Open-label placebos as adjunctive therapy for patients with depression

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ABSTRACT

Background: Placebos prescribed as ‘regular’ medication can reduce symptoms of depression. However, using a placebo without patients’ informed consent presents ethical issues. Therefore, the present study assessed the efficacy of an open-label placebo (OLP), which was administered concurrently with cognitive-behavioral therapy (CBT).

Methods: Sixty patients (mean age: 48 years) diagnosed with major depressive disorder were randomly assigned to a 4-week CBT outpatient program with or without daily OLP treatment. The patients were assessed directly before and after the program as well as three months after the therapy.

Results: Compared to the CBT group, the CBT+OLP group showed a greater reduction in symptoms of depression at the end of the program. Changes in categories pertaining to severity of depression did not differ between groups. All patients completed the program. Noncompliance with the follow-up appointment differed significantly between CBT+OLP (27%) and CBT (7%). Noncompliance was associated with a negative evaluation of the OLP.

Conclusions: The OLP intervention reduced symptoms of depression, however, these changes were not clinically meaningful. The OLP increased the risk for loss to follow-up. The high dropout rate in the present study raises questions concerning the acceptance of OLPs in the treatment of depression.

1. Introduction

Placebos prescribed as a ‘regular’ medication can reduce symptoms of depression in patients with major depressive disorder (MDD). These placebos are referred to as ‘deceptive placebos’ (DP) since they are administered with deception by concealing the true nature of the treatment. The positive effects of DPs for people with MDD have been identified in clinical trials of antidepressants. In some of these trials, placebo response rates were seen to be almost as high as response rates to antidepressants e.g., Refs. [1,2]. Further, beneficial effects of DPs have been demonstrated when given as an adjunctive treatment to cognitive-behavioral therapy (CBT). In a randomized controlled trial by Ref. [3]; patients with MDD participated in a 4-week outpatient CBT program with or without daily placebo treatment. Compared to the standard CBT program, the placebo group showed greater improvement; the DP was associated with a more sizeable reduction in symptoms of depression. Additionally, participants who had received the DP carried out their therapeutic homework (relaxation training) more frequently and experienced greater relaxation effects. Thus, the placebo enhanced therapy outcomes. This was a temporally stable effect. The CBT + placebo group still showed reduced depression scores compared to the standard group after the debriefing at the 3-month follow-up assessment [4].

Even though the use of DPs has been shown to improve therapy outcomes, administering a placebo in a clinical setting without patients’ informed consent presents ethical issues. This approach can be seen to violate the principles of transparency in therapy and respect for the autonomy of patients e.g., Ref. [5]. Moreover, it has been argued that the prescription of DPs may negatively affect the patient-practitioner relationship [6].

The ethical issues surrounding deceptive placebos can be circumvented by using open-label placebos (OLPs). These OLPs are openly administered, meaning that placebo recipients are fully informed that they have received an inert substance or intervention that is not known to directly cause an effect on a certain outcome. The efficacy of OLPs was examined in two meta-analyses [7,8]; overall, OLPs were shown to be associated with a statistically significant symptom reduction in different disorders (e.g., irritable bowel syndrome, back pain, attention deficit

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hyperactivity disorder).

Specifically, two studies have investigated the effects of OLPs in the treatment of depression. In a first pilot study [9], 20 patients were assigned to either an OLP group (n = 11) or a waiting-list group (n = 9). After two weeks, there were no statistically significant differences between the OLP and waitlist groups. Following this, the participants who had been originally randomized to the OLP group continued with the OLP treatment for an additional two weeks, whereas the participants in the waitlist group were then switched to being administered an OLP for four weeks. The total patient group then showed a pre-post improvement in reduction of depressive symptoms after four weeks of OLP treatment. Recently [10], conducted a randomized controlled trial that assessed the efficacy of an OLP as an adjunctive treatment for MDD. Participants in that study received either eight weeks of OLP treatment (n = 18; two capsules in the morning and evening) or four weeks of treatment as usual (TAU) followed by four weeks of OLP (n = 20). It was found that a subgroup of patients (12 non-geriatric patients <65 years) did show a reduction in symptoms of depression during the first four weeks of OLP treatment. However, no overall OLP effect was observed.

