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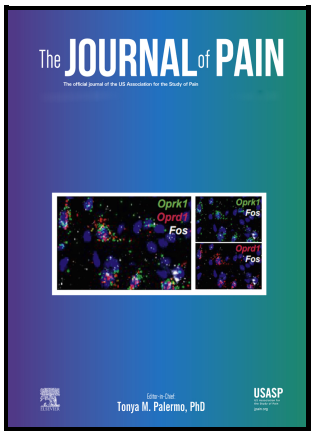

Treatment expectation: you get what you expect – and depression plays a role›Running title: Treatment expectations and the role of depression

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Treatment expectation: you get what you expect – and depression plays a role

Running title: Treatment expectations and the role of depression

Claudia G. Levenig[a], Monika I. Hasenbring[a,b], Lea Günnewig[a], Christina Titze[c], Sigrid Elsenbruch[a], Tobias L. Schulte[c]

a Dept. of Medical Psychology and Medical Sociology, Faculty of Medicine, Ruhr University Bochum, Germany
b Faculty of Health Sciences, University of Southern Denmark SDU, Odense, Denmark
c Clinic of Orthopaedics and Trauma Surgery, St. Josef-Hospital Bochum, Germany

The data that support the findings of this study are available upon reasonable request from the corresponding author, CGL. The data are not publicly available due to the privacy of research participants.

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Corresponding author: Claudia G. Levenig
Department of Medical Psychology and Medical Sociology
Ruhr University Bochum
Faculty of Medicine
Universitätsstr. 105
44789 Bochum (Germany)

claudia.levenig@rub.de
Phone: +49 234 32-24994
www.medpsych.rub.de

Abstract:

Positive treatment expectations demonstrably shape treatment outcomes regarding pain and disability in patients with chronic low back pain (LBP). However, knowledge about positive and negative treatment expectations as putative predictors of interindividual variability in treatment outcomes is sparse, and the role of other psychological variables of interest, especially of depression as a known predictor of long-term disability, is lacking. We present results of the first prospective study considering expectations in concert with depression in a sample of 200 patients with chronic LBP undergoing an inpatient interdisciplinary multimodal pain therapy (IMPT). We analyzed characteristics of pain and disability, treatment expectation, and depression assessed at the beginning (T0), at the end of (T1) and at 3-month-follow-up (T2) of IMPT. Treatment expectations did emerge as significant predictor of changes in pain intensity and disability, respectively, showing that positive expectations were associated with better

treatment outcomes. Mediation analyses revealed a partially mediating effect of treatment expectations on the relation between depression and pain outcomes.

Perspective: These results expand knowledge regarding the role of treatment expectations in individual treatment outcome trajectories in chronic pain patients, paving the way for much needed efforts towards optimizing patient expectations and personalized approaches in clinical settings.

Keywords:

chronic low back pain, treatment expectations, interdisciplinary multimodal pain therapy, depression

1. Introduction

As one of the most frequent types of chronic primary pain, chronic low back pain (LBP) causes substantial individual and socioeconomic burden,[1,2] sometimes serious limitations in quality of life[3] and is associated with significant functional disability or distress.[4] The multifactorial nature of LBP is reflected within the biopsychosocial model[5] as a conceptual basis for multifactorial treatment approaches such as the interdisciplinary multimodal pain therapy (IMPT). IMPT comprises cognitive, operant-behavioural, and physiological elements[6], and has been shown to be more effective in reducing pain and pain-related disability than usual care.[2,6,7] However, there exist considerable interindividual differences in treatment efficacy.[8]

The crucial importance of patients' treatment expectations in shaping treatment outcomes is increasingly recognized, building on proof-of-concept studies demonstrating expectation effects on pain-related measures relevant to chronic LBP both in healthy individuals,[9,10] clinical work for acute, sub-acute or chronic LBP patients,[11,12] and broad mechanistic knowledge regarding the underlying neurobiological changes in central pain processing.[13] Within the psychosocial treatment context, expectations are indeed powerful modulators of treatment responses, and the "driving forces" of placebo and nocebo effects.[14] Treatment expectations as a multidimensional construct comprises future-directed cognitions concerning treatment or process-related outcomes,[15,16] shaped by information and communication of healthcare providers, peers, and the media[17] together with own prior pain and recovery experiences and by psychological factors such as depression.[18,19] Previous work in LBP patients provided evidence that moderate or high positive treatment expectations were followed by more positive outcomes regarding pain and disability compared to patients with low expectations.[20-23] However, existing knowledge is incomplete and in part inconsistent for several reasons. Firstly, treatment expectation has been heterogeneously defined and quantified, and most prior studies have used non-standardized questions to evaluate patients' treatment expectations.[16] Secondly, different treatment outcomes have been assessed, such as recovery or treatment outcomes with a focus on recovery expectations. Finally, individual

psychological factors such as comorbid symptoms of depression, which are evidentially associated with pain and disability,[15,24] have rarely been considered in relation to treatment expectations and outcomes in IMPT targeting chronic LBP.[20,24] Given broad evidence that depression constitutes the most significant predictor of long-term disability,[15,25,26] and that symptoms of depression upon admission are associated with poorer outcomes at follow-up,[24] it appears crucial to fill this research gap.

