Research Paper

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Open-label placebo for chronic low back pain: a 5-year follow-up

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Abstract

Long-term follow-up of patients treated with open-label placebo (OLP) are nonexistent. In this article, we report a 5-year follow-up of a 3-week OLP randomized controlled trial (RCT) in patients with chronic low back pain. We recontacted the participants of original RCT and reassessed their pain, disability, and use of pain medication. We obtained follow-up data from 55 participants (82% of those who took OLP during the parent RCT), with a mean elapsed time between the end of the 3 weeks placebo trial and the follow-up interview of 55 months (SD = 7.85). We found significant reductions in both pain and disability between the baseline assessment immediately before the 3 weeks trial with placebo pills and the original trial endpoint ($P < 0.00001$ for the 2 primary outcomes of pain and disability). At the 5-year follow-up, we found no significant differences in either outcome between original trial endpoint and follow-up. Improvements persisted after 5 years and were accompanied by substantial reductions compared with baseline in the use of pain medication (from 87% to 38%), comprising analgesics (from 80% to 31%), antidepressants (from 24% to 11%), and benzodiazepines (from 15% to 5%). By contrast, the use of alternative approaches to pain management increased (from 18% to 29%). Although the reduction in pain and medication is comparable with the improvements that occurred in the original study, a major limitation of this long-term follow-up is the absence of controls for spontaneous improvement and new cointerventions. Nonetheless, our data suggest that reductions in pain and disability after OLP may be long lasting.

Keywords: Chronic low back pain, Open-label placebo, Follow-up

1. Introduction

Chronic pain is defined as persistent or recurring pain lasting longer than 3 months. Chronic nonspecific low back pain (cLBP) is associated with significant emotional distress or significant emotional disability, specifically interference with activities of daily life and participation in social roles.[35] It is a common health problem worldwide,[6] and the Global Burden of Disease 2016[36] estimated that cLBP is among the leading causes of years lived with disability, imposing a high economic burden on individuals, families, communities, industries, and governments. In Portugal, it affects 36.6% of the population,[18] and in the United States, it is ranked third among all diseases in terms of disability-adjusted life years.[23] The prevalence of cLBP increases and peaks between the ages of 35 and 55 years and is higher in women.[18,36]

Some randomized placebo-controlled clinical trials have failed to find superiority over placebo controls for commonly prescribed first-line therapies for LBP[20,37] suggesting that their effectiveness is due to placebo effects. However, prescribing placebos would pose an ethical conundrum in clinical practice due to the widespread belief that deception is necessary for placebo pills to work.[14,34] In 1965, however, Park and Covi[27] raised the possibility that placebos might be given openly without deception and demonstrated this in a small pilot study with psychiatric patients. However, there was no control group in that study. To date, 14 open-label placebo (OLP) randomized controlled trials (RCT) have demonstrated therapeutic benefits of OLP over control groups. Significant positive results of OLP administration in symptoms of patients in clinical settings have been found for irritable bowel syndrome,[13] fatigue in cancer patients,[11,38] episodic migraine,[12] allergic rhinitis,[30,31] depression,[25] and chronic pain.[1,3,19,26] Two additional studies on attention deficit hyperactivity disorder used a conditioning dose extent paradigm.[28,29] A meta-analysis[5] has shown a medium-sized effect of OLP on symptom reduction suggesting that OLP may have clinical utility.

In 2016, we published the first RCT comparing OLP with treatment as usual (TAU) in patients with cLPB.[3] Both groups were embedded in a supportive patient–physician relationship. We found significant effects with large effect sizes for OLP vs TAU in both pain (g = 0.76) and pain-related disability (g = 0.74). After the initial 3-week treatment period, patients in the TAU control group were given OLP for 3 weeks and showed reductions in pain and disability comparable with those shown by patients in the experimental group. We also found that 87% of patients were taking pain medication at the beginning of the study and that 64% of these reported decreasing their medication while taking OLP.[4]

Our OLP trial for cLBP pain was conducted at a Pain Unit of a General Hospital in Lisbon, Portugal, between November 2013 and December 2015. In this follow-up, we recontacted the original participants of that study and reassessed their pain,

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disability, and use of pain medication, 5 years after having taken OLP pills for 3 weeks.

