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# A comparative study with depressed patients on the acceptability of placebo use

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ABSTRACT

*Objective:* High rates of placebo responses are consistently reported in patients with major depressive disorder. Nonetheless, treating depression with placebo is still ethically controversial and generally prohibited in the clinical setting. In the present study, we assess the acceptability of placebo usage among depressed patients.
*Method:* Ninety-six outpatients with major depressive disorder were matched to 114 healthy controls. After a thorough explanation of the placebo effect, its efficacy and limitations in the treatment of depression, the study participants completed a 32-item self-report questionnaire. The five core questions addressed the attitude and willingness of subjects to be treated with a placebo in the clinical setting.
*Results:* Among study group patients, the majority (56.7%) conveyed consent for placebo treatment if they were to suffer another depressive episode. Both study group and control group expressed high rates of willingness to waive their right to informed consent (55.6% and 50%, respectively), and they did not consider placebo treatment to be a deceit (56%) or to diminish their sense of autonomy (56.7%).
*Conclusions:* Most patients with depression are willing to waive their right to informed consent in order to receive placebo treatment. These findings should encourage further studies of placebo usage and its legitimacy in clinical practice.



## 1. Introduction

Depression is one of the most common and debilitating of psychiatric disorders [1]. Awareness of the high prevalence of depression has grown, and the use of medication is now commonplace. Metaanalyses have indicated that antidepressants (AD) show only a slight therapeutic benefit compared with placebos [2–6] and that the drug–placebo difference may disappear altogether in treating mild to moderate depression [7]. Accordingly, a placebo arm is still the gold standard in the design of double-blind randomized controlled studies [8]. Clinically, the placebo seems to be an efficient treatment for depression, with few side effects, reduced cost and a long-lasting effect [3]. Brain imaging has demonstrated neurobiological changes produced by placebo AD treatment. Placebo effects can help explain mechanistically how clinicians can be therapeutic agents in the ways they relate to their patients. They rely on complex neurobiological mechanisms involving neurotransmitters and activation of specific and relevant areas of the brain [9]. More specifically, brain imaging has demonstrated neurobiological changes produced by placebo AD treatment among patients suffering from depression [10].

Nonetheless, placebo usage in clinical practice is still ethically controversial and generally prohibited [11,12]. This can be attributed to three elements: the availability of approved, specific and presumably superior biological treatments; the possibility that the discovery of placebo use will damage the therapeutic alliance [13]; and the concern that secretly administering a placebo involves deception, which would be a violation of patient autonomy and the right to informed consent [14]. Patient autonomy requires the patient to provide informed consent. As medicine is currently practiced, the patient lacks the option of consenting not to be informed and of waiving his right to full and detailed disclosure of his treatment and its mechanism of action.

The widespread underground usage of placebo treatments in clinical practice indicates that many physicians choose to ignore the ethical complexity regarding placebo treatments, and frequent usage of placebo treatments has been reported by many physicians [15–17]. To the best of our knowledge, very limited data have been published in recent years regarding the patients' perspective on the use of placebos in clinical practice [18,19]. Previous studies do not directly address the complex, and clinically crucial, question: Are patients willing to be deceived and to waive their right to informed consent in order to receive

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placebo? Avoiding this question is problematic not only clinically but also ethically since, in current clinical practice, we do not offer a possibly safe and effective treatment choice (placebo) to our patients. The widespread use of AD renders this question particularly important [1].

In a previous study, we investigated the opinions of healthy subjects regarding the acceptability of placebo treatment if they were to experience depression [20]. The majority of the study participants found placebos acceptable for the treatment of depression in the clinical setting. The essential limitation of the survey was that it focused on healthy subjects, for whom the question is more hypothetical, and its findings cannot be generalized to a patient population.

In the present study, we attempt to assess the acceptability of placebo usage among patients suffering from depression with current AD medications compared with healthy subjects. Additionally, we conducted within group comparison of attitudes toward placebo usage in depression versus other chronic medical conditions.

## 2. Materials and methods

### 2.1. Sampling design

Between January 2010 and October 2011, a questionnaire survey was conducted at the outpatient clinic of the Shalvata Mental Health Center in Israel. The outpatient clinic serves as the major public mental health clinic in the Sharon district, with more than 19,000 visits annually. It provides multidisciplinary treatment to patients suffering from a wide range of chronic and acute mental disorders.

All patients enrolled in the study were treated with AD medication. Patients were recruited to the study during their routine visit in the outpatient clinic. They were offered to participate in 'a study that aims to learn the patient's perspectives about placebo treatment and involves reading a short passage and completing a questionnaire'. After expressing preliminary interest to participate in the study, patients signed the informed consent form.

The study group (SG) was matched with 114 healthy adults, who constituted the control group (CG). The CG was recruited in various public venues, such as a shopping mall, a railway station and a café, in order to prevent possible selection bias. Matching was based on sex and age. Sociodemographic variables of the respondents are presented in Table 1.

