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No long-term effects after a 3-week open-label placebo treatment for chronic low back pain: a 3-year follow-up of a randomized controlled trial

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Abstract

Chronic low back pain is prevalent, highly disabling, and a relevant socioeconomic health concern. Although allocated to placebo groups, patients in randomized controlled trials show significant pain relief, pointing to the relevance of placebo effects. Overcoming ethical and legal concerns related to deceptive placebos, recent studies have demonstrated the efficacy of short-term treatments for chronic low back pain with open-label (ie, nondeceptive) placebos. However, data on long-term efficacy of open-label placebos are sparse. Here, we report a 3-year follow-up of our previously published randomized controlled trial demonstrating pain reduction, improvement in disability, and depressive symptoms after a 3-week treatment with open-label placebos. Including records from 89 previously enrolled patients, we investigated changes between the groups with and without previous open-label placebo treatment in pain intensity (primary outcome), disability and mood (secondary outcomes), biopsychosocial factors and lifestyle (exploratory outcomes) from parent baseline to follow-up. Over the 3-year period, there were no differences in any outcome between groups with and without open-label placebo treatment. Therefore, our follow-up data do not support the previously suggested assumption that a 3-week open-label placebo treatment has long-term effects. This study was preregistered on April 14, 2020, in the German Clinical Trials Register (registration number DRKS00021405).

Keywords: Back pain, Chronic pain, Placebo effect, Nondeceptive placebo, Open-label placebo, Longitudinal study

1. Introduction

As the leading cause, low back pain contributes to approximately 11% of all years lived with disability worldwide.[44] With a prevalence of nearly 10% in the United States,[2] chronic back pain (CBP, ie, back pain lasting ≥3 months) is an important social and economic health concern.[44] Best estimates suggest that CBP may be even more prevalent in Europe,[1,3] underscoring the need for effective treatment. However, despite notable efforts to improve treatment strategies, current first-line therapies are often not more effective than placebos or frequently accompanied by side effects.[1,11]

Although allocated to placebo groups, CBP patients in randomized controlled trials (RCTs) show significant pain relief, pointing to the relevance of placebo effects in CBP.[9] Because prescribing deceptive placebos (ie, without patient consent) is inextricably linked to ethical concerns,[13] harnessing of placebo effects for treatment is hampered. A novel approach supported by a growing body of evidence[10,45] is open-label placebos (OLPs), which are provided with full consent about the nature of a placebo pill. In the field of pain, studies have shown that OLP in addition to treatment as usual (TAU) can improve outcomes, for instance in irritable bowel syndrome,[25,29] episodic migraine,[23] and CBP.[7,27] Given OLP's tolerability and safety, these findings indicate that they can have clinically relevant short-term benefits.

Because most trials used a 2- to 3-week treatment period, data on long-term effects of OLP are sparse. Most recently, Carvalho et al.[8] reported a 5-year follow-up of 54 patients of their landmark RCT on the efficacy of a 3-week OLP treatment for CBP.[7] Both primary outcomes (ie, pain intensity and disability) showed significant improvement from the trial's baseline to follow-up, with no difference between the trial's endpoint and follow-up, indicating maintained improvement over the course of 5 years. Secondary outcomes showed a 38% decrease in medication usage from baseline to follow-up, whereas participants reported an increase in the use of alternative treatment strategies (18%-29%), pointing towards a shift from pharmacological to nonpharmacological treatment. However, as the authors noted, because of a predefined crossover from TAU to OLP treatment, in which all patients received OLP at the end of the study, follow-up was performed as an observational analysis without a control group, preventing causal attribution of continued improvements to OLP treatment.

From 2017 to 2018, we conducted an RCT with 122 patients suffering from CBP and reported significant pain reduction, improved disability, and fewer depressive symptoms after a

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 164 (2023) 645–652

http://dx.doi.org/10.1097/j.pain.0000000000002752

3-week OLP (in addition to TAU) treatment compared with TAU only.[27] Here, we present a 3-year follow-up investigation of data from 89 patients (n = 47 OLP + TAU, n = 42 TAU), who completed this previous RCT. In our parallelly designed study, the objective was to examine potential long-term effects of OLP + TAU compared with TAU on pain intensity (primary endpoint) as well as disability and mood (ie, depression, anxiety, stress; all secondary endpoints). Exploratory analyses included biopsychosocial factors, treatment efficacy, lifestyle changes, and treatment expectancy regarding a potential future OLP treatment.