Together, prospective research dedicated to elucidating the role of expectations in treatment responses of chronic LBP patients undergoing IMPT, especially on pain intensity and disability as key outcomes, remains scarce, and the putative mediating influence on the association between depression and pain outcomes remains unclear. Translation of knowledge from placebo studies into improved clinical care requires more research in routine clinical care settings. Optimizing treatment expectations may offer avenues to improve treatment outcomes,[18,27,28] and the assessment of expectations may aid in identifying patients at risk for treatment failure. Therefore, the main objective of the present prospective observational study in a comparatively large sample of 200 patients suffering from chronic LBP undergoing an inpatient IMPT was to elucidate treatment expectations as predictors of treatment outcomes. We assessed whether interindividual differences in treatment expectations prior to IMPT contributed to variability in treatment outcomes at a three-month-follow-up. Secondly, we explored the role of treatment expectations as a putative mediator. Based on recent evidence that expectations mediated effects of negative emotional states on postoperative pain outcomes,[29] we expected an interaction between depression, treatment expectations and treatment outcomes. Thirdly, we hypothesized that treatment expectations would emerge as a predictor of pain intensity and disability as main outcomes, and that patients clustered based on expectations would differ in treatment responses.

2. Methods

IMPT

Inpatient IMPT was accomplished based on established and standardized treatment recommendations from the German national treatment guidelines for back pain,[30] based on the biopsychosocial model of chronic pain.[31] The IMPT is in Germany an evidence-based treatment covered by health insurance and the gold standard in treating chronic pain with lasting improvement in pain-related outcomes.[32,33] It comprises pharmacological, physiotherapeutic, cognitive-behavioural approaches, patient education combined with one-on-one sessions with a pain psychologist, strengthening and endurance exercises (e.g., circuit training, back school), cardiovascular training (e.g. water treading), and relaxation techniques.[6,34] Treatment was implemented by a multidisciplinary team of physicians, physiotherapists, and psychotherapists. All patients received the same treatment components, with some individual adjustments based on individual medical situation, ability, and response to treatment. Note that due to COVID-related restrictions during the pandemic, not all group interventions were offered, and the clinic had strong limitations concerning rules of contact.

Patients

Three-hundred-ten patients with chronic LBP undergoing an inpatient IMPT were screened for study participation. Inclusion criteria were an established diagnosis of chronic LBP, defined as lasting longer than 12 weeks or recurring episodes,[1] and localised below the costal margin and above the inferior gluteal folds, with and without radiating to the leg and age >18 years. Exclusion criteria consisted of serious red flag pathology, especially recent trauma with significant injury, acute fractures, joint infection, cancer, inflammatory arthropathy (e.g., rheumatoid arthritis, polymyalgia rheumatica), severe psychiatric comorbidity (e.g., psychosis, substance abuse), dementia, and insufficient German language proficiency. Patients who did not complete IMPT, defined as a treatment duration <11 days, were also excluded.

Study design and procedures

This prospective observational questionnaire study was conducted in a specialized pain clinic in Blankenstein, University Hospital Bochum, Germany, between November 2020 and January 2022. The clinic treats annually an average number of about 800 patients with different chronic pain disorders. Patients are typically referred for treatment by their family physician or orthopaedist. Before admission to the inpatient IMPT (usual inpatient duration of stay: 17 days), patients are routinely seen and advised in the orthopaedics outpatient clinic by our physicians. This appointment entails the confirmation of the diagnosis (or diagnoses), determination of the proper indication for undergoing the IMPT, and communication regarding all relevant and possible therapy options. Note that patients included in this study did not receive any specific instructions or interventions that would result in a systematic alteration of their treatment expectations, i.e., we did not instruct physicians specifically about this study but rather this part of care was strictly care as usual.

On the day of arrival for their inpatient treatment stay, patients with chronic LBP were approached by one out of two study coordinators after the routine medical examination. All patients who met the study criteria were invited to participate. Besides the routine clinical data collection, patients filled in a comprehensive questionnaire battery at three assessment points: Prior to or at the beginning of admission (T0) and at the end of the therapy (T1). After three months (T2), patients were contacted via phone or e-mail before the questionnaire was sent by mail with a prepaid envelope. The trial was registered at the German Clinical Trials Center (Study ID DRKS00024103) on March 3, 2021. The study protocol was performed in accordance with the Declaration of Helsinki and approved by the local Medical Ethics Committee of the Ruhr University Bochum (No. 20-7047). All participants provided written informed consent.

Questionnaires

For the purposes of addressing the specific study aims herein, we selected the following questionnaires from a comprehensive questionnaire battery:

Clinical chronic pain characteristics

Clinical pain characteristics such as pain intensity and disability were assessed prior to or on the day of admission with the German Pain Questionnaire (GPQ),[35] which includes a standardized assessment of sociodemographic characteristics and various clinically relevant aspects of chronic pain, pain-related behaviors, pain medications, disability. The GPQ is recommended by the German Pain Society. Note that race/ethnicity was not systematically assessed. Regarding sex/gender, we herein assigned volunteers to the category "male/men" or "female/women" based on self-report on a dichotomous question, likely reflecting sex assigned at birth.

At all three assessment time points, patients completed the German version of the Chronic Pain Grade Scale (CPGS).[36,37] The CPGS quantifies self-rated pain intensity using a 0 ("no pain") to 10 ("pain as bad as could be") numeric rating scale, differentiating current pain intensity, as well as average and worst pain intensity in the last four weeks. The means score of the three items is multiplied by 10, resulting in a range of 0-100.

Pain-related disability was quantified with three items assessing interference of pain with occupational, social, and leisure activities in the last three months, using rating scales ranging from 0 ("no interference") to 10 ("unable to carry on any activities"). An overall disability score was calculated by averaging the three items and multiplying them by 10, resulting in a range of 0-100.[36,37] Of note, given the longer time frame and content of these items, we did not collect data on disability at T1.

