Supplement

Effects of open-label placebo on pain, functional disability and spine mobility in chronic back pain patients: A randomized controlled trial

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Study protocol, statistical protocol and raw data

Please find the study protocol online. Raw data will be shared upon request.

Transcript and video instruction for all participating patients

Please find the video sequence online.

Author U. B.: Dear patient, I am pleased that you are interested in one of our studies. At the Essen Back Pain Centre we offer comprehensive multidisciplinary medical care to those with chronic back pain but also aim to understand pain through scientific research. Recently published international studies suggest that chronic pain can be reduced significantly when treated with placebo tablets. These findings have also found their way into the international media. The following article by an American news channel provides a nice summary of the findings.

Speaker: Can the knowledge of taking a placebo actually improve your health? Studies show that it is possible. Some patients may no longer need proper medication. More and more patients are prescribed placebos.

Speaker: It looks like a normal pill, but turns out to be a placebo. These, doctors confirm, can be used to treat some of the most common diseases.

Patient: I felt fantastic, better than ever.

Speaker: For Linda Buonanno, the placebo pills worked. She suffers from irritable bowel syndrome, which often develops without warning.

Patient: I felt terrible, I had no life. I couldn't plan or do anything.

Speaker: When she found out about the study, she applied immediately.

Patient: I was very happy.

Speaker: But she was shocked when she heard that she was getting a placebo instead of real medication. We said: You don't have to believe it, just do it. Even if it's kind of a crazy idea.

Patient: I was so disappointed, I said: A placebo? A sugar pill, is that a joke? It's never going to work.

Speaker: But it worked. Her symptoms disappeared.

Patient: I'm making plans again, I don't have to worry anymore. I live my life again.

Speaker: In another study the same was done with migraine patients. Their pain was reduced by 30 percent.

Expert 1: This is an incredible thing.

Speaker: Psychologist Dr Stratyner says other factors may play a role.

Expert 2: I think the patients think paritally: Hm, I am wondering if it really is a placebo. Maybe I'm just being told that.

Speaker: Kaptchuk says that there are physiological reasons why placebos activate the same neurotransmitters as many powerful drugs.

Expert 1: We have our own pharmacy for certain diseases.

Speaker: But there are limits to the effect of placebo.

Expert 1: We will not be able to shrink a tumor with the placebo pill.

Speaker: But for certain diseases, placebos could fundamentally change the treatment.

Expert 1: If a placebo helps, this would be the best approach instead of putting patients on strong medication for a long time.

Author U. B.: As this summary shows, placebo treatments may have a positive effect on various chronic pain syndromes. We would like to investigate this phenomenon in a separate study. In addition to the effect on pain itself, we would also like to examine the influence on your physical functioning, such as your individual range of motion. Of course, we would be delighted if you would be willing to take part in this study.

Exploratory follow-up analysis of TAU-group

Follow-up included the assessment of pain intensity and disability ratings (ODI) 90 days upon completion of the 3-week trial phase. During this phase OLP-treatment was offered to the TAU-group to raise compliance to the study protocol and to compensate for potential disadvantages. 44 patients (75 %) of the TAU-group requested the OLP treatment and were provided with the placebo pills for 3 weeks and were included in the follow-up analysis. Explorative analysis revealed a significant reduction of the pain intensity composite score in the TAU-group for day 90 compared to day 21 (main effect *time;* estimated parameters: day 21 = 5.08±0.26, day 90 = 4.50±0.22, p = .01, d = -0.87). Explorative analysis of ODI scores of the TAU-group revealed no significant effect of time from day 21 to day 90 (estimated parameters: day 21 = 30.22±1.96, day 90 = 30.34±1.69, p = .94). Please note however, that the study protocol did not include any standardized assessment of the actual intake of the offered OLP treatment during this phase. Hence, the interpretation that the improvement in pain ratings in the (former) TAU-group during follow-up was induced by the switch to OLP is speculative and should be seen with caution.