2. Methods

2.1. Parent trial and follow-up design

2.1.1. Parent trial

We report a 3-year follow-up of our previously reported RCT (in the following referred to as "parent trial") comparing the efficacy of a 3-week OLP treatment (2 capsules OLP daily + TAU) vs TAU only (for full report see Ref. 27). In the present study, 122 patients suffering from CBP lasting >12 weeks were randomized to either an OLP + TAU or a TAU group. To maintain protocol compliance, patients in the TAU group were offered a voluntary OLP treatment after trial participation, which 11 patients used (see *Patients* and **Fig. 1**). The trial was conducted at a tertiary center (Back Pain Center, University Hospital Essen, Germany) between March 27, 2017, and May 29, 2018. The primary outcome was pain intensity, and secondary outcomes included patient-reported functional disability, objective measures of spine mobility, and symptoms of depression, anxiety, and stress. In summary, we reported a reduction of pain intensity (d = 0.44) as well as patient-reported functional disability (d = 0.45) and depression scores (d = 0.50) after OLP administration compared with TAU only. Open-label placebo treatment did not affect objective mobility parameters, anxiety, and stress.

2.1.2. Follow-up study

This study was performed in accordance with the Declaration of Helsinki and approved by the Duisburg-Essen University's Ethics Committee (study ID 16-7218-BO). It was preregistered on April 14, 2020, in the German Clinical Trials Register (registration number DRKS00021405). Participating patients received monetary compensation.

The follow-up study intended to investigate potential long-term effects after a 3-week OLP treatment for CBP. All patients (N = 122) previously included in our parent trial's analysis were eligible for participation in the follow-up study. Similar to the parent trial, TAU was defined as any pharmacological or nonpharmacological treatment. Extending our preregistration, which only included consent withdrawal as exclusion criterion, we decided to also exclude CBP patients with potentially confounding conditions (ie, pain other than CBP, cancer pain, and postsurgical pain).[8] Invalid address or telephone details resulted in loss to follow-up of 9 patients, resulting in a total sample of 113 (92.6% of the original sample, n = 60 former OLP + TAU group, n = 53 former TAU group). These patients were invited to participate by mail 36 ± 3 months after enrollment, so that the data collection period ranged from April 20, 2020, to March 2, 2021. All outcomes were assessed using paper-based questionnaires (see below).

To determine whether OLP treatment was self-initiated after participation in the parent trial, all participants were asked: "Since trial participation, have you ever knowingly taken placebos again (tablets or capsules without active ingredient)?" If answered with "yes," crossover status was validated in a short, standardized phone interview by one of our subinvestigators (mean call duration 5.1 minutes, range 1-10 minutes). In total, 6 patients previously randomized to the TAU group confirmed a voluntary OLP intake after trial participation and 5 remained unavailable. If OLP treatment was confirmed, route of administration (ie, capsule [n = 3] or tablet [n = 2]), intake period (ie, less than one week [n = 3]; between one and 2 weeks [n = 2]; between 3 and 4 weeks; and other), and frequency (ie, as rescue medication; twice daily [n = 3]; daily [n = 2]; and other) were recorded. In all cases of confirmed posttrial OLP treatment, this treatment duration fell below the 3-week OLP period of the parent trial, so that we decided to categorize these patients as TAU-randomized to increase statistical power. However, a sensitivity analysis excluding these cases from the TAU group revealed similar results (see Table S1, available as supplemental digital content at http://links.lww.com/PAIN/B693).

2.2. Outcome assessments

The paper-based questionnaires contained the following sections: general information and demography, current state of health and medical history since parent trial completion, current medication, nonpharmacologic treatment, mindset regarding OLPs, pain intensity, expectancy and credibility regarding a potential feature OLP treatment, functional disability, self-efficacy, global impression of change, symptoms of depression, anxiety, and stress.

2.2.1. Primary outcome

The primary outcome was the change in pain intensity from parent baseline to follow-up at 3 years, which was compared between groups. Like in our parent trial, pain intensity over a 4-week period before assessment was rated as minimum, average, and maximum pain intensity rating on an 11-point numeric rating scale (NRS, 0-10; no pain to strongest pain imaginable). The single ratings were then averaged to a composite pain score by calculating the mean of the 3 ratings.[7,27]

2.2.2. Secondary outcomes

Secondary outcomes included the change in disability, depression, anxiety, and stress from baseline to 3-year follow-up, which were compared between groups. Disability was assessed using the Oswestry Disability Index (ODI),[16] a widely used, validated questionnaire assessing functional status and quality-of-life impairment over a 4-week period in patients with back pain and spinal cord disorders, resulting in a percentage (0%-100%), with higher scores representing greater impairment. Depression, anxiety, and stress were assessed using the Depression Anxiety Stress Scale,[31] a 42-item self-report instrument designed to measure the 3 related negative emotional states of depression, anxiety and tension/stress over one week before assessment. Evaluation of the 3 subscales reveal sum scores ranging from 0 to 21, with higher scores representing stronger negative emotion.