2. Methods

2.1. Study design

The original parent study[3] was designed to assess pain and disability outcomes after taking OLP for 3 weeks. Ninety-seven adults suffering from cLBP were randomly assigned to a TAU group and an OLP group in which they were asked to take placebo pills knowingly for 3 weeks. Both groups were asked to continue their usual care for cLBP. After completion, participants in the TAU group were offered placebo pills for 3 weeks. Participants were included if they were ≥18 years old and had persistent lower back pain for more than 3 months duration. Participants were excluded if they were medicated with opioids in the previous 6 months, had a history of refusing to take oral medication, had potentially confounding conditions (eg, severe fibromyalgia), and had a surgery within the past 30 days.

For this follow-up study, we tried to reach all 67 participants (38 in the experimental group and 29 in the control group after the crossover) who had completed the study and taken OLP pills for 3 weeks during the original trial. The exclusion criterion was current pain related to musculoskeletal sequelae of trauma occurring after the parent trial had ended. Participants were contacted between April and June 2019 through phone, email, or WhatsApp and asked the set of questions described below. Those reached by email were sent a paper version of the interview as an attachment, and those reached through WhatsApp were sent a link to the questionnaire on Google Forms. Forty participants responded to phone interviews (72.7%) and 15 (27.3%) responded to written questionnaires. The questions asked electronically and by phone were the same.

Phone calls were initially made by a licensed psychologist (M.P.) who was not part of the original study and had no previous contact with participants and did not know whether participants had improved or not. She also followed up with nonresponders. Twenty-seven percent of participants eventually responded to her invitations. To increase the response rate, the principal investigator (C.C.) then reached out to the remaining nonresponding participants (45%). Remaining participants (27%) responded through email and/or WhatsApp. The principal investigator had contact with participants in the original study but did not review any individual information about a participant before contacting them to remain unbiased. Each set of questions began with a brief statement:

"Do you remember having participated in a study about the placebo effect on low back pain 5 years ago at the Hospital de Egas Moniz? We are contacting you because we are interested in knowing how you are doing currently regarding your back pain complaints that led to voluntary participation in the open-label placebo study 5 years ago, as well as the way pain might or might not currently affect your life."

Participants were then asked the questions on the pain and disability scales. In the written questionnaire format, the layout was exactly the same as the questionnaires in the previous study 5 years ago. Each phone interview took approximately 10 to 15 minutes, and the written questionnaire took approximately the 5 to 10 minutes to complete. No financial or other incentive was offered to participants for their participation.

The Comissão de Ética do Centro Hospitalar de Lisboa Ocidental (Western Lisbon Hospital Centre's Ethics Committee) approved the follow-up study design and waived the written informed consent in accordance with Deliberation nº 1704/2015 of the Comissão Nacional de Protecção de Dados and the European General Data Protection Regulation nº 2016/679, artº4, nº11.

2.2. Outcome assessments

The interview and the questionnaire contained basic demographic questions as follows: age, sex, current pain medication, current medication for any medical condition, and complementary and alternative medicine (CAM) usage. As in the original study,[3] primary outcomes were a composite pain intensity scale and a pain-related disability scale. Pain intensity was assessed at the time of the interview by asking participants to rate their maximum, minimum, and usual pain during the previous week using numeric rating scales, ranging from 0 ("no pain") to 10 ("the worst pain imaginable"). The composite pain intensity score is the mean of these 3 pain measures. Pain-related disability was assessed using the validated Portuguese adaptation of the Roland-Morris Disability Questionnaire (RMDQ).[22] The RMDQ includes 24 yes or no statements about difficulty in daily activities, such as difficulties in getting dressed or climbing stairs. The overall score is a sum of positive responses, ranging from 0 to 24, with a higher score signifying more disability.