Explorative Correlations

For exploratory purposes, correlational analyses were performed between the outcome variables for both groups. Here, differences were calculated between outcome variables at day 21 and baseline. Moreover, both groups were separated into subgroups of high and low NRS pain intensity scores (i.e. subgroup high pain: NRS ≥ 5.5 and subgroup low pain: NRS < 5.5). Subgroup limits were set based on the mean composite pain intensity scores in both groups at baseline (TAU: 4.90 (1.96) vs. OLP+TAU: 5.24 (1.95), mean ± SD) and subgroup sizes (TAU high pain:

22 [38 %], TAU low pain: 36 [62 %], OLP+TAU high pain: 29 [46 %], OLP+TAU low pain: 34 [54 %]). Within these subgroups, further correlational analyses were performed. All p-values are corrected for multiple comparisons using Benjamini & Hochberg correction[1]. These exploratory correlational analyses in the OLP+TAU-group between the changes in outcome variables over the course of the experiment revealed a significant correlation between changes in pain intensity and changes in velocity of motion ($r = -0.40$, $p = .02$) indicating increases in the velocity of motion with decreasing pain intensity in the OLP+TAU-group (see figure 5). There were no significant correlations found in the TAU-group.

Bibliography

1. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B (Methodological).* 1995;57(1):289-300.

Supplementary tables

Supplement, Table 1. Normalized outcome analyses.

Outcome	Beta ± SE	t	p	d
Pain intensity (VAS composite score)				
OLP treatment × time (day 21)	-0.46 ± 0.12	-3.16	.002	-0.43
OLP treatment × time (day 11)	-0.34 ± 0.12	-2.04	.043	-0.28
Disability (ODI)				
OLP treatment × time (day 21)	-0.27 ± 0.12	-2.44	.016	-0.45
Depression (DASS-D)				
OLP treatment × time (day 21)	-0.33 ± 0.13	-2.73	.007	-0.52

Normalized estimates (beta) ± standard error of the mean, calculated by the general linear mixed model taking the TAU group as reference group are listed. Only significant interactions are shown (p≤.05).

Supplement, Table 2. Characterization of concomitant medication.

Characteristic in No. (%)	**TAU**	**OLP+TAU**	**ALL**
Daily low-potent opioid use	2 (3)	1 (2)	3 (2)
Daily high-potent opioid use	6 (10)	3 (5)	9 (7)
Daily tricyclic antidepressants use	2 (3)	5 (8)	7 (6)
Daily gabapentin use	2 (3)	3 (5)	5 (4)
Daily pregabalin use	2 (3)	5 (8)	7 (6)
Daily use of analgesics	11 (19)	15 (24)	26 (21)
Use of NSAID [days per month]	30 (51)	19 (30)	49 (40)
Rescue use of analgesics [days per month, Mean ± SD]	3.98 ± 6.70	1.59 ± 3.56	2.79 ± 5.48
No daily analgesic medication	47 (80)	49 (78)	96 (79)
Total number of medications [Mean ± SD]	3.50 ± 2.50	3.80 ± 2.96	3.66 ± 2.74
Protocol Days [baseline to day 21, Mean ± SD]	18.65 ± 4.61	17.98 ± 6.09	18.30 ± 5.42

Characterization of the medication taken at baseline separately for the TAU-group and OLP+TAU-group and pooled for all participants. NSAID: Nonsteroidal anti-inflammatory drugs. Unless stated otherwise, absolute values and percentage share of the group are presented. Mean ± SD: Mean ± standard deviation.

Supplement, Table 3. Characterization of the chronic back pain etiology by The Quebec Task Force Classification for Spinal Disorders.