2.2.3. Exploratory outcomes

We investigated different exploratory outcomes including biopsychosocial factors contributing to the development and maintenance of chronic pain (ie, self-efficacy), factors potentially involved in mechanisms of or resulting from OLP treatment (ie, use of nonpharmacologic [ie, physical, manual, psychological,

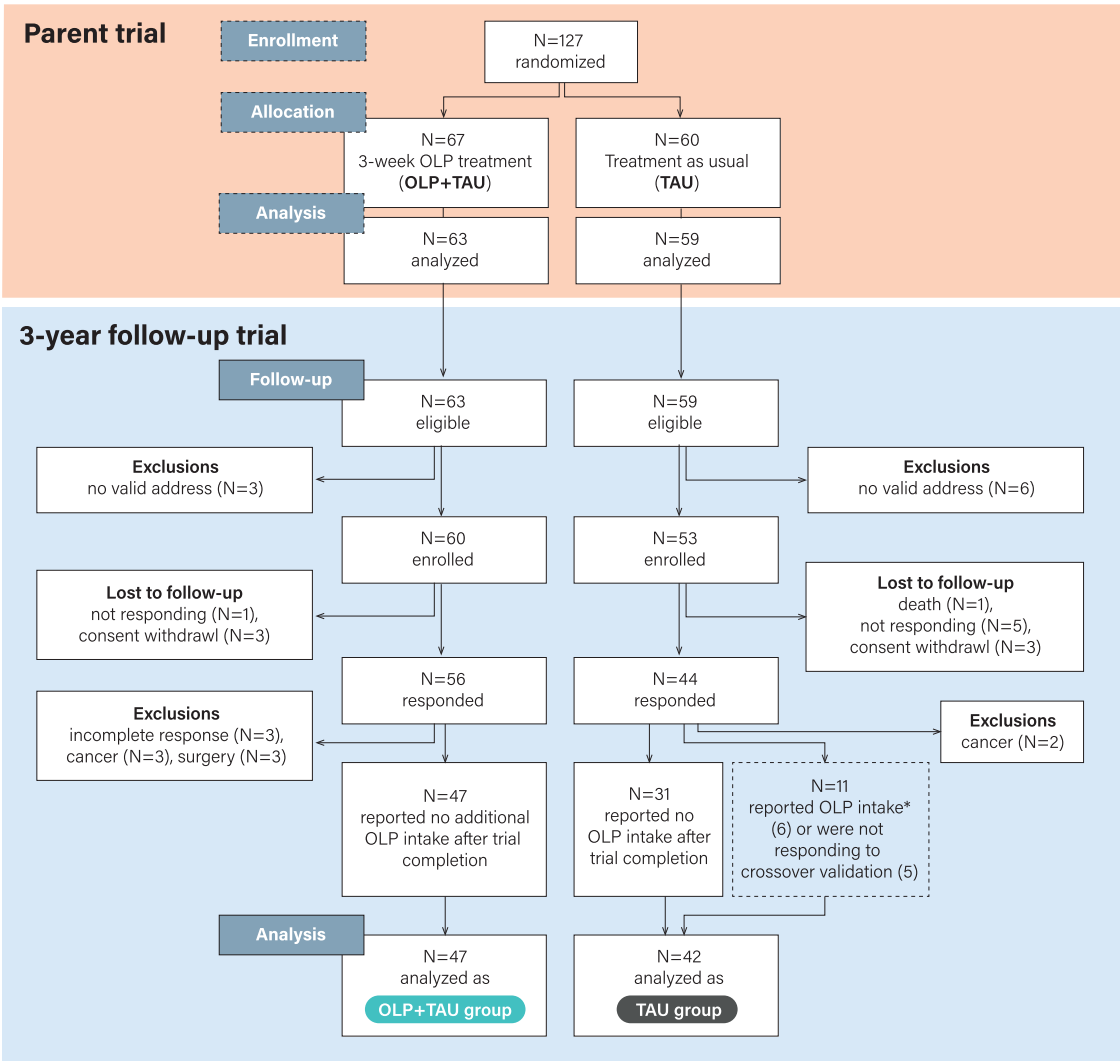

Figure 1. Patient flow chart. The chart illustrates the flow of patients in our parent trial (see Kleine-Borgmann et al.[27]) and in this follow-up study after 3 years. *In all cases of confirmed posttrial OLP treatment, this treatment duration fell below the 3-week OLP period of the parent trial, so that we decided to categorize these patients as TAU-randomized to increase statistical power. OLP, open-label placebo; TAU, treatment as usual.

and complementary]), treatment expectancy, treatment efficacy, and lifestyle changes (ie, sports and relaxation techniques). Self-efficacy was assessed by the German adaptation of the Pain Self-Efficacy Questionnaire.[33] For treatment efficacy, the Patient Global Impression of Change Scale was used.[22] Furthermore, use of inpatient and outpatient pain associated healthcare were recorded. Treatment expectancy regarding a future OLP treatment was assessed by the Credibility/Expectancy Questionnaire.[14] A change of pharmacological treatment was assessed based on self-report (yes/no). All other outcomes were recorded by standardized in-house questionnaires.