In the present study, patients with MDD participated in either a standardized 4-week CBT program (‘Coping with Depression’ course) or the same program plus the daily intake of an OLP. The patients were asked to take the placebo (three drops of a placebo oil) once every day before their therapeutic homework (relaxation training).

We hypothesized that the CBT + OLP group would show a greater reduction of symptoms of depression (primary outcome measure) and improved relaxation responses (secondary outcome measure) compared to the CBT group.

2. Method

2.1. Participants

A total of 60 patients (M = 47.48 years, SD = 11.74) with a primary diagnosis of major depressive disorder (MDD) participated in the study. The patients were randomly assigned (with a random number table) to one of two groups; one group (n = 30) received standard CBT, whereas the other group (n = 30) received CBT plus the daily OLP treatment. The two groups did not differ in mean age, level of education, marital status, number of previous depressive episodes, depression severity, and antidepressant medication (all p > 0.05; see Table 1).

Table 1

| Group characteristics | CBT (n = 30) | CBT + OLP (n = 30) | Group differences |
|-----------------------|-------------|-------------------|------------------|
| Mean age in years (SD)| 48.9        | 46.0 (11.7)       | t(58) = 0.96, p = .34 |
| Female, %             | 83          | 83                | χ(1) = 0.61, p = .44 |
| Education (≥12 years), % | 87          | 67                | χ(1) = 3.35, p = .07 |
| Employed (vs. unemployed/retired) % | 50         | 60                | χ(1) = 2.46, p = .12 |
| In a relationship (vs. single/separated/divorced/widowed), % | 87          | 67                | χ(1) = 1.36, p = .24 |
| Children, %           | 80          | 67                | χ(1) = 0.08, p = .77 |
| Recurrent depression, % | 70          | 67                | χ(1) = 0.65, p = .72 |
| Depression severity* (mild, moderate, severe), n | 10,15,5 | 13,13,4 | χ(1) = 0.34, p = .56 |
| Antidepressants, %    | 70 (n = 21) | 76 (n = 23)       | χ(1) = 0.34, p = .56 |

Note: CBT: Cognitive-behavioral therapy; OLP: open-label placebo; SD = standard deviation; *according to Beck-Depression-Inventory-II; SSRI: selective serotonin reuptake inhibitor; SARI: serotonin antagonist reuptake inhibitor.

The required sample size was calculated using the power analysis program G × Power ( Faul et al., 2009). Based on Kelley et al. (2012, p. 313) and the recommended 0.80 power (f = 0.32), it indicated that 30 participants per group would be sufficient to show a significant differential change in the primary outcome measure (BDI-II score) between the groups (before/after course).

Exclusion criteria for the study were severe comorbidity (e.g., psychotic disorder, substance dependence) and acute suicide risk. Participants receiving antidepressant medication were required to be on a stable dosage for at least eight weeks before study entry.

2.2. Procedure

The present study had been approved by the ethics committee of the University of Graz (Austria) and followed the Declaration of Helsinki. All participants provided written informed consent.

Patients diagnosed with MDD by a psychiatrist or a general practitioner according to ICD-10 [11], were transferred to a community health center where they participated in the brief version of the ‘Coping with Depression’ program [12], implemented by the National Institute of Public Health of Slovenia (NLIŽ). The program consists of four group sessions (six patients per course, 90 min, weekly, over four weeks) and focuses on psychoeducation (e.g., models of depression) and intervention strategies to influence mood (e.g., cognitive restructuring, pleasant activities, and relaxation training). The teaching is combined with homework assignments (e.g., practicing relaxation training at home). All courses (CBT, CBT + OLP) were conducted by the same licensed psychologist.

The OLP group received 30 mL sunflower oil provided in a blue glass bottle with a dropper (for self-administration at home). The bottle had the label ‘placebo’. The information provided to the patients followed the suggestions by Ref. [9]: ‘This oil is a placebo. Placebos are widely used in the treatment of depression. Placebos do not contain any active components and are inert (like sugar pills). Placebos are no drugs. Nevertheless, placebos prescribed in clinical trials have produced significant improvements in various conditions. A possible placebo mechanism is classical conditioning. That is, the body reacts automatically to placebo pills/oil because it has learned to associate the pill/oil intake with symptom reduction. Positive expectations are helpful but are not necessary for the placebo to be effective. Doubts are ok but taking the pills faithfully is critical for the generation of a positive effect. The placebo oil can support you with your relaxation exercises at home. The placebo oil has already been tested as part of a scientific study [3] and found to be effective. This study is now being continued here at this outpatient clinic. If you want to participate, take 3 drops (0.15 mL) orally before your daily relaxation exercise.’