Furthermore, pain severity was graded into four hierarchical classes based on the pain intensity and disability points of the CPGS, ranging from Grade I (low disability/low intensity) to Grade IV (high disability/severely limiting – regardless of pain intensity). Disability points were assessed by asking for the amount of days in the last six months experiencing constraints concerning usual activities such as work or housework.[37]

Treatment expectations

At T0, patients' treatment expectations were assessed with the 15-item Therapy Expectation Questionnaire (TEX-Q).[38] The TEX-Q comprises six subscales (i.e., treatment benefit, positive impact, adverse events, negative impact, process, and extent of behavioural control), with each scale containing two or three items. Each item ranges from 0 (representing no expectation of treatment benefit/positive impact at all) to 10 (broadest conceivable benefit), with higher total scores representing a more positive treatment expectation. For the present analyses, total mean scores and subscale mean scores were computed.

To complement the TEX-Q, prior IMPT treatment experiences were assessed. Specifically, we asked whether patients had undergone prior IMPT, and if so, how many times. Using two numeric rating scales, each ranging from 0 to 10, patients who had undergone prior IMPT expressed the extent to which

it alleviated their LBP (0 = "no improvement", 10 = "broadest conceivable improvement") and the extent to which it exacerbated their pain (0 = "no worsening", 10 = "broadest conceivable worsening"). Mean scores were reported.

Depressive symptoms

The German version of the Beck Depression Inventory Fast Screen (BDI-FS)[39] was used to quantify symptoms of depression at all three measuring points. The BDP-FS is a self-report instrument consisting of seven items, evaluating individual assessment of sadness, loss of pleasure, suicidal thoughts or wishes, pessimism, self-dislike, and self-criticism during the past two weeks (scores range from 0 to 3). Scores of 4 or higher were classified as depression with higher scores representing higher levels of depression.

Analyses

All validated questionnaires were scored and analysed according to published manuals. Statistical analyses were conducted using SPSS 27[40] and PROCESS.[41] Sample characterization regarding sociodemographic and clinical variables was accomplished with descriptive statistics computed as means and standard deviations (SD) or absolute and relative frequencies. Patients who were lost to follow-up and participants with complete data were compared with t-tests to investigate differences regarding age, pain intensity, disability, depression, and treatment expectation, and a Chi^2-test to evaluate differences based on patients' sex/gender. Shapiro Wilk-tests and Levene tests were used to examine the assumptions of normality and homogeneity, respectively. For analyses on lost to follow-up, see supplement, Table 1.

We conducted three mixed analyses of variance with the between-subjects factor "group" (sex) and the within-subjects factor "time" (T0, T1, T2 for pain intensity and depression; T0, T2 for disability) to determine if there were differences in pain, disability, and depression between men and women (see supplemental Table 2). Changes between time points in pain intensity (T0, T1, T2), disability scores (T0, T2), and BDI-FS-scores (T0, T1, T2) for the whole sample were computed with paired t-tests. Independent t-tests were calculated to ascertain if there were differences in age and treatment expectation between men and women. Shapiro Wilk-tests and Levene tests were conducted to examine the assumption of normality and homogeneity.

To assess treatment expectations as predictor of main treatment outcomes, multiple linear regression analyses were computed with TEX-Q total score as predictor variable and pain intensity and disability, respectively, assessed with the Graded Chronic Pain Scale at T2, as outcome variables. Variables entered blockwise in the models were depression score, age and education. Age and education were added as supplementary variables that significantly correlated with outcomes (see supplemental Table 3). Pain intensity at T0 was additionally added in the model for pain disability. Supplemental regression models were conducted including the six TEX-Q-subscales. Homoscedasticity was inspected with the Breusch-

Pagan test. In case of heteroscedasticity, robust standard errors are reported. Variance inflation factors were checked regarding multicollinearity. Cohen f^2 were calculated as effect size for multiple linear regression.[42]

Mediation analyses were performed using PROCESS (v4.2)[41] with depression at T0 as independent variable, pain intensity and disability at T2 as dependent variables, respectively, and treatment expectations as mediator. Unstandardized path coefficients for total, direct, and indirect effects were applied. Bootstrapping with 5000 samples together with heteroscedasticity consistent standard errors were employed to compute intervals and inferential statistics. Effects were deemed significant when the confidence interval did not include zero. According to Cohen[42] we interpreted an adjusted $R^2 = 0.02$ indicating a weak, $R^2 = 0.13$ a mediate, and $R^2 = 0.26$ a high goodness-of fit for the overall model.

Based on TEX-Q total scores, three subgroups were generated by a cluster analysis using the K-means method, yielding a group with low expectations (LOW-EXP), a group with moderate expectations (MOD-EXP), and a group with high expectations (HIGH-EXP). In line with the approach outlined by Cormier et al.[20] three clusters were formed based on the notion (driven by our clinical experience and practical considerations envisioning translation into personalized therapy based on a relatively simple stratification) that some individuals may start treatment with little or no positive expectations, while others may have moderate or even high positive treatment expectations. To confirm that the three subgroups differ in terms of treatment expectations, we ran a one-way analysis of variance (ANOVA). To assess subgroup differences in pain intensity, disability and depression, two-way mixed analysis of variance with the between-subjects factor "group" (low, moderate, high) and the within-subjects factor "time" (T0, T1, T2 for intensity; T0, T2 for disability) were computed. In all analyses, the Greenhouse-Geisser adjustment was applied in case of violation of sphericity, and a Welch-ANOVA was conducted in case that Levene's Test suggested that homogeneity of variances could not be assumed. In case of significant correlations between potentially confounding variables (i.e., age, sex, education) and outcomes, analysis of covariance (ANCOVA) were computed. Note that we only report ANOVA results when inclusion of covariates did not alter results. Post-hoc group comparisons were accomplished with Bonferroni-corrected t-tests. Standardized Mean Difference Scores (SMD) were conducted to show differences between groups. Additionally, two one-way ANOVAs and Bonferroni corrected post-hoc tests were computed to show differences in treatment expectation subgroups regarding experiences concerning pain relief or pain increase in prior IMPT. Effect sizes of group effects were calculated as partial η^2. A partial $\eta^2 < .01$ represents a small, partial $\eta^2 < .06$ a medium, and partial $\eta^2 > .14$ a large effect.[43] Effect sizes for pairwise comparisons were calculated as Cohen *d*, with $d = .2$ representing a small, $d = .5$ a medium, and $d = .8$ a large effect.[42] Spearmen's r was computed for correlational analyses.