Characteristic	TAU	OLP+TAU	ALL
Pain without radiation	7 (11.9)	2 (3.2)	9 (7.4)
Pain with proximal extremity radiation	6 (10.2)	10 (15.9)	16 (13.1)
Pain with distal extremity radiation	4 (6.8)	9 (14.3)	13 (10.7)
Pain with radiation and neurologic finding	11 (18.6)	4 (6.3)	15 (12.3)
Spinal nerve root compression	0	0	0
Spinal stenosis	2 (3.4)	7 (11.1)	9 (7.4)
Postsurgical status, 1-6 months after surgery	0	0	0
Postsurgical status, >6 months after surgery	4 (6.6)	4 (6.3)	8 (6.5)
Unspecific chronic pain syndrome	25 (42.5)	27 (42.9)	52 (42.6)
Other diagnoses	0	0	0

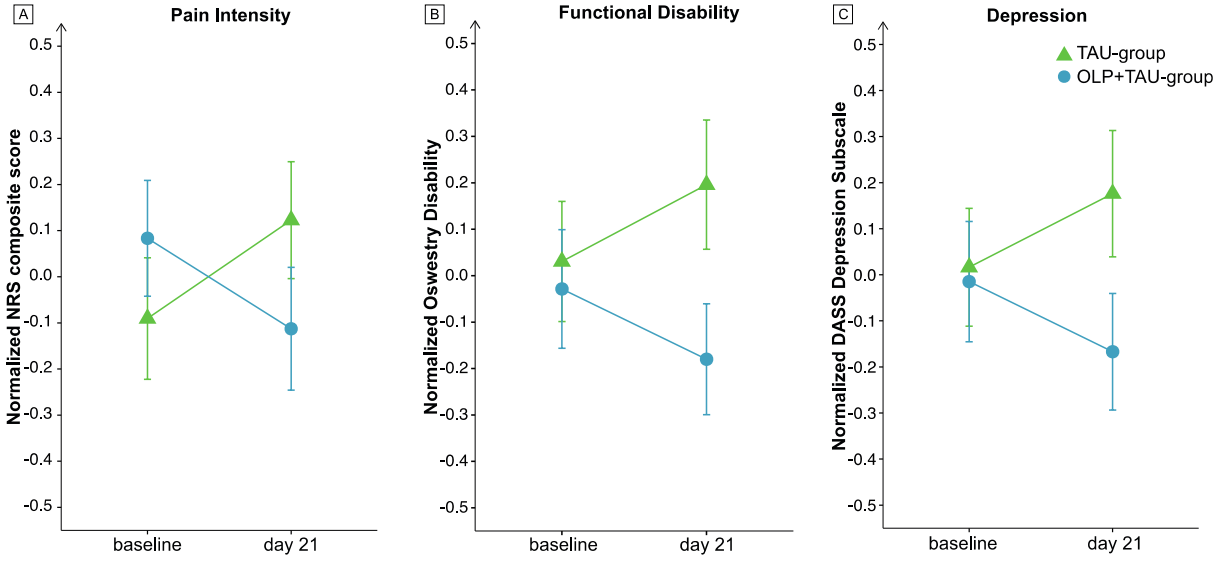
Characterization of the underlying diagnoses leading to chronic back pain. The Quebec Task Force Classification for Spinal Disorders was used to categorize the diagnoses and was rated by a trained specialist (J. K-B., U. B.). Unless stated otherwise, absolute values and percentage share of the group are presented.

Supplement, Table 4. Outcome measures for the TAU-group and OLP+TAU-group.