All participants received a guided audio recording for their daily relaxation exercise (duration: 15 min). The practicing period for the relaxation training was three weeks. Directly after the program, the participants of the OLP group returned the bottle to measure the amount of oil used (in ml).

All participants were invited to a 3-month follow-up session (see CONSORT diagram; Fig. 1). Nine participants from the CBT + OLP group and four participants from the CBT group did not return to the follow-up meeting. The non-attendance had been excused by one participant from the CBT + placebo group, and two participants from the CBT group (reported reasons: physical problems).

The participants of the CBT groups and CBT + OLP groups had no contact with each other throughout this research project and were not aware of the different treatment components.

2.3. Measures

The participants completed the following questionnaires directly before and after the program, and during the 3-month follow-up.
a) The Beck Depression Inventory (BDI-II [13]; consists of 21 items rated on 4-point scales from 0 to 3, with higher scores indicating more severe depression symptoms (0–13: minimal depression, 14–19: mild depression, 20–28: moderate depression, 29–63: severe depression).

b) Relaxation quantity and quality (assessed during the course): The participants received a homework booklet for their daily ratings of the relaxation level before and after the exercise (10-point Likert scale: 1 = “not relaxed at all”, 10 = “totally relaxed”).

c) The perceived overall effectiveness of the OLP was rated on a 10-point Likert scale at the end of the course (1 = “not at all effective”, 10 = “extremely effective”).

d) Placebo usage: Participants of the CBT + OLP group returned the placebo bottles at the end of the course. The amount of oil intake (in ml) was measured.

e) Clinician rating: The psychologist who conducted the course reported a change score for each patient on a 7-point Likert scale (1: “strong increase in depression symptoms/worsening”; 4 = “no change”; 7: “strong decrease of depression symptoms/improvement”).

2.4. Statistical analysis

A mixed-model analysis of variance (ANOVA) was computed to test the effects of Group (CBT, CBT + OLP) and Time (before, after course) on reported symptoms of depression (BDI-II scores). Because of the high dropout rate during follow-up (n = 9 in the CBT + OLP group; n = 4 in the CBT group), this session was not included in the ANOVA. However, we compared BDI-II scores at follow-up between the two groups in separate analyses (ANOVAs: pre-course vs. follow-up).

Changes in severity levels of depression (pre vs. post-course) according to BDI-II (minimal; mild; moderate; severe depression) were compared between groups with a Chi-square test. Additionally, patients with vs. without a reduction in depression severity were compared between CBT and CBT + OLP (Chi-square test).

A mixed-model ANOVA was conducted to test the effect of Group (CBT, CBT + OLP) and Time (before/after daily relaxation exercise) on the reported relaxation level. To compare the frequency of relaxation training between the two groups, a t-test was computed.

Finally, correlation analyses were performed to investigate the relationship between the assessed variables (e.g., changes in depression symptoms, perceived effectiveness of the placebo). The statistical analyses were performed using IBM SPSS Statistics, version 26.

3. Results

3.1. Symptoms of depression: before vs. after the program

The ANOVA revealed significant effects for Time (F(1,58) = 352.37; p < .001; ηp² = 0.86) and Group x Time (F(1,58) = 11.94; p = .001; ηp² = 0.20) on the BDI-II scores. The Group effect was not significant (p = .33). The course reduced the BDI-II scores (Mpre = 22.25 (SD = 5.11), Mpost = 15.55 (SD = 5.76; t(59) = 17.24; p < .001). The BDI scores of the two groups did neither differ before the program (CBT: M = 22.30, SD = 4.80; CBT + OLP: M = 22.20, SD = 5.49; t(58) = 0.08; p = .94), nor after the program (CBT + OLP: M = 14.27, SD = 5.66; CBT: M = 16.83, SD = 5.67; p = .08; Fig. 2). However, the score reduction differed between the groups (CBT + OLP: M = −7.93, SD = 2.26; CBT: M = −5.47, SD = 3.19; p = .001).