Our secondary outcome in this follow-up was changes in the use of pain medication from the baseline assessment immediately before the 3 weeks trial with placebo pills to the follow-up, by asking at the time of the interview whether they were currently taking pain medication and compared this with their reported use of pain medication at baseline. Participants were also asked about changes that occurred in their pain treatment and/or their lives that might have contributed to their current back pain condition regardless of whether they were better or worse with the open-ended question: "After completion of the study did you make any change in your treatment for pain and/or in your lifestyle, such as increasing/decreasing medication, usage of alternative and complementary therapies, increasing or decreasing physical activity, and or dietary changes?" Finally, they were asked whether they would take OLP again if suggested by their medical practitioner with the question: "If your doctor gave you the possibility of taking placebo pills again, would you consider it?" Participants could choose between one of 3 options "Yes, for alleviating pain only," "yes, for alleviating other conditions if my doctor suggest it," and "no, never again" and were asked to explain their option. As these questions were not assessed at baseline, they were not subjected to statistical analysis.

2.3. Statistical analysis

Pain intensity and pain-related disability were analyzed using a repeated measures analysis of variance, with time (baseline, endpoint, and follow-up) as the within-subjects factor, with repeated contrasts (baseline vs endpoint and endpoint vs follow-up). Changes in the use of pain medication, antidepressants, benzodiazepines, and alternative medicine were analyzed using the McNemar test. Data were analyzed in SPSS version 26.

3. Results

The mean elapsed time between the end of the 3 weeks original OLP treatment and our follow-up interview was 55 months (SD = 7.84), with a minimum of 39 months and a maximum of 66 months (mode = 60 months). We attempted to contact all 67 participants who took placebo pills during the trial. Six were unreachable, one was excluded because of a recent back injury, and 5 declined to answer the questionnaire. Thus, we were able to obtain follow-up

data from 55 participants, which constitutes 82% of those who took OLP during the original trial. One participant contacted by phone did not answer the RMDQ questionnaire because of time constraints on participant's part. Thus, we have 54 valid answers for the disability outcome and 55 valid answers for all remaining variables. There was no difference between pain and disability reports to the 2 contact researchers and in the pain composite measure between the telephone interview and the written questionnaire. However, significant differences were found between telephone interview and written questionnaire on the RMDQ with respondents to the telephone interview scoring higher (a mean score of 7.32 [SD = 6.68] for the phone interview and 3.33 [SD = 3.99] for the written questionnaire [$P = 0.02$]).

The mean age of respondents at follow-up was 50.6 years old (SD = 13.71). The proportion of women in the original study (71.1%) and the follow-up sample was similar (63.6%).

Table 1 shows pain and disability scores, medication use, and CAM use at baseline and immediately after 3 weeks of OLP treatment in the parent study. These data are shown for the full original sample and for participants who were included in the 5 years follow-up. They indicate that the pain and disability scores at baseline and at endpoint of OLP treatment of the follow-up sample are similar to and not significantly different than those of the full original sample.

3.1. Primary outcomes

Figure 1 show the composite pain and disability scores for baseline, endpoint, and 5 years. The analysis of variance revealed significant effects for both pain [F (2,108) = 21.47, $P < 0.00001$] and disability [F (2,106) = 10.34, $P = 0.00005$]. Repeated contrasts revealed significant reductions in both pain and pain-related disability between baseline and endpoint ($P < 0.00001$ for both pain and disability), with no significant differences in either outcome between endpoint and the 5-year follow-up, indicating that the reduction in pain and disability obtained at the end of the trial was maintained after 5 years.

3.2. Additional outcomes

We asked participants about the medication used at baseline (ie, the week immediately before initiating the 3-week OLP intake) and at the 5-year follow-up reported here. At baseline, 87% of the participants had reported taking medication for their back pain during the previous week. In our 5-year follow-up, we found that the usage of medication had decreased to 38% in the previous week to the assessment (OR = 3.00, $P = 0.013$).