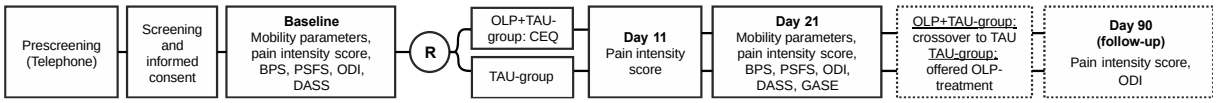
Outcome at day 21	**TAU**	**OLP+TAU**
NRS composite (day 21)	5.10 (1.86)	4.64 (2.04)
NRS minimum (day 21)	3.44 (2.35)	2.93 (2.11)
NRS average (day 21)	5.10 (1.99)	4.75 (2.27)
NRS maximum (day 21)	6.76 (2.00)	6.24 (2.25)
DASS depression (day 21)	5.00 (4.23)	3.56 (4.02)
DASS anxiety (day 21)	3.23 (3.13)	2.86 (3.59)
DASS stress (day 21)	6.80 (3.99)	5.35 (4.27)
ODI score (day 21)	30.79 (13.37)	25.96 (11.98)
PSFS score (day 21)	4.35 (1.94)	5.07 (2.13)
BPS score (day 21)	3.36 (3.16)	3.88 (3.74)
Spinal range of motion (day 21)	0.08 (0.69)	-0.09 (0.81)
Spinal velocity of motion (day 21)	0.06 (0.74)	0.05 (1.02)
Exploratory outcomes at day 90 (follow-up)	**TAU**	**OLP+TAU**
NRS composite (FU)	4.61 (1.86)	4.57 (1.72)
NRS minimum (FU)	2.81 (1.87)	2.71 (1.88)
NRS average (FU)	4.63 (1.96)	4.76 (1.92)
NRS maximum (FU)	6.38 (2.26)	6.25 (1.91)
ODI score (FU)	31.39 (12.70)	26.12 (13.74)

NRS: Numeric rating scale; DASS: Depression Anxiety Stress Scale; ODI: Oswestry Disability Index; PSFS: Patient-specific Functional Scale; BPS: Back Performance Scale; Numeric rating scale measures report pain intensity during the last 7 days before assessment. All reported parameters are given in means ± SD. Mobility parameters are given as z-transformed means.