3. Results

Sample characteristics

Sociodemographic and clinical characteristics of the whole sample are provided in Table 1. In total, 200 patients completed questionnaire assessments at T0, 184 patients at T1 (response rate 92%), and 148 patients at T2 (response rate 74%) (see Figure 1). The lost to follow-up analyses indicated no differences in age, depression, treatment expectations, sex/gender, or pain-related variables at T0 between participants who completed all assessment time points versus those who did not (see supplemental Table 1).[44] Average treatment duration (inpatient stay) was 16.78 (SD + 0.85) days. The sample consisted of more women than men, the majority was middle-aged or elderly, and 49% were not employed or were retired, 22.5% were incapacitated for work. Independent t-tests and mixed ANOVAs indicated no differences in pain, disability, age, treatment expectations, and depression between men and women (all $p > 0.05$; see supplemental Table 2). Regarding clinical pain characteristics, the majority reported a pain duration of > 5 years, and a substantial proportion had undergone prior IMPT at least once. Pain intensity and disability were relatively high at T0. At admission, nearly a third of patients reported using opioids, and 43.3% reported taking psychoactive drugs, such as antidepressants or cannabis (see Table 1).

[Please insert Figure 1 here]

Changes in pain intensity, disability, and depression from T0 to T2

Patients of the whole sample reported significant reductions in pain intensity, assessed with the CPGS, from T0 to T1 ($t(183) = -12.59$, $p < 0.001$, $d = 0.93$) and from T0 to T2 ($t(147) = -9.48$, $p < 0.001$, $d = 0.78$). There was no significant difference from T1 to T2 ($t(139) = -0{,}515$, $p = 0.61$, $d = 0.21$). Pain-related disability, assessed at T0 and T2, was also significantly reduced at T2 ($t(147) = -7{,}29$, $p < 0.001$, $d = 0.60$). Depression scores decreased significantly from T0 to T1 ($t(170) = -4.81$, $p < 0.001$, $d = 0.37$), yet this was not maintained, as evidenced by a significant increase in depression scores from T1 to T2 ($t(139) = 2.86$, $p < 0.005$, $d = -0.24$). A clinically relevant improvement (minimal important change, MIC), i.e., a reduction in pain intensity of > 20 mm[45] from baseline to T1 was observed in 22.5% and from baseline to T2 in 27% of the patients. For disability, a MIC of 30% of baseline scores is stated, which was achieved in 12% of the sample. (Supplemental analyses exploring effects of sex on outcome variables over assessment time points are provided in supplemental Table 2.)

[Please insert Table 1 here]

Multiple regression analyses

Blockwise multiple linear regression analyses were conducted on the whole sample to clarify the influence of treatment expectations on pain intensity and disability at T2 as dependent variables. The correlating variables age and education were not significant. The first regression model tested treatment expectations (TEX-Q total score) as predictor of changes in pain intensity. Since depression demonstrably shapes treatment expectations[18,19] and pain intensity[15,26] and was herein correlated with pain intensity (see supplemental Table 2), depression score was a variable entered into the model. Since there was no homoscedasticity ($\chi^2 = 7.277$, $p = 0.007$), robust standard errors are reported. Results revealed that reductions in pain intensity were significantly predicted by depression and treatment expectations ($F(2,136) = 14.166$, $p < 0.001$, adj. $R^2 = 0.162$, robust standard error = 0.30), with a high effect size according to Cohen[42] and no evidence of autocorrelation (see Table 2). Treatment expectations accounted for approximately 4% of the variance. The second regression model tested treatment expectations as predictor of disability at T2. Pain intensity at T0 as possible confounder and depression were entered into the model. Results of the overall multiple linear regression model including all predictors were significant ($F(3,136) = 19.494$, $p < 0.001$, adj. $R^2 = 0.29$, with a large effect size (see Table 2). Expectations contributed to roughly 5% of observed variance.

[Please insert Table 2 here]

Mediation analyses

Two simple mediations were computed to analyse depression at T0 as a predictor of pain intensity (n = 137) and disability (n = 137) at T2, and to test if the direct path was mediated by treatment expectations. We observed an effect of depression on pain intensity. After entering the mediator variable treatment expectation into the model, depression predicted the mediator significantly (B = -0.058, $p = 0.021$), which in turn predicted pain intensity significantly (B = -3.332, $p = 0.011$). We found that the relationship between depression and pain intensity at T2 was partially mediated by treatment expectations (indirect effect $ab = 0.193$, 95%-CI[0.019, 0.467]; see Figure 2A). Treatment expectations also partially mediated the relationship between depression and disability at T2 (indirect effect $ab = 0.263$, 95%-CI[0.038, 0.612]; see Figure 2B).

[Please insert Figures 2A and 2B here]

Subgroup analyses

Based on results of a cluster analysis, three expectations subgroups high (M = 8.2, SD + 0.57), moderate (M = 6.68, SD + 0.35), and low (M = 5.47, SD + 0.53) were formed that differed significantly in TEX-Q total scores (see Figure 3).