The use of analgesics had decreased from 80% to 31% at follow-up, the consumption of antidepressants to control pain was reduced from 24% at baseline to 11% at the 5-year follow-up (OR = 7.00, $P < 0.00001$), and the use of benzodiazepines decreased from 16% at baseline to 6% at follow-up (OR = 15.33, $P < 0.00001$). In addition, participants reported an increase in the use of alternative approaches to manage pain increasing from 18% of participants at baseline to 29% at follow-up (OR = 2.81, $P = 0.00026$). These data suggest that taking OLP for 3 weeks may have contributed to a significant reduction in pain medication consumption and that some participants replaced a pharmacological approach to pain management with a nonpharmacological and self-care pain managing approach.

3.3. Life and lifestyle changes

Table 2 displays the life and lifestyle changes reported by patients. The most frequently reported category of life change at 5 years was positive changes in lifestyle (eg, changes in diet, exercise, weight, and/or medication use), which was endorsed by 52.7% of participants.

Finally, we asked participants whether or not they would take OLP again if prescribed by their doctor. Thirty-six participants reported being receptive to the idea of taking OLP again, either for pain alone (12 participants) or for other medical conditions (24), 18 participants reported that they would not take OLP pills again, and 1 participant did not respond to this question. Reasons expressed by the ones that were willing to take placebo again were "pain depends on our attitude" (8 participants), "it worked" (5 participants), and curiosity about how it would work for other conditions (5 participants). The main reason mentioned for not be willing to take OLP again is that "it did not work" (8 participants). Other reasons mentioned were "I do not need it, I am doing other things to manage my pain (dieting and/or CAM) (3 participants)," "not wanting to take pills on a daily basis, even placebo" (2 participants), "I can fool my mind without pills" (1 participant), "I would have to waste time by going to the doctor" (1 participant),

Table 1

Pain, disability scores, medication, and complementary medicine for pain relief usage at baseline and at endpoint (after 3 weeks of open-label placebo treatment) for the full original sample on the parent study and for the participants included in the 5-year follow-up.

Characteristic	Original sample (parent study n = 83)	Follow-up sample (n = 55)
Baseline		
Mean (SD) minimum pain	2.98 (2.0)	2.82 (1.9)
Mean (SD) usual pain	4.98 (1.8)	4.95 (1.7)
Mean (SD) maximum pain	7.11 (1.7)	7.07 (1.4)
Mean (SD) composite pain	4.99 (1.79)	4.83 (1.68)
Mean (SD) disability (RMQD score)	9.17 (4.92)	9.09 (4.87)
% Using pain medication	86.7%	87.2%
% Taking antidepressants	22.9%	23.6%
% Taking benzodiazepines	15.7%	16.4%
% Using complementary medicine for pain	14.5%	18.2%
After 3 wk OLP		
Mean (SD) composite pain	3.38 (2.40)*	3.25 (2.37)
Mean (SD) disability (RMQD score)	6.01 (5.22)†	5.76 (5.3)

* n = 69.

† N = 70 because of missing data (1 pain score), drop out, and/or declined 3 weeks follow-up at the parent study. RMDQ, Roland-Morris Disability Questionnaire