Each participant in both SG and CG attended a single meeting with one of our researchers, lasting between 20 and 30 min. In the first part of the meeting, we provided the subject a thorough written explanation about the placebo, its efficacy in treating mild to moderate depression and the ethical and professional difficulties involved in prescribing placebo medications. Each subject read the information sheet in the presence of one of our researchers. Understanding was verified by the researcher's direct questions and only then was the subject asked to anonymously answer a self-administered questionnaire. In order to minimize the risk for bias, created by the information sheet, we used two methods: first, 5 senior independent psychiatrists assessed the information sheet for possible bias. Only after receiving their corrections and clearance for the final version did we start to recruit subjects for the study. Secondly, 30 healthy individuals read the information sheet and thought that the information given is not in favor for placebo usage nor against it.

Exclusion criteria were a lack of fluency in Hebrew, not having had an encounter with a family physician or a psychiatrist during the past 2 years or not being administered medications for that period. The study was approved by the local institutional review board.

### 2.2. Questionnaire

Five senior psychiatrists and a statistician composed a 32-item questionnaire (the questionnaire is available online at http://hospitals.clalit.co.il/hospitals/Shalvata/he-il/ArticlesAndResearch/Documents/.Placebo%20questionnaire%20doc.pdf). Sociodemographic and health-related data of respondents were collected, including past or present depressive episodes and use of AD and the subject's prior experience regarding medical encounters and informed consent. The five core questions addressed the attitude and willingness of subjects to be treated with placebos if they were to suffer a depressive episode or general medical conditions such as migraine, back pain and high blood pressure. These questions were rated on a dichotomous scale (Yes/No) in order to ensure clear and unavoidable answers. The rest of the questions addressed our subjects' experience of the medical encounter and their ethical attitude toward different elements of informed consent. These questions were rated on a 5-point Likert scale enabling a range of responses (1 = Never, 3 = Sometimes, 5 = Always).

**Table 1**
Demographic variables of CG ($N = 114$) and depressed group ($N = 94$)

| Variable | Group | Nondepressed | Depressed | Significance |
|---|---|---|---|---|
| Gender | Male | 43 (37.4%) | 42 (43.6%) | $X^2_{(2)}=2.56$ ($P=.34$) |
| | Female | 71 (62.6%) | 52 (55.3%) | |
| Marital status | Single | 37 (33.1%) | 23 (23.4%) | $X^2_{(2)}=4.36$ ($P>.36$) |
| | Married | 65 (56.5%) | 53 (56.5%) | |
| | Divorced | 10 (8.7%) | 16 (17%) | |
| | Widowed | 2 (1.7%) | 2 (2.2%) | |
| Education | Up to 12 years | 25 (21.4%) | 47 (50%) | $X^2_{(2)}=25.11$ ($P<.001$) |
| | BA[a] | 45 (39.3%) | 34 (36.2%) | |
| | MA+[b] | 44 (39.3%) | 13 (13.8%) | |
| Use of drugs and alcohol | Yes | 11 (9.5%) | 4 (4.3%) | $X^2_{(2)}=1.42$ ($P=.14$) |
| Age | | Nondepressed | Depressed | Significance |
| | Mean | 40.63 | 47.22 | $t_{(207)}=3.79$ |
| | SD | 12.79 | 12.12 | $P<.001$ |
| | Range | 19–66 | 19.66 | |
| | | **Medical Variables** | | |
| Variable | Group | Nondepressed | Depressed | Significance |
| Chronic disease | Yes | 22 (21.4%) | 32 (34%) | $X^2_{(2)}=1.42$ ($P=.14$) |
| Relatives who suffered a depressive episode | Yes | | 42 (37.6%) | $X^2_{(2)}=7.12$ ($P<.01$) |

[a] BA — Bachelor of Arts.
[b] MA — Master of Arts.

### 2.3. Statistical analysis

Statistical analyses were conducted by using SPSS version 19.0 for Windows. Computing an a priori required sample size using the G*Power 3 program for $X^2$ test. Indicating comparison of two groups ($df = 1$) and aiming to yield a medium effect size (Critical $X^2 = 3.84$) resulted in a total sample size of 145, which is smaller than the sample we collected. Both differences in proportions of demographic variables and comparison of groups or gender regarding questionnaire items were conducted using the Chi-square test. The significance level was set at $P<.05$. Additional analysis was done using Pearson Moment correlation.

## 3. Results

The SG comprised 96 patients, aged 18–60 years (mean [M]=28.60; standard deviation [SD]=7.76), with a history of major depressive episode at some point during the past 12 months that necessitated a psychiatric consultation. We did not assess SG for depression severity at time of enrolment or during the last episode. Nonetheless, since we are a secondary/tertiary psychiatric referral center, our patients usually