[Please insert Figure 3 here]

To confirm that the three subgroups differed in treatment expectations, we conducted a Welch-ANOVA. Homogeneity of variances was tested using Levene's Test which showed that equal variances could be not assumed (p = 0.02). The treatment expectation subgroups differed significantly regarding TEX-Q mean scores (Welch's $F(2,93.14) = 323.91$, $p < 0.001$; Games-Howell post-hoc analyses: all $p < 0.001$; Figure 3).

For pain intensity (see Figure 4A), rmANOVAs revealed a significant interaction of time and group ($F(3.78, 258.88) = 2.86$, $p = 0.026$, partial $\eta^2 = 0.04$) as well as significant main effects of time ($F(1.89, 258.88) = 69.68$, $p < 0.001$, partial $\eta^2 = 0.34$) and group ($F(2, 137) = 4.79$, $p = 0.010$, partial $\eta^2 = 0.07$). Post-hoc-tests revealed significant standardized mean differences (SMD) between groups emerging from T1. The group with LOW-EXP differed significantly from the group with HIGH-EXP (SMD = 9.73, $p = 0.003$) at T1 as well as at T2 (SMD = 11.99, $p = 0.007$), indicating that the LOW-EXP group revealed higher pain intensity. In addition, the MOD-EXP group reported significantly higher pain intensity at T2 when compared to the group with HIGH-EXP (SMD = 8.33, $p = 0.046$). No group differences were observed between the LOW-EXP and MOD-EXP groups. Note that after including depression as a covariate, assessed with the BDI-FS, the interaction between time and group ($F(3.74, 235.75) = 2.71$, $p = 0.034$, partial $\eta^2 = 0.04$) as well as the main effect time ($F(1.87, 235.75) = 31.45$, $p < 0.001$, partial $\eta^2 = 0.20$) remained significant. However, differences between groups no longer reached significance ($F(2,126) = 2.53$, $p = 0.08$, partial $\eta^2 = 0.04$), and the covariate depression had a significant effect ($F(1,126) = 16.0$, $p < 0.001$, partial $\eta^2 = 0.11$).

For disability (see Figure 4B), rmANOVA revealed a significant group x time interaction ($F(2,145) = 3.31$, $p = 0.04$, partial $\eta^2 = 0.04$). Post-hoc-tests demonstrated higher disability scores at T2 in the LOW-EXP group when compared to the HIGH-EXP group (SMD = 9.37, $p = 0.04$), but not other group differences at any time point. In a next step, a rmANCOVA with pain intensity and depression as covariates was computed given that pain intensity ($r = 0.56$, $p < 0.001$) and BDI-FS ($r = 0.18$, $p = 0.01$) at T0 correlated with disability. Pain intensity T0 ($F(1,132) = 50.19$, $p < 0.001$) as well as depression at T0 ($F(1,132) = 16.80$, $p < 0.001$) were significant covariates for disability T2. No group x time interaction was found $F(2,132) = 2.49$, $p = 0.09$, partial $\eta^2 = 0.04$). Furthermore, there were no significant main effects for time ($p = 0.87$) or for group ($p = 0.049$).

For depression, assessed with the BDI-FS, rmANOVA (n = 130) revealed significant main effects of time ($F(1.90, 240.87) = 9.05$, $p < 0.001$, $\eta^2 = .07$) and group ($F(2, 127) = 4.16$, $p = 0.018$, $\eta^2 = 0.06$), whereas the interaction was non-significant ($F(3.79, 240.87) = 0.81$, $p = 0.51$). Treatment expectations groups differed at T0 ($p = 0.018$, see Table 1) and T1 ($p = 0.036$, see Figure 4C). Post-hoc tests indicated higher BDI-scores in the LOW-EXP group when compared to the HIGH-EXP group at T0 (SMD = 2.80, $p = 0.012$) and at T1 (SMD = 2.53, $p = 0.032$). Furthermore, results revealed a significant reduction of depression scores between baseline and T1 for the HIGH-EXP (SMD = -1.17, $p = 0.005$) and the LOW-EXP (SMD = -1.43, $p = 0.03$) groups, as well as a significant rebound between T1 and T2 in the HIGH-EXP group (SMD = 1.21, $p = 0.02$).

[Please insert Figure 4 A-C here]

In addition to the TEX-Q total mean score, we accomplished exploratory analyses to elucidate the TEX-Q subscale mean scores as putative predictors. All three therapy expectations groups differed significantly in each subscale, indicating that patients with HIGH-EXP revealed more positive and less negative expectations and vice versa (see Table 3). Regarding pain intensity, multiple regression analyses for each of the subscales revealed a significant model only for the subscale *adverse effects* adjusted for depression, indicating that higher expectations of side effects predicted pain at T2 ($F(1,137) = 7.859$, $p = 0.006$, adj. $R^2 = 0.05$). For disability, the model included depression, pain intensity at T0, and *adverse events* as significant predictors of disability with a significant increase in model fit ($F(3,128) = 16.296$, $p < 0.001$, adj. $R^2 = 0.26$), indicating that higher side effect expectations predicted greater disability. For all other subscales, no significant regression models emerged neither for pain intensity nor for disability as outcome variable.