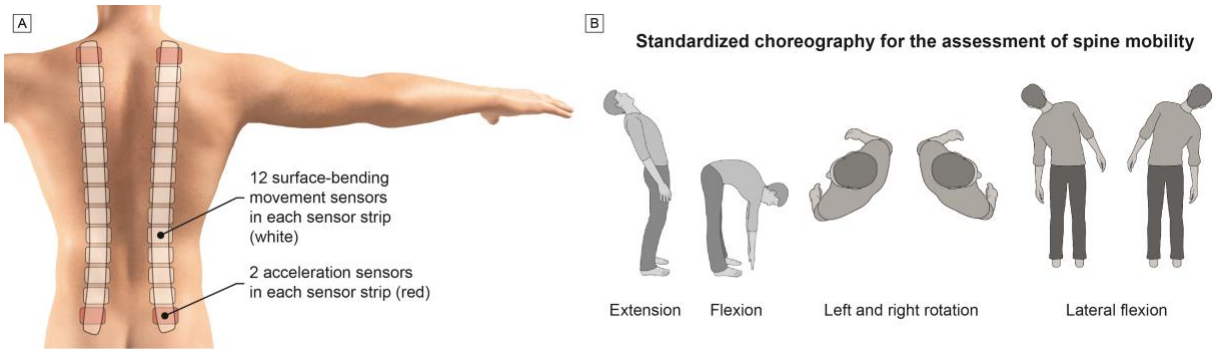
Supplementary figures



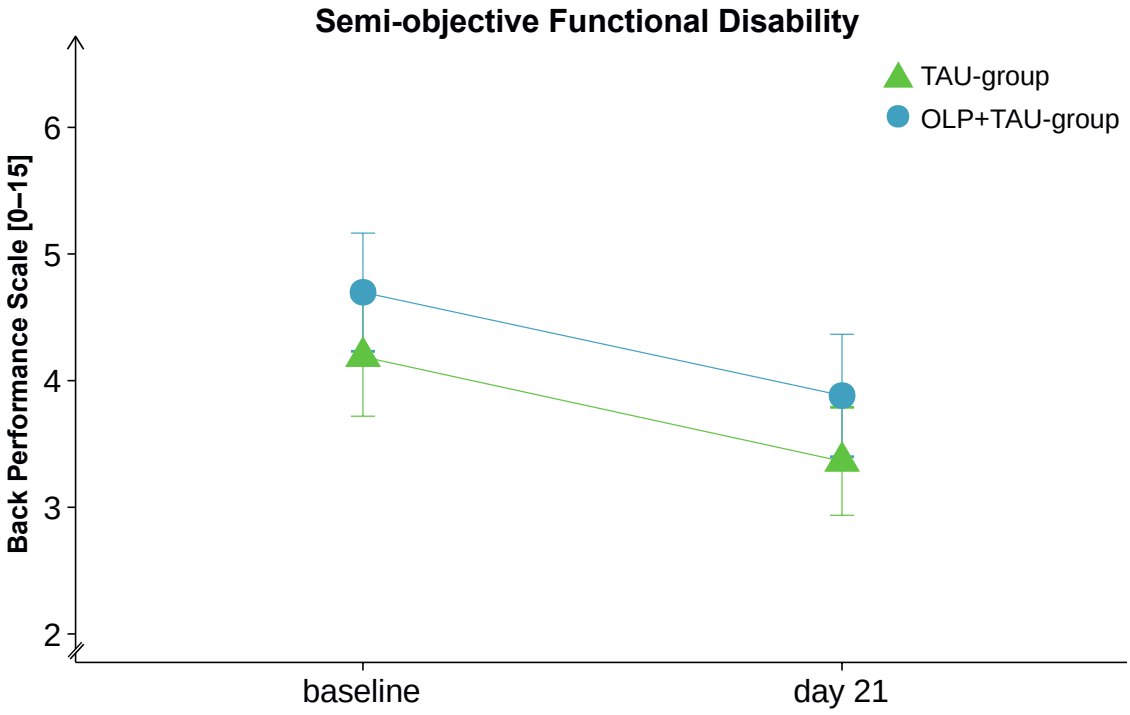
Supplement, Figure 1. Normalized Pain Intensity, Functional Disability and Depression. Pain intensity (A), subjective functional disability (B) and depression (C) before (baseline) and after the 21-day test phase (day 21) for the TAU- (green) and OLP+TAU-group (blue). Z-transformed Mean ± SE (standard error of the mean) are presented.



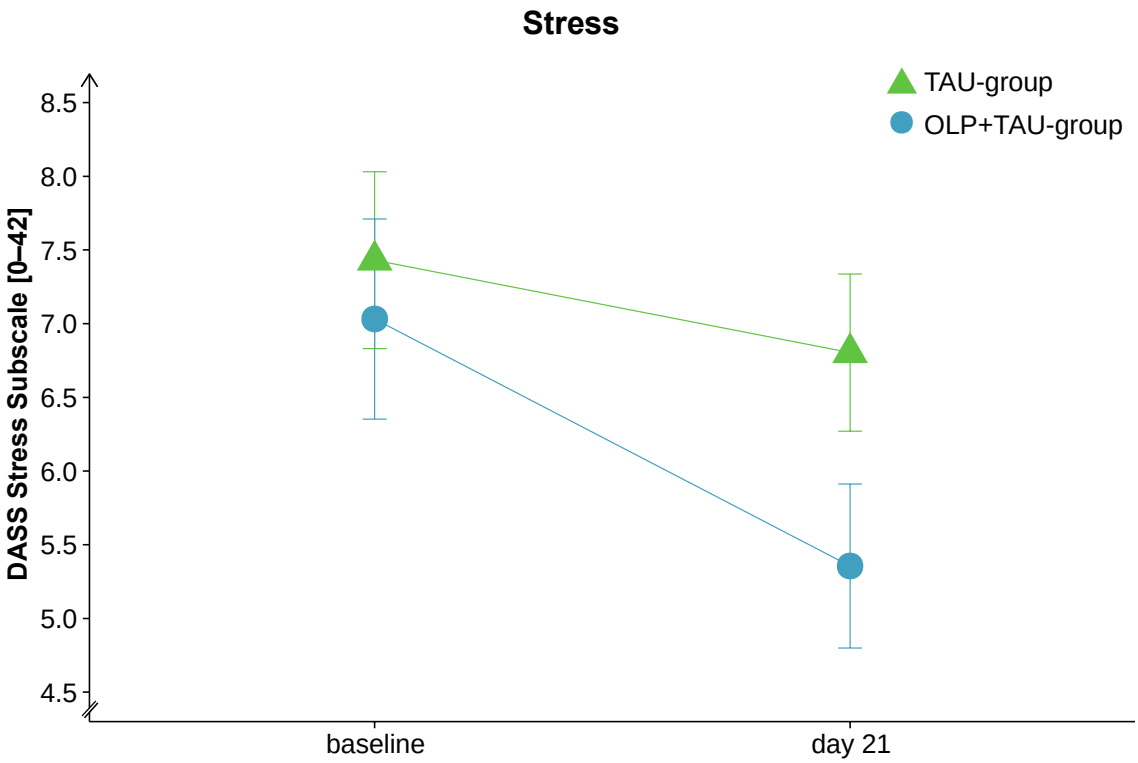
Supplement, Figure 2. Study design including assessed outcomes and timepoints. BPS: Back Performance Scale; PSFS: Patient-Specific Functional Scale; ODI: Oswestry Disability Index; DASS: Depression Anxiety Stress Scale; R: Randomization; OLP: Open-label Placebo; TAU: Treatment as usual; CEQ: Credibility and Expectancy Questionnaire; GASE: Generic Assessment of Side Effects in Clinical Trials.