After the course, 83% of the patients were in a lower severity category of depression. The two groups did not differ concerning the number of patients in the three post-therapy severity categories (below clinical cut-off, mild, moderate depression; χ²(2) = 2.83, p = .244). The number of patients with and without a change in depression severity did not differ between groups (χ²(1) = 4.32, p = .083; with continuity correction because n < 5 in one cell).

The clinician reported a higher change score for the CBT + OLP group (M = 6.03, SD = 0.81) than for the CBT group (M = 5.43, SD = 1.07; t(53.92) = −2.45; p = .02). The change score was substantially correlated with the BDI-II change score (post minus pre-course; r = −0.82, p < 0.001).

3.2. Relaxation training: frequency and quality

The CBT + OLP group (M = 14.57 days, SD = 3.44) practiced more often during the course than the CBT group (M = 11.87 days, SD = 5.20; t(58) = 2.37; p < .02). An exploratory ANOVA to compare the temporal stability of practicing frequency between the two groups during the three weeks of relaxation practice (Time: week 1, week 2, week 3) identified no significant effect of Time and no interaction Time x Group (both p > .78).

For relaxation quality, the ANOVA revealed a significant effect for Time (F(1,58) = 1214.97; p < .001; ηp² = 0.95). The participants reported a higher relaxation level after the exercise (M = 6.80, SD = 0.83) than before the exercise (M = 4.31, SD = 0.76; p < .001). The interaction Group x Time was not significant (F(1,58) = 2.70; p = .11; ηp² = 0.04).

3.3. Follow-up assessment

Eight participants (27%) from the CBT + OLP group and two participants from the CBT group (7%) missed the 3-month follow-up session unexcused (p = .039). Those who dropped out and those who completed the study did not differ in the assessed demographic variables, and BDI-II scores before therapy, all p > .20.

The two groups with the remaining participants (CBT + OLP: n = 21; CBT: n = 26) did not differ in BDI-II scores during the follow-up assessment (CBT + OLP: M = 11.90, SD = 4.95; CBT: M = 14.77, SD = 5.76; t(45) = 1.80; p = .080). The group difference in score reduction (pre course vs. follow-up) was not significant (CBT + OLP: M = −9.86,
SD = 3.26; CBT: M = −7.92; SD = 3.35; t(45) = 1.99; p = .052). The changes in BDI-II scores from post-course to follow-up did not differ between the groups (p = .96).

The reported frequency of relaxation practice after the course did not differ between groups (CBT: M = 2.85, SD = 0.88; CBT + OLP group: M = 3.00, SD = 0.55; t(42.50) = −0.73; p = .47).

3.3.1. Exploratory analysis

Due to the high dropout rate, the psychologist who conducted the program tried to contact the participants to obtain information about the reasons for the noncompliance with the follow-up appointment. Contact was able to be made (telephone call) with eight patients from the OLP group and the following reasons were given for their absence: four participants stated that they did not notice any effect of the placebo and that they perceived the placebo as not being helpful; the remaining four participants gave other reasons for nonattendance (scheduling problems) or no reason. Within the group of patients who perceived the placebo as not being helpful, two participants stated that they did not want to disclose this information in the follow-up session because they did not want to discourage the other group members; one participant did not want to disappoint the therapist.

3.4. Correlation analyses

The reported effectiveness for the placebo (at the end of the course) was M = 7.00 (SD = 1.37; range: 5–10). The average intake of the placebo oil was M = 1.81 ml (SD = 0.41). (The expected intake over the 21-day practicing period with 0.15 ml/day is 3.15 ml).

A higher effectiveness rating for the placebo was associated with more placebo intake (r = 0.87, p < .001), and a greater BDI-II score reduction (pre minus post course; r = −0.71, p < .001).