[Please insert Table 3 here]

Treatment expectations and previous IMPT experience

In relation to the effectiveness of previous IMPT, patients (n = 109) reported a mean score of 4.53 (SD + 2.85) for alleviation of LBP, while a mean score of 1.73 (SD + 2.33) was indicated for exacerbation. To explore the potential influence of prior experience of IMPT, correlational analyses (see Supplement Table 2) showed that treatment expectations of the whole sample were positively associated with positive experiences in prior IMPT ($r = 0.32$, $p = 0.001$). Negative experiences in prior IMPT were negatively correlated with treatment expectations ($r = -0.20$, $p = 0.04$). Two one-way ANOVAs were conducted to show differences in treatment expectations subgroups. Treatment expectations groups

differed significantly in previous experiences of pain relief ($F(2,109) = 5.58$, $p = 0.005$, $\eta^2 = 0.1$) or pain increase after IMPT ($F(2,106) = 4.57$, $p = 0.013$, $\eta^2 = 0.08$). Post-hoc-tests revealed that patients with HIGH-EXP experienced significantly more pain relief in former IMPT compared to patients with LOW-EXP ($p = 0.004$). In addition, patients with LOW-EXP experienced significantly more pain increase after prior IMPT than patients with MOD-EXP ($p = 0.010$).

4. Discussion

Treatment expectations within the psychosocial treatment context demonstrably shape the experience of pain, and hence likely contribute to interindividual differences in treatment outcomes. In clinical treatment settings, however, the role of expectations remains incompletely understood, especially in IMPT as the recommended treatment for chronic pain. Consistent with prior evidence on the efficacy of IMPT for chronic back pain ,[22,23,32,46] our cohort showed an overall improvement in pain intensity at the end of IMPT, which was maintained at the 3-month follow-up. In addition, an overall decrease in pain-related disability was observed. As expected, there was considerable interindividual variability in patient-reported outcomes. While outcomes herein were likely affected by Covid-related restrictions, clearly any treatment approach for chronic pain, including IMPT does not work equally well for every patient but is rather shaped by a number of biopsychosocial context factors. Given limited access to therapy, socioeconomic considerations, and ultimately to improve treatment outcomes, it is important to gain knowledge into predictors of treatment success. To elucidate the role of expectations in IMPT outcomes, our analysis strategy comprised different steps, all based on the assessment of treatment expectations prior to therapy (T0) with a validated questionnaire, i.e., the TEX-Q.

To initially test whether differences in individual treatment expectations constituted predictors of changes in pain intensity and disability as primary outcomes, multiple regression analyses were computed. Treatment expectations did emerge as significant predictors of changes in pain intensity as well as pain-related disability. While this is in line with earlier findings suggesting a contribution of treatment expectations to improved pain intensity in chronic pain patients undergoing multimodal treatment,[20,23,47] the present analysis is the first to identify treatment expectations as a significant predictor of improvements in disability in a routine inpatient IMPT clinic setting. To further elucidate the putative role of the different facets of treatment expectations, we additionally computed exploratory regression analyses of the TEX-Q subscales. As significant model emerged only the subscale '*adverse events'*. Negative treatment-related expectations, including the expectations of side effects of adverse events, can be generated by learning/conditioning, verbal suggestion, or social observation,[48] inducing nocebo effects even within effective interventions.[14] In the present clinic setting, negative treatment expectations were conceivably shaped by prior treatment experiences. We capitalized on the fact that a substantial proportion of our patients had undergone prior IMPT treatments to interrogate this assumption, observing that lower pain relief experienced in prior IMPT correlated with lower (i.e., more negative) treatment expectations herein. This is consistent with earlier evidence that extensive and

unsuccessful experiences in pain treatment can result in lower expectations,[19] and that patients with chronic pain who had experienced treatments before did not expect alleviation from medical interventions alone.[49]

Since depression reportedly constitutes the strongest predictor of long-term disability[15] and may be even more relevant than pain relief alone,[25,26] depression scores were entered into the regression models. In both models, depression at T0 emerged as a significant predictor, which explained more variability in outcomes than treatment expectations. For pain intensity, the final model including depression and treatment expectations explained 16% of variance. For disability, the final model including pain intensity at T0, depression, and treatment expectations as predictor variables explained 29% of variance. The role of depression in the context of expectation effects in treatment of chronic back pain is also supported by open-label placebo (OLP) treatment.[50] In the present patient cohort, a substantial proportion of patients reported clinically relevant depressive symptoms, or had a pre-existing diagnosis (43%), reflecting high psychiatric comorbidity in line with the literature[15,24,51] Our mediation analyses revealed a partial mediating effect of treatment expectations on the association between depression symptoms at baseline and pain intensity as well as disability outcomes at T2. These results complement recent evidence supporting that preoperative negative emotional states, including sadness as a key symptom of depression, predicted negative expectations that were in turn drivers of postoperative pain intensity.[29] Together, these findings suggest that patients with depression, anxiety or other negative mood states may be more likely to have negative treatment expectations and may hence be more vulnerable to nocebo effects. It is similarly conceivable that affective comorbidity interferes with the ability to generate positive expectations, thereby limiting the benefits of placebo mechanisms. Either way, these converging data strongly support that future research into strategies to improve treatment outcomes for chronic pain should consider depression in concert with both positive as well as negative treatment expectations. Clearly, the association between chronic pain, depression, expectations and treatment response is complex,[51] as these factors are undoubtedly intricately intertwined.[52,53] Several psychobiological mechanisms could play a role, including motivation and approach-avoidance factors impacting on cognitions and adherence,[54] enhanced pain sensitivity,[51] maladaptive beliefs about control of pain as a cause of depression,[55] or optimism (see below), calling for more study that should ideally also clarify if and how prior treatment experiences may impact on the decision to seek the same or novel treatments, on the generation of expectations as well as on symptoms of depression and motivational factors relevant to treatment adherence.