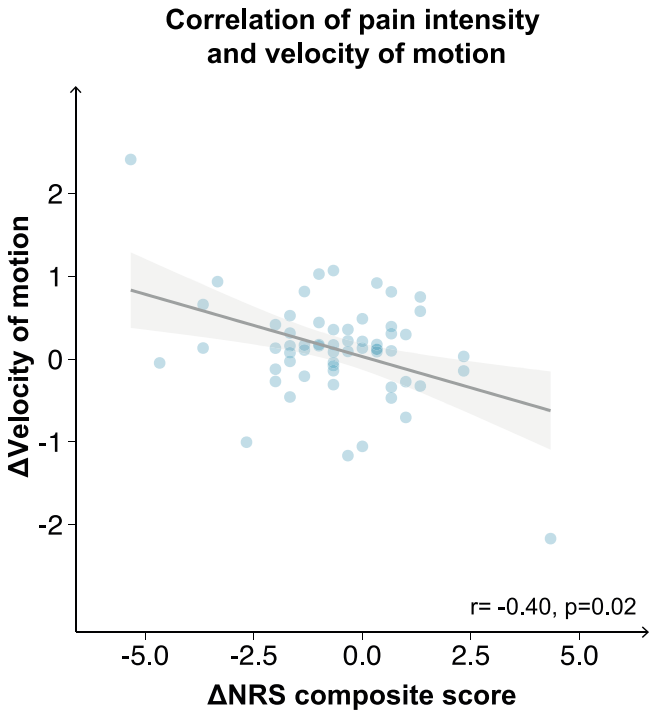
Supplement, Figure 3 – Assessment of lumbar mobility. A) Installation of sensor strips for motion analysis. B) Standardized choreography for the assessment of spine mobility by extension, flexion, left and right rotation, as well as lateral flexion of the spine.



Supplement, Figure 4. Back Performance Scale scores at baseline and day 21. Means ± SE are displayed separately for the TAU-group (green) and OLP+TAU-group (blue).



Supplement, Figure 5. Stress at baseline and day 21. Means ± SE are displayed separately for the TAU-group (green) and OLP+TAU-group (blue).



Supplement, Figure 6. Correlation of pain intensity and velocity of motion of the OLP+TAU-group.

Correlation analysis of changes in pain intensity and velocity of motion revealed a significant negative correlation indicating increased velocity of motion with decreased pain intensity in the OLP+TAU-group. P-value corrected by Benjamini & Hochberg correction.