy of new drugs in clinical trials (Murray and Lopez, 1997).

To identify new drug applications, the placebo arm is still the gold standard in the design of clinical studies (Tashiro et al., 2012). However, article 33 of the Declaration of Helsinki describes that "where no proven intervention exists, the use of placebo or no intervention is acceptable" (World Medical Association, 2013). The Pharmaceutical

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and Medical Devices Agency (Subcommittee on Placebo-controlled Studies, 2016), a Japanese regulatory agency, also stated that "the conduct of a placebo-controlled study should be carefully discussed on a case-by-case basis for individual clinical trials based on the severity and irreversibility of the target disease, and, if appropriate, relief measures may be prepared". In the case that there are good reasons for placebo use or the condition being studied is minor and the additional risk is negligible, placebo-controlled clinical trials in depressed patients would be acceptable. However, controversy remains due to ethical and medical concerns. Furthermore, the attitudes of depressed patients toward placebo-controlled clinical trials are an unexplored yet critical factor.

The objectives of this investigation were (1) to obtain information on patients' attitudes toward placebo-controlled clinical trials and (2) to assess factors related to the willingness to participate in placebo-controlled clinical trials among depressed patients in Japan. To the best of our knowledge, this article presents the first study on attitudes toward placebo use in clinical trials in depressed populations.

## 2. Method

### 2.1. Participants

This study was conducted between June 2015 and March 2016. The data collection protocol for this study (2013-324) was approved by the Ethics Committee of the Hirosaki University School of Medicine, and all subjects provided written informed consent before participating in this study. This protocol was conducted in accordance with the Declaration of Helsinki. The subjects included 206 outpatients (153 males and 53 females) at three psychiatric hospitals in Japan who were diagnosed with major depressive disorder, dysthymia, or adjustment disorder with depressed mood according to the DSM-IV. Participants were selected based on the available sampling method. The diagnoses of the patients were recorded based on their medical charts. The demographic data (age, sex, duration of education) and medical history of the subjects were obtained from their medical records.

Depressive symptoms were evaluated with the Japanese version of the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-J) (Rush et al., 2003; Kudo et al., 2015). The QIDS-J is comprised of 16 questions with a 4-point Likert scale as a measure of the severity of depressive symptoms. Total scores on the QIDS-J range from 0 to 27 0–5 = none, 6–10 = mild, 11–15 moderate, 16–20 = severe, and 21–27 = very severe).

The Clinical Global Impressions-Severity of Illness (CGI-S) Scale is a well-established research rating tool used to measure symptom severity that is applicable to all psychiatric disorders and can easily be used by

practicing clinicians. The CGI-S uses ratings from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). These ratings are based on all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, and behavior, as well as the impact of the symptoms on the patient's ability to function (Busner and Targum, 2007).

The Global Assessment of Functioning (GAF) is a scoring system (from 0 to 100) used by mental health clinicians to subjectively evaluate a patient's social, occupational, and psychological functions. The clinician assesses either the symptom severity or the level of functioning, depending on which is the most severe. Higher GAF scores indicate that participants either have less severe symptoms or have higher functioning (Aas, 2011).

To assess the participants' attitudes toward placebo-controlled clinical trials, a brief 14-item questionnaire used in previous epidemiological surveys was employed (Sugawara et al., 2015). After the participants were informed that placebos were pills with no active medication inside of them and were told that the assignment to each treatment was random and not related to their own preferences, they were asked to complete a brief questionnaire.

### 2.2. Statistical analysis

Descriptive analyses were performed to investigate the demographic and clinical variables. To compare the main demographic and clinical characteristics between groups, an unpaired Student's *t*-test was performed to analyze the continuous variables, and a chi-square test was performed to analyze the categorical variables. The data are presented as the mean ± SD. After adjusting for confounding factors (age, gender, amount of education, duration of illness, QIDS-J score, CGI-S score, GAF score, and status of antidepressant therapy), we conducted a multivariate logistic regression analysis with a forward selection method to assess the influence of attitude (Q2-Q14) toward placebo-controlled clinical trials as a predictor of participation in placebo-controlled clinical trials (Q1). A value of *p* < 0.05 was considered significant. The data were analyzed using the SPSS Statistics PC software for Windows, Version 24 (SPSS Inc., Chicago, IL, USA).

## 3. Results

The mean age of the full sample was 49.5 ± 15.7 years, the mean number of years of education was 9.5 ± 1.8 years, and the mean duration of illness was 6.4 ± 5.0 years. The average QIDS-J, CGI-S, and GAF scores were 9.2 ± 6.2, 3.1 ± 1.1, and 71.2 ± 15.3, respectively. Among all the participants, 46.6% indicated that they would hypothetically participate in a placebo-controlled clinical trial (Q1)

**Table 1**  
Attitudes toward placebo-controlled clinical trials of depressed patients in Japan.

	Yes	No
Q1 Would you be willing to participate in a placebo-controlled clinical trial?	46.6% (96/206)	53.4% (110/206)
Q2 Do you think that it takes a lot of time (for medical examinations) to participate in a placebo-controlled clinical trial?	58.3% (120/206)	41.7% (86/206)
Q3 Do you want to try a new drug that could possibly improve your disease?	70.2% (144/205)	29.8% (61/205)
Q4 Do you think that placebo might worsen or slow improvement in your condition?	57.3% (118/206)	42.7% (88/206)
Q5 Do you think that your disease does not improve even when taking a new drug?	15.7% (32/204)	84.3% (172/204)
Q6 When you participate in a placebo-controlled clinical trial, do you think that you would receive more medical care?	30.9% (63/204)	69.1% (141/204)
Q7 When you participate in a placebo-controlled clinical trial, do you think that you would be able to talk to your physician more often?	64.2% (131/204)	35.8% (73/204)
Q8 When you participate in a placebo-controlled clinical trial, do you think that you would be guaranteed to be treated in this hospital?	41.3% (83/201)	58.7% (118/201)
Q9 Do you think that your doctor is pleased when you participate in a placebo-controlled clinical trial?	56.7% (114/201)	43.3% (87/201)
Q10 If your family or friends encouraged you, would you participate in a placebo-controlled clinical trial?	44.2% (91/206)	55.8% (115/206)
Q11 Have you ever participated in a clinical trial before?	4.4% (9/205)	95.6% (196/205)
Q12 In principle, do you approve of clinical trials?	85.3% (174/204)	14.7% (30/204)
Q13 Do you think that long-term medical treatment is necessary for you?	65.9% (135/205)	34.1% (70/205)
Q14 Do you want to support the development of new drugs?	81.1% (167/206)	18.9% (39/206)

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