To further elucidate interindividual variability in treatment expectations from the perspective of a possible applicability in clinical settings, e.g., for a determination of individual risk and protective factors as a basis for more personalized interventions, we accomplished analyses on expectation subgroups, created by a cluster analysis. Corroborating and extending regression analyses, improvements in pain intensity at the end of and three months after IMPT as well as in disability three

months after IMPT were greater in the subgroup of patients with HIGH-EXP. These findings support the notion that patients with more positive treatment expectations benefit more from IMPT, in line with previous research .[20,27] Cormier et al.[20] found positive relationships between expectations and changes in pain intensity, depressive symptoms, and disability in patients undergoing an IMPT after six months. They concluded that patients with high expectations may have a higher motivation to be compliant.

While our data do not allow to firm conclusions regarding cause-effect or temporal relationships, we did observe that depression scores were significantly reduced during IMPT irrespective of level of expectation. In fact, the subgroup with the highest pre-treatment expectations showed a significant rebound at the 3-month-follow-up despite stable pain intensity and disability. The reasons for this remain unclear, however, there is evidence that unrealistic high positive expectations (e.g., expectation of immediate and complete pain relief) can elevate the risk of depression.[24] Hence, the present results may be explained by an expectancy violation. Alternatively, it is also conceivable yet remains speculative that depression was ameliorated by daily inpatient treatment and/or factors with the treatment context that were no longer present in the home setting. This raises conceptual questions regarding a possible assessment of realistic vs. unrealistic expectations as well as practical consequences for the design of interventions suitable to improve treatment outcomes by boosting positive expectations. Although a clear definition is lacking, we cautiously interpreted "high" expectations as "positive" or "optimistic", due to previous research on optimism and pain.[56] Moreover, the belief in restored health was an important predictor for improvements in multimodal rehabilitation.[57] For example, Meints et al.[58] described optimism as feelings of control and better functional performance leading to positive outcome expectancies. Maybe optimists tend to focus on other aspects of the body, specifically on no pain areas or functioning. Optimists appear to show better pain adjustment and less pain sensitivity.[56] Future studies should focus on interventions addressing expectations as well as on the perception of improvement. However, Geurts et al.[59] concluded that focussing on improvement alone may not be sufficient and that expectations must be differentiated with respect to structure and process expectations and outcomes, respectively. Unhelpful beliefs and attitudes,[18] which influence expectations and perceptions negatively, should be detected, and modified. A key factor for changing expectations is sufficient and positive information about pain and helpful interventions, its causes, and possible consequences, communicated from health care providers.[27,28] Therefore, clinicians should evaluate previous experiences and expectations and modify negative expectations, e.g., by giving information transparently. Maximizing positive expectations and minimizing negative expectations provides opportunities to improve treatment outcomes in patients. In chronic back pain this is elegantly illustrated by OLP studies,[48] albeit long-term efficacy is unclear,[60,61] and work on enhancing pharmacological pain treatment using social observational learning as a means to augment positive treatment expectations.[62]

The present study has several strengths, including the use of validated measures, the consideration of depression, and the combination of different statistical approaches including the comparison of

expectation subgroups with putative applicability in routine care settings. Nevertheless, some limitations must be considered. This study was mostly based on self-report-instruments and did not incorporate assessment of functional capacity as previously accomplished for a more comprehensive understanding of improvements in pain-related disability.[50,61] Furthermore, we did not assess the reasons why patients returned for treatment and have not data on healthcare use after completion of the study. While we did not assess longer-term changes beyond the 3-month follow-up herein, there is evidence from a recent meta-analysis supporting that treatment benefits from IMPT are maintained over longer time periods.[32] Finally, the study was implemented during the pandemic, which resulted in fewer group interventions in IMPT and prohibited visits of relatives. Therefore, results do not entirely reflect the treatment reality as it is without restrictions, and generalizability to other treatment settings and patient cohorts is limited.

5. Conclusions

Nevertheless, the present study supports that treatment expectations in patients suffering from chronic LBP play an important role in shaping pain outcomes. Patients undergoing IMPT with high positive expectations have better outcomes. Depression plays a major role and should be considered in future studies. Ultimately, these results can aid the development of personalized treatment concepts[63] for patients with chronic pain.

Disclosures:

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All authors declare no conflicts of interest.

Figure legend

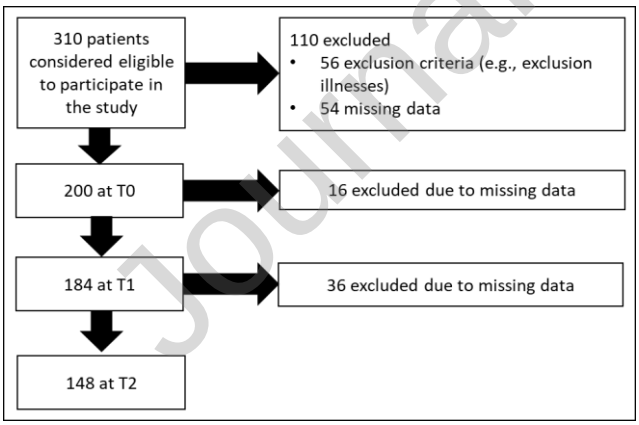

Figure 1. Flow chart of patient recruitment and study participation across time points. Note: Data were missing at random and refer back to incompletely filled out questionnaires or due to patients leaving the clinic prior to scheduled therapy for various reasons (e.g., acute Covid-19 infection) or withdrawal from the study.