2.3. Statistical analysis

Analyses were performed using generalized linear mixed models using the software R and RStudio (The R Project for Statistical Computing, Version 3.6.3, The R Foundation, https://www.r-project.org/ and RStudio, PBC, Boston, MA, https://www.rstudio.com/). Using mixed model analyses accounting for potential confounders, in accordance with Assmann et al.,[4] we did not test for baseline imbalances between the experimental groups. Separate analyses were performed for the following dependent variables: pain intensity, functional disability, depression, anxiety, and stress. Fixed effects included the factor *time* (4 levels: baseline [reference], day 11 [for pain intensity model only], day 21, day 90, and 3-year follow-up) and *group* (2 levels: OLP + TAU vs TAU [reference]). Furthermore, to investigate any differences between the parent trial's endpoint (day 21) and 3-year follow-up, we performed an exploratory analysis with the parent trial's endpoint (ie, day 21) as the model's reference. All models included a random intercept and random slope for patients and *time* as a random effects factor. Considering the robustness of mixed models, missing data were included into the models without using multiple imputation.[42] Model estimates are reported as absolute beta values (β) with 95% confidence intervals. R^2 is presented for each model as a measure of explained variance of fixed and random effects. Furthermore, Cohen d is reported for each fixed effect factor. For continuous exploratory outcomes (ie, self-efficacy and treatment expectancy), Shapiro–Wilk tests were performed, which revealed a nonnormal distribution of the data. Thus, nonparametric Wilcoxon rank sum tests were performed to test for group differences. Categorical outcomes (ie, medication change, non-pharmacological treatment, inpatient and outpatient treatment,

sport activity, physical therapy, manual therapy, relaxation techniques, complementary treatment, and treatment efficacy) were tested in cross tabulations for group differences with Pearson χ^2 tests (using Yates continuity correction, if applicable).

3. Results

3.1. Patients

Based on a sample size of 122 patients in our parent trial, we succeeded in inviting 113 patients (92.6% of the original sample) to participate in this follow-up study. Although 13 patients were lost to follow-up (**Fig. 1**), 100 patients responded (11.5% dropout). We excluded 8 patients who reported relevant additional causes for pain (ie, cancer pain or postoperative pain) and 3 patients with incomplete reports, resulting in a total of 89 patients included in our analysis (n = 47 OLP + TAU and n = 42 TAU). The mean time difference between the parent trial's inclusion date and the follow-up assessment was 34.2 months (95% CI [33.8, 34.4]). Patient characteristics at baseline for the follow-up sample are shown in **Table 1**.

3.2. Primary outcome

When comparing the OLP + TAU group with the TAU group regarding the change in pain composite scores over a 4-week period from parent baseline to follow-up, we did not observe any differences (OLP + TAU vs TAU: $\beta = -0.40$, 95% CI [−1.04 to 0.23], t[408] = −1.24, $P = 0.214$, d = −0.14, $R^2 = 0.69$), indicating that OLP did not add benefits to TAU for our CBP patients in long term. Pain intensity ratings over the course of time are shown in **Figure 2**.

3.3. Secondary outcomes

Secondary outcomes comprised the change in disability (assessed by the Oswestry Disability Index with disability reported in %), depression, anxiety, and stress (reported as DASS score) from baseline to 3-year follow-up (**Fig. 3**). Patients in the OLP + TAU group showed no significant changes compared with TAU patients in any secondary outcome (for statistical terms, see Table S2, available as supplemental digital content at http://links.lww.com/PAIN/B693).

Table 1

Baseline characteristics of the treatment as usual and open-label placebo in addition to treatment as usual groups.

Characteristic	OLP + TAU n = 47	TAU-only n = 42
Female, n (%)	29 (62)	32 (76)
Age (in years)	62.5 (58.0-67.1)	58.5 (53.8-63.2)
Composite pain score over the past 7 d	5.3 (4.7-5.9)	5.1 (4.5-5.7)
NRS minimum	3.3 (2.6-4.0)	3.0 (2.3-3.7)
NRS average	5.5 (4.8-6.2)	5.6 (4.8-6.3)
NRS maximum	6.9 (6.2-7.6)	6.7 (6.1-7.3)
Depression Anxiety Stress Scale (DASS subscale score, range 0–21)		
Depression subscale	4.4 (3.1-5.9)	4.3 (3.1-5.5)
Anxiety subscale	4.2 (2.9-5.5)	3.3 (2.3-4.4)
Stress subscale	6.5 (4.9-8.1)	7.5 (6.2-8.8)
Disability		
Oswestry disability index (%)	29.1 (25.1-33.2)	28.3 (24.5-32.0)
Disability days per month	1.2 (0.8-1.6)	1.1 (0.7-1.5)

All characteristics are provided as mean and 95% confidence intervals (in parentheses) if not stated otherwise.
NRS, numeric rating scale; OLP, open-label placebo; TAU, treatment as usual.