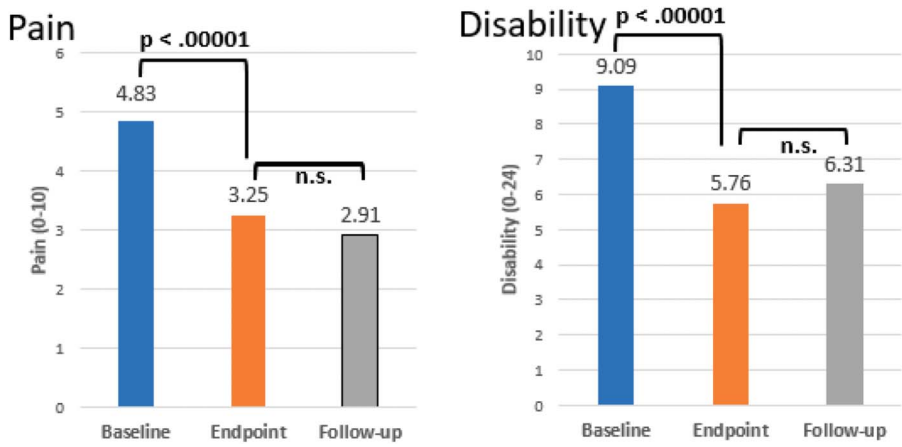

Figure 1. Outcomes at 3 points in time (baseline, endpoint after the 3 weeks OLP trial, and 5 years follow-up). The mean composite score for the pain measure. The mean disability score on the 24-item Roland-Morris Disability Questionnaire. Error bars are standard errors of the mean. OLP, open-label placebo.

and "I am too far away from the hospital to get placebo pills" (1 participant). Two participants did not provide a reason for not wanting to take OLP again.

4. Discussion

Our original 2016 study on cLBP showed significant reductions in pain and pain-related disability after OLP intake for 3 weeks. The results of this follow-up indicate that these benefits persisted after 5 years and were accompanied by substantial reductions in the use of pain medication (from 87% to 39%), antidepressants (from 24% to 11%), and benzodiazepines (from 15% to 5%). By contrast, the use of alternative approaches to pain management increased (from 18% to 29%), suggesting that some participants changed their approach to pain management to a more nonpharmacological approach compared with baseline.

Table 2

Participants self-reported life and life style changes reported since the termination of the trial.

Self-reported changes in life	N (%)
Attitude change towards pain	10 (18.2%)
Positive life events (eg, better job, less hours work, and less physical demands)	3 (5.5%)
Negative life events (eg, unemployment, retirement, divorce, and other morbidities)	8 (14.5%)
Positive lifestyle changes (eg, diet, exercise, lost weight, increased social activities, and reduced medication)	29 (52.7%)
Negative lifestyle changes (eg, increased weight and stopped exercise)	3 (5.5%)
Complementary and alternative treatments to pain (eg, acupuncture, osteopathy, and supplements)	16 (29.1%)
Standard alternative treatments to pain (eg, physical therapy and surgery)	8 (14.5%)
No reported changes	8 (14.5%)

Values are represented as numbers (percentages) of participants unless stated otherwise. Binary variables indicate the number (percentage) for whom the response is "yes."

Participant's self-report on changes that occurred after the endpoint seems to confirm this hypothesis, as more than half of participants reported at time of follow-up an increase in self-care and pain management strategies. As reported earlier, the percentage of participants engaging in alternative treatments for low back pain, such as acupuncture or osteopathy, also increased. Moreover, when asked why they would be willing to take OLP again, some participants reported they have realized that their attitude played a role in pain perception and behavior, which together with the decrease in medication intake, and increase in healthy behaviors may suggest that as a result of the trial they have moved back from the status of a "docile patient" to the initial position (before disease) of "free agent" of their health.[15,17] It is also possible that taking OLP may have offered the chance of a real-world practice that challenged patient's beliefs about back pain and induced cognitive restructuring about their condition.

4.1. Limitations

The main limitation of our study is that it is observational and had no control group (eg, a notreatment control) that would allow us to assess whether the persistence of improvement was due to the original OLP intervention or spontaneous improvement, the natural long-term natural course of cLBP or new interventions (eg, alternative therapies). To address that concern and to find data that could be compared with ours, we performed a MEDLINE search for studies in which changes in pain in patients diagnosed with chronic low back pain were followed up years later. We found 7 long-term studies with pain intensity ratings measured on 0 to 10 or 0 to 100 scales, comprising 13 treatment arms and one notreatment arm (**Table 3**),[2,7–10,16,32] including one that also reported the percent of patients still using analgesics.[32]

The mean pain change weighted for sample size across the treatment arms was 2.97 points, (48% improvement). That of the untreated control arm was 1 point (17% improvement). Long-term improvement for OLP in our study was 1.92 points (40% improvement). In addition, Sköld et al.[32] reported on the use of analgesic medication 5 years after disk replacement and disk fusion. In that study, analgesics were still being used for low back pain by 41% of patients after disk replacement and 62% of patients after disk fusion. Our 5-year follow-up data indicate analgesic use by 31% of patients after OLP.