4. Discussion

The present study investigated the efficacy of adjunctive OLP treatment in patients with depression. The outpatients participated in a 4-week CBT course as the primary intervention, which was combined with the OLP (the secondary intervention). Compared to the regular ‘Coping with depression’ program, the additional OLP treatment reduced self-reported symptoms of depression. The effect of the OLP over standard therapy was M = −2.4 points on the BDI-II. Moreover, the clinician perceived a slightly greater change in symptoms of depression in the CBT + OLP group compared to the CBT group (difference: 0.6 points). Changes in categories pertaining to severity of depression (pre vs. post-CBT) did not differ between groups.

Thus, the OLP treatment was associated with a statistically significant reduction in BDI-II scores, but the practical value (clinical significance) of the OLP in reducing symptoms of depression could not be demonstrated. Our findings are in line with previous studies which also identified modest OLP effects in patients with depression Kelly et al., 2012; [10]. Another OLP study assessed depression symptoms in the context of chronic back pain [14]. The authors found a statistically significant reduction in self-reported symptoms of depression of M ≈ −1 point (depression scale of the Depression Anxiety Stress Scales by Ref. [15] after three weeks of treatment with a non-deceptive placebo. A commentary on this study questioned the clinical relevance of this outcome [16].

Additionally, we assessed OLP effects on the frequency and quality of completed therapeutic homework (relaxation training). The CBT + OLP group practiced more often (on average three additional days (~45 min) during the course). Reported relaxation effects (i.e., relaxation level) did not differ between groups. Thus, the placebo improved the compliance with relaxation training but was not associated with greater training effects.

The analysis of the data from the follow-up assessment indicated no statistically significant group differences concerning the reduction of depression scores and the use of relaxation training. These findings however have to be judged with caution because of the substantial dropout in the CBT + OLP group. A previous placebo study with the same study design (except for a deceptive administration of the placebo) and the same psychologist conducting the course, had shown no dropout in the placebo group [4]. The high dropout rate in the present study raises questions concerning the acceptance of OLPS in the treatment of depression. Four participants from the OLP group stated that they did not attend the follow-up meeting because they perceived the placebo as not being helpful (as revealed by a telephone interview). Dropout and refusal of treatment have been reported before in OLP studies. In the investigation by Ref. [10]; a total of n = 54 patients with MDD were assessed for eligibility. Of these, n = 6 declined to participate and four patients in the OLP group dropped out of the study. In a randomized controlled trial by Ref. [17] on OLP treatment to improve relaxation training effects in healthy students, 15% of the participants refused to take the placebo. Of the participants who had taken the OLP, 69% reported no or only minimal effects. These findings show, that OLPS are not an option for everyone. However, those participants of the present study with higher effectiveness ratings for the OLP showed a higher placebo intake (oil intake in ml) and a greater score reduction on the BDI-II (pre minus post-course). This observation is in line with previous placebo research demonstrating that positive expectations and beliefs about the treatment are an important mechanism in the placebo response (e.g., Refs. [18,19]). However, more research is needed to find out what specific components of the OLP treatment are effective and which patients are most likely to benefit from this type of treatment [5, 20].

This randomized controlled trial has several limitations. The psychologist who provided the placebo also conducted the CBT course. We chose a non-blinded procedure because otherwise, the patients would have been required to withhold information about their group assignment (coupled with the therapeutic homework) from the therapist in charge. In our opinion, this does not seem appropriate because honest disclosure is central to the work of all psychotherapy. However, an additional evaluation of OLP-related effects by an independent (masked) observer should be included in future studies.

Another potential limitation of our study may be the issue of report bias (e.g., ‘wishing to please the psychologist’). In the telephone interview, we found out that those patients who were not satisfied with the OLP treatment were hesitant to reveal this information during the therapy. Finally, the current study differs from previous OLP investigations. We used a placebo oil, and the placebo administration was coupled to a specific behavior (the practicing of relaxation training). Other studies used pills that were taken at fixed time points during the day [9,10]. These differences may affect the placebo response.

5. Conclusion

The present study demonstrated that OLP treatment administered concurrently with CBT was associated with a statistically significant reduction of self-reported clinician-rated symptoms of depression and improved compliance with relaxation training. However, these effects were not clinically meaningful. The increased risk for loss to follow-up due to OLP treatment requires further investigation.

Author statements

The authors have no conflict to declare.
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Declaration of competing interest

The authors have no conflict of interest.

Data availability

Data will be made available on request.

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