3.4. Exploratory outcomes

Exploratory outcomes comprised self-efficacy (FESS), treatment expectancy (CEQ), treatment efficacy (PGIC), lifestyle modifications, and treatment changes reported at 3-year follow-up (see Tables S3 and S4 for statistical terms and Figure S1, available as supplemental digital content at http://links.lww.com/PAIN/B693). The analysis revealed that OLP + TAU-treated patients were less likely to report use of relaxation techniques at 3-year follow-up compared with patients in the TAU group ($X^2(3, n = 67) = 8.19$, $P = 0.042$). However, groups did not differ in any other exploratory outcome, including treatment efficacy, nonpharmacological treatment, inpatient and outpatient treatment, sports, physical or manual therapy, or use of complementary treatment. Thus, despite the frequency of using relaxation techniques, there are no indications for clinically relevant long-term OLP-associated lifestyle or treatment changes. Extending our analysis of primary and secondary outcomes, we changed the time frame from baseline to parent trial's endpoint and follow-up. Primary and secondary outcomes were then reanalyzed as exploratory outcomes. However, we observed no differences in changes from day 21 to follow-up in any primary or secondary outcome when comparing the trial groups (see Table S5, available as supplemental digital content at http://links.lww.com/PAIN/B693).

4. Discussion

Here, we present the follow-up of our RCT published in 2019, in which we reported the short-term efficacy of a 3-week OLP treatment on pain intensity, disability, and depressive symptoms.[27] Compared with the parent trial's baseline, there were no significant differences in pain intensity between the OLP + TAU group and the TAU group after 3 years. Also, disability and depressive symptoms did not differ between groups at follow-up. Exploratory analyses of potential mediators of OLP effects, such as self-efficacy, treatment expectancy towards a potential future OLP treatment, perceived treatment efficacy, and lifestyle changes, showed no differences between groups. Thus, our data do not support the assumption that a short-term OLP treatment in addition to TAU has long-term effects.

Our results contradict those of Carvalho et al.,[8] who recently published a 5-year follow up on their RCT of a 3-week OLP treatment for CBP. Within this period, no significant time effect, on either pain intensity or disability, was observed between the end point of the original study and the follow-up, suggesting continued efficacy of OLP. In addition, their patients reported a significant decrease in the reliance on medications, although the use of alternative therapies had increased. The authors suggest that some patients might have substituted a pharmacological for a nonpharmacological and self-care approach to pain management after OLP intervention. However, their study was observational, ie, lacking a control group because of a predefined crossover to OLP in all patients who were randomized to TAU during the parent study. Thus, it was impossible to dissociate the "stable response to OLP" from the natural course of CBP over the course of 5 years, although comparisons with other long-term follow-up studies in the field of CBP (ie, comparison with a no treatment arm[5] and with an exercise motivational program[18]) may support such notion. Our follow-up study, in addition to a large sample within this research field and a low dropout rate