Table 3

Mean and % improvement from baseline pain in long-term follow-up studies of cLBP.*

Study	Treatment (follow-up n)	Improvement†
Carvalho et al.	OLP (55)	1.92 (40%)
Bendix et al.,[2] 1998	Physical training + psychological support + education (83)	1.00 (18%)
	Physical training + psychological support (29)	0.00 (0%)
	Physical training (31)	0.00 (0%)
	No treatment (42)	1.00 (17%)
Friedrich et al.,[9] 2005	Exercise program + motivational support (26)	3.4 (67%)
	Exercise program (30)	0.7 (13%)
Sköld et al.,[32] 2013	Disk replacement (80)	3.96 (45%)
	Disk fusion (72)	2.80 (38%)
Endler et al.,[7] 2019 (7 years)	Noninstrumented fusion (124)	3.00 (48%)
	Instrumented fusion (711)	3.00 (48%)
	Interbody fusion (683)	3.30 (53%)
Groot et al.,[10] 2019 (6.5 years)	Cognitive behavioral program (277)	2.70 (45%)
Fischgrund et al.,[8] 2020	Intraosseous basivertebral nerve ablation (100)	4.38 (65%)
Kareem et al.,[16] 2020	Spine stabilization (35)	3.10 (43%)

* Except as otherwise noted, all follow-ups were at 5 years after end of treatment.
† Improvement on visual analogue scale (VAS) or numerical rating scale (NRS). 0 to 100 scales were converted to 0 to 10.
cLBP, chronic nonspecific low back pain; OLP, open-label placebo.

Taken together, our data suggest that a brief intervention with OLP can produce substantially greater long-term benefits in patients suffering from cLBP than those seen in notreatment arms[2] or with an exercise program aimed at improving spinal mobility,[9] although somewhat less than that seen in more invasive or multidisciplinary treatments.[7–10,16,32] However, strong inferences from these comparisons may be confounded by differences in patient populations.

Another limitation of our study is that we were not able to reach the total number of participants that took placebo pills during the original study. Nevertheless, we were able to reach 82% of participants. In addition, our outcome measures were subjective and rely solely on self-report. However, self-reported pain and disability are the standard outcome RCTs of cLPB.

We used 2 methods to contact participants, electronic, by sending a questionnaire and by telephone interview. No differences were found on the reports of pain between these 2 methods. However, we found differences on disability with participants reporting higher disability scores on the phone interview. One might expect the telephone interview to be more prone to effects of social desirability and report bias. However, our results are in the opposite direction of this hypothesis. Nevertheless, the mean score of the RMDQ for both groups was low and similar to the scores reported immediately after OLP treatment in the original study.

Finally, our original study and follow-up did not assess psychological variables, such as pain expectation, self-efficacy (one's confidence regarding one's ability to function effectively while in pain[24]), nor pain acceptance (one's willingness to acknowledge pain as part of the life experience without attempts to control or avoid it[21]), all important constructs that might serve as resilience factors.[33] Future studies should include such variables at baseline, endpoint, and long-term follow-up.

5. Conclusion

Our study is the first long-term follow-up on the results of OLP treatment. Our data indicate that reductions in pain and disability after the administration of OLP may be long lasting. There was no significant deterioration in either pain or disability 5 years after the termination of successful OLP treatment. Further long-term follow-up studies on OLP with appropriate controls are warranted.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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