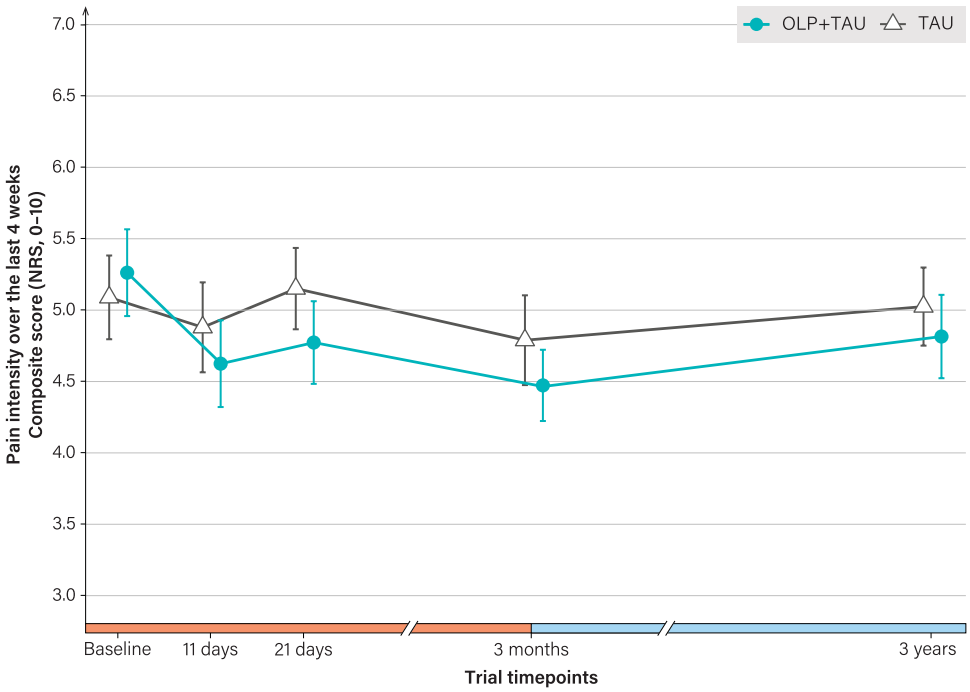

Figure 2. Primary outcome. Group differences (OLP + TAU: turquoise dots; TAU: white triangles) in change in pain intensity over a 4-week period. Group-wise mean values and SEs (error bars) are shown for all study time points. The colored x-axis illustrates the respective study (orange: main study time points; blue: 3-year follow-up study). NRS, numeric rating scale; OLP + TAU, open-label placebo in addition to treatment as usual group; TAU, treatment as usual group.

compared with other clinical trials,[46] has the strength of preserving its parallel group design (ie, OLP + TAU and TAU group) and therefore allowing causal inference.

We did not observe any relevant medication or lifestyle changes in our sample besides fewer use of relaxation techniques in patients allocated to the OLP group. Again, this finding deviates from the results of Carvalho et al.[8] who reported a decrease in medication use and a tendency of their patients to use alternative pain management approaches. We believe that it was legitimate to speculate that a novel, unconventional, and maybe counter-intuitive treatment like OLP might enable established treatments (eg, pain medication) to be critically reviewed and, for example, alternative treatment options to be given consideration. Indeed, recent research on the experiences of patients treated with open-label vs double-blind placebo in the United States found that patients receiving OLP had more ambivalent and self-reflective thoughts.[20] However, because our study was conducted in Germany, regional, cultural, and socioeconomic differences (eg, healthcare access) between the samples should be considered.

The results of our study should be interpreted considering the following limitations. First, our study is susceptible to recall bias, similar to other follow-up studies evaluating self-reported outcomes. Future research should implement more frequent assessments, for instance by using app-based solutions. Second, during the follow-up period, a variety of factors might have affected potential long-term effects of the initial short-term OLP treatment (eg, pain because of reasons other than CBP, other somatic or psychiatric comorbidities, and surgery). However, we made extensive efforts to account for these potential confounders and included multiple items in our questionnaires addressing them (eg, use of open-label or deceptive placebos, participation in clinical trials after our parent trial, comorbidities, surgeries). This resulted in exclusion of patients with pain conditions other than CBP. Furthermore, our results were robust in a sensitivity analysis (see *Methods*). Finally, although the effect size of a 3-week OLP treatment on pain intensity in our parent trial was moderate, the absolute mean difference was rather small (0.7 points on a 0 to 10 NRS, d = 0.44), yet comparable with the effect of nonsteroidal anti-inflammatory drugs.[32,36] This might have contributed to the lack of significance in the follow-up study, although—in our view—the lack of long-lasting symptom improvements after 3 years is already well explained given the short duration of OLP treatment in our primary study.

Although a considerable body of evidence documents significant placebo effects in experimental and clinical trials,[43] and modern accounts recognize the relevance of placebo effects to treatment outcomes in routine clinical practice (reviewed in Ref. 6), research on nondeceptive placebos is still in its early stages, and studies on long-term effects are almost nonexistent. Since the first report of OLP in 1965,[35] its efficacy after a short-term administration has been demonstrated in various clinical pain conditions.[7,23,25,27,29] So far, the majority of trials on OLP have not exceeded 3 weeks of OLP treatment.[45] In our view, given this relatively short duration of OLP treatment in our parent trial and comparable studies, the absence of long-lasting symptom improvements after 3 years is plausible rather than surprising and in no way limits its potential clinical value. However, to fully explore the clinical potential of OLP treatments, future studies should focus on much longer treatment periods (eg, 12 weeks or more), as is currently being investigated in the context of migraine.[38] Furthermore, the extent to which OLP could function as a routine long-term maintenance intervention, like state-of-the-art medications for CBP,[1,11] should be investigated with a randomized withdrawal design. These studies are expected to give a more in-depth evaluation of OLP's long-term efficacy as well as the temporal dynamics of its effects.

Further, a deeper knowledge of its mechanistic principles is required. Although the number of scientific contributions on OLP

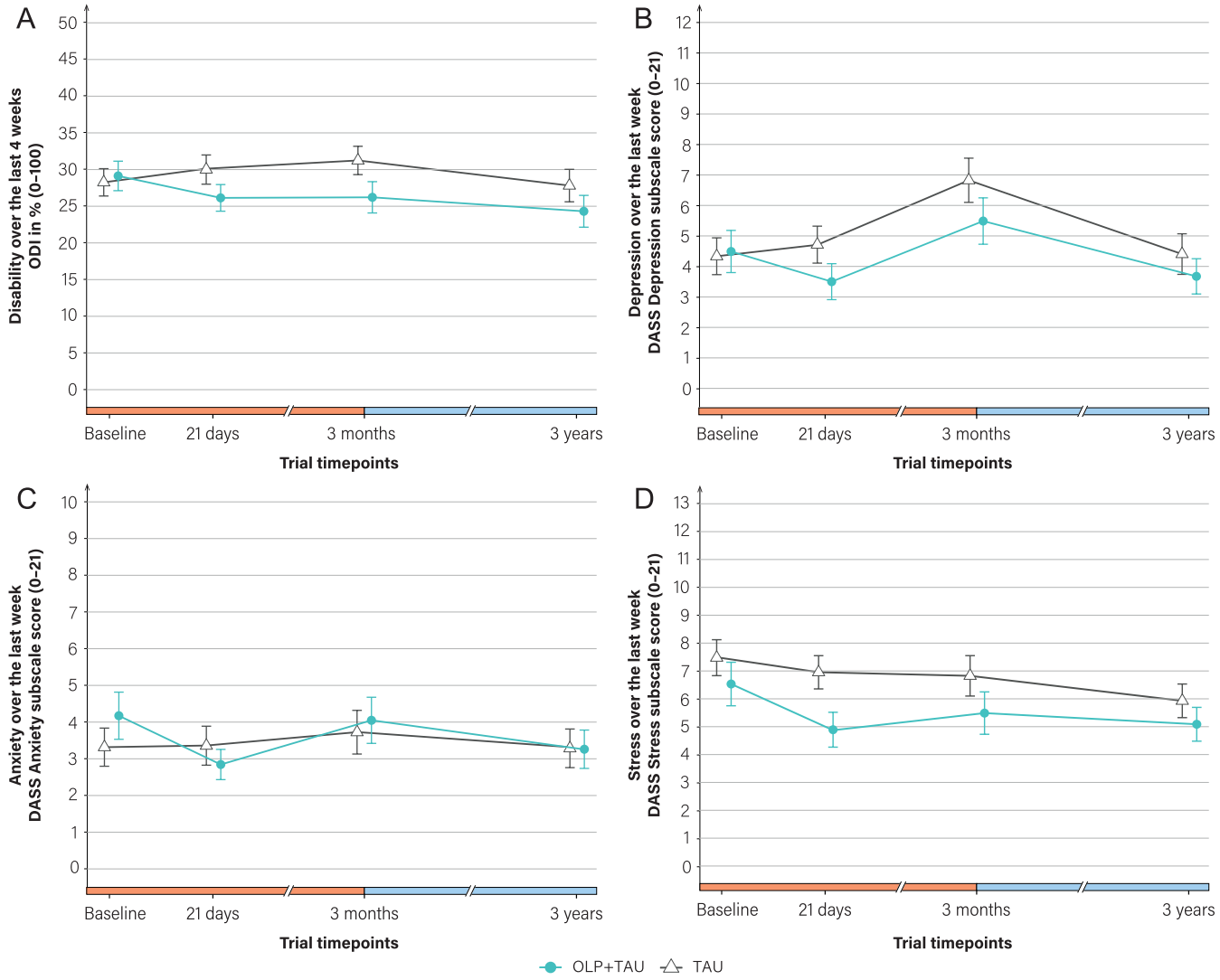

Figure 3. Secondary outcomes. The figure shows groupwise mean disability (A), depression (B), anxiety (C), and stress (D). Error bars represent SEs. The colored x-axis illustrates the respective study (orange: main study time points; blue: 3-year follow-up study). DASS, Depression Anxiety Stress Scale; ODI, Oswestry Disability Index; OLP + TAU, open-label placebo in addition to treatment as usual group; TAU, treatment as usual group.

treatments has increased substantially over the recent years, the underlying mechanisms remain unclear. Various theories including predictive processing, Bayesian brain, and "embodied cognition" are now being debated, as well as the reattribution of spontaneous improvements and OLP-triggered changes in beliefs and lifestyle. A first experimental study in healthy volunteers has documented EEG correlates of reduction in emotional distress after a single OLP treatment.[19] But much further research is needed to elucidate the neuropsychobiological mechanisms and potential predictors of OLP-related pain relief in patients, especially those suffering from chronic pain conditions. Although the involvement of expectancy in deceptive placebo treatments is widely accepted, data on the impact of treatment expectancy in the efficacy of OLP in healthy volunteers and patients is ambiguous.[24,26,30,39] In this follow-up study, treatment expectancy ratings for a hypothetical future OLP treatment did not differ between patients who received OLP and those who received TAU only. In fact, only a few OLP studies have measured treatment expectancy in patients, and none have shown a link between baseline expectancy and OLP outcomes at the trial endpoint.[27–29,34,37] Also, the time-varying character of treatment expectancy should be explored further to better understand the function of treatment expectancy in OLP effectiveness. Particularly in patients with chronic pain conditions with natural fluctuations in symptom severity (eg, chronic back pain), treatment expectancy may change over time and increasingly fuel OLP's effects in the sense of a self-fulfilling prophecy.

Combining OLP with psychological interventions such as conditioning or observational learning, both empirically proven to contribute to placebo effects,[12,15,21] represents a promising avenue of future research and may extend the longevity of a short-term OLP treatment. In classical conditioning, unconditioned stimuli (eg, a drug) are frequently combined with conditioned stimuli (eg, an OLP capsule), resulting in a newly acquired response in which the placebo alone can elicit behaviors that resemble the drug's response.[15,21] Such an approach does not necessitate the use of deception, and preliminary research suggests that conditioning may help to sustain OLP efficacy. In a recent trial, conditioned OLP provided as an additional analgesic therapy reduced opioid intake in acute postoperative pain.[17] However, whether conditioning is advantageous for chronic pain is unknown, and the absence of highly effective pharmaceutical therapies to generate the conditioned response may further complicate

matters. Instead of combining OLP with an efficient pain reliever, social learning may be able to bridge the gap. Social learning refers to learning processes in which a demonstrator's behavior or its byproducts alter an observer's subsequent behavior. Social observational learning has been shown to enhance (deceptive) placebo analgesia both in healthy volunteers[12] and in patients with chronic low back pain.[40] Ongoing research is testing whether observational learning via video demonstration may enhance nondeceptive, ie, open-label placebo efficacy in a comparable manner, offering a second feasible approach to extend short-term OLP efficacy.[41] Given that a 3-week, short-term OLP treatment in addition to TAU did not result in persistent benefits after 3 years in our sample, these mentioned approaches may advance the magnitude and longevity of OLP effects in future trials.

In conclusion, OLP-treated patients showed no differences in pain intensity, disability, or mood (ie, depressive, anxiety, and stress symptoms) compared with patients who received TAU only in this 3-year follow-up of our RCT. In addition, OLP treatment did not result in any lifestyle changes in our sample. As there is a growing body of evidence supporting short-term OLP effectiveness, future RCTs should explore longer-term OLP interventions and evaluate if psychological techniques such as social observation or conditioning may also increase the efficacy and duration of OLP treatments.

Conflict of interest statement

J. Kleine-Borgmann received personal fees from Novartis Pharma GmbH outside the submitted work. T.-N. Dietz declares no competing interests. K. Schmidt received personal fees from Novartis Pharma GmbH and Bayer Pharma AG outside the submitted work. U. Bingel reports personal fees from Biogen GmbH, personal fees from Lilly Deutschland GmbH, personal fees from Novartis Pharma GmbH, personal fees from Grünenthal GmbH, personal fees from Bionorica SE, personal fees from Chugai Pharma Germany GmbH, personal fees from Eisai GmbH, personal fees from Mylan Germany GmbH, and personal fees from Roche Deutschland Holding GmbH, all outside the submitted work.

Acknowledgements

Joshua Weyer and Johannes Wilhelmi deserve special thanks for their invaluable assistance with data collection. The authors also highly appreciate the great technical help provided by Sarah Hoppen and Detlef Pucher.
Gefördert durch die Deutsche Forschungsgemeinschaft (DFG)—Projektnummer 422744262—TRR 289. Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—Project-ID 422744262—TRR 289. J. Kleine-Borgmann was supported as a Clinician Scientist within the University Medicine Essen Academy (UMEA) program, funded by the German Research Foundation (DFG; grant FU356/12-1) and the Faculty of Medicine, University of Duisburg-Essen. T.-N. Dietz was supported within the graduate program "Essener Ausbildungsprogramm Labor und Wissenschaft für den ärztlichen Nachwuchs" at the Faculty of Medicine, University of Duisburg-Essen, funded by the Else Kröner-Fresenius-Stiftung.
Data availability statement: The data that support the findings of this study are available from the corresponding author, J. Kleine-Borgmann, upon reasonable request.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B693.

Article history:
Received 15 April 2022
Received in revised form 3 June 2022
Accepted 6 June 2022
Available online 10 August 2022

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