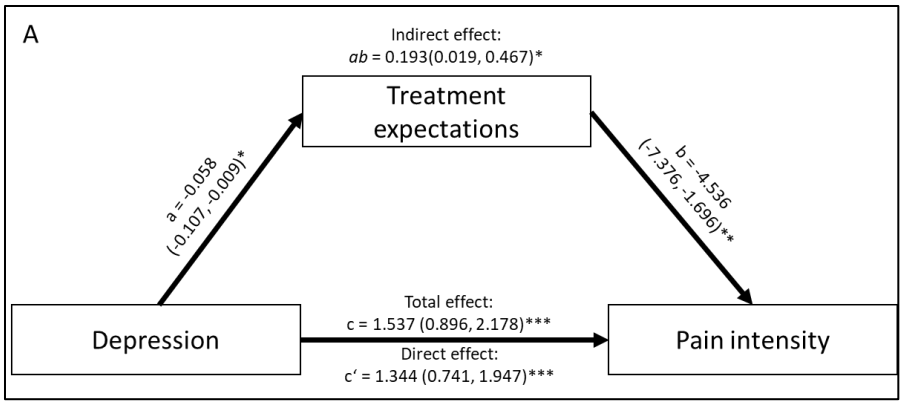

Figure 2. Total effect of depression at T0 on pain intensity (A) and disability (B), both assessed at T2, and indirect effect mediated by treatment expectations. Unstandardized coefficients with 95% Confidence Intervals (CIs) are shown. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

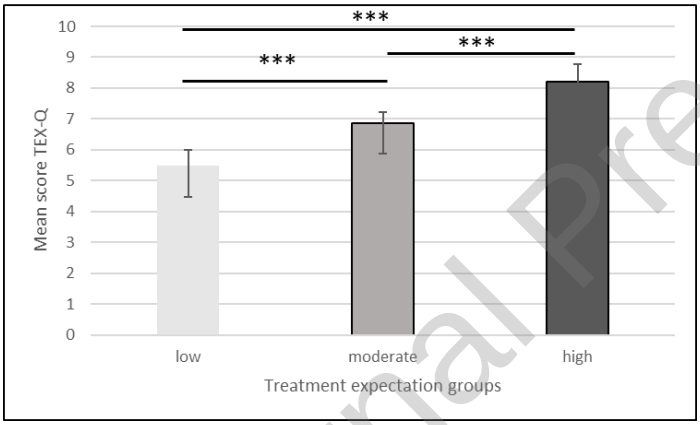

Figure 3. Significant differences in expectations between treatment expectation subgroups based on cluster analysis. TEX-Q = Treatment expectation questionnaire (total score). *** $p < 0.001$ results of post-hoc tests between groups; for ANOVA results, see text.

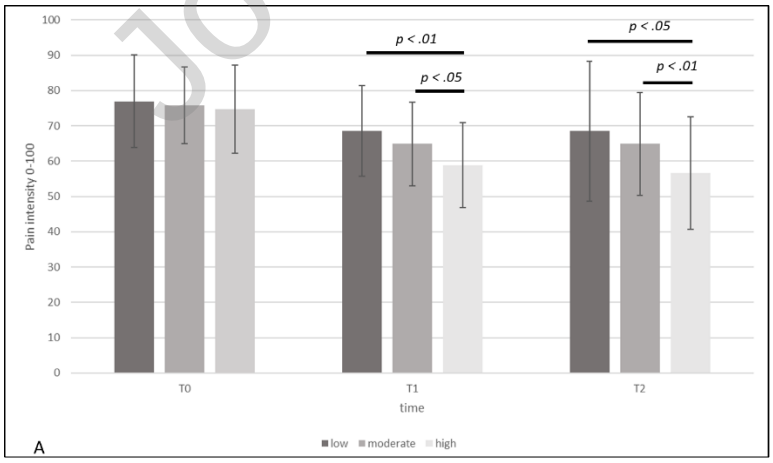

Figure 4. Pain intensity (A), disability (B), and depression (C) before treatment (T0), at the end of treatment (T1) and at the 3-month follow-up (T2) in three treatment expectations subgroups with low, moderate or high treatment expectations, respectively. Note that scores for disability are adjusted for pain intensity and depression at T0. *p*-values refer to Bonferroni-corrected post-hoc tests. BDI-FS = Beck Depression Inventory Fast Screen.

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Table 1. Sociodemographic, clinical, and psychological characteristics of the full sample and of treatment expectation subgroups at baseline (T0)

	Total N=200	High expectations 29 (n=58)	Moderate expectations 47 (n=94)	Low expectations 24 (n=48)	*p**, partial η^2

Age (years)	60.23 + 12.99	60.29 + 14.15	59.20 + 12.01	62.63 + 13.6	ns
Sex/Gender (%)		29	47	24	
female	68.5	28.47	49.64	21.9	ns
male	21.5	30.16	41.27	28.57	
Civil status (%)		30.22	40.11	24.18	
single	34.5	26.09	34.78	26.64	ns
married/steady partner	56.5	32.74	43.36	23.89	
Education (%)		29.95	48.13	21.93	*0.004***, 0.04
no school-leaving qualification	3.5	28.57	57.14	14.29	
(intermediate) secondary general school	37	29.10	54.48	16.42	
higher education/A-level	23	32.61	28.26	39.13	
Pain intensity (CPGS 0-100)	75.62 + 12.36	74.38 + 12.52	75.03 + 10.93	75.56 + 13.78	ns
Disability (CPGS 0-100)	72.57 + 17.66	69.50 + 14.46	71.91 + 17.62	74.89 + 14.84	ns
Pain duration (years)					
< 1	7.0	28.57	64.29	7.14	ns
1-2	17.0	35.29	41.18	23.53	
2-5	12.5	32	48	20	
> 5	61.5	26.02	46.34	27.64	
Chronic Pain Grade[a] (%)	100	27.06	50	22.94	ns
1	1.18	0	50	50	
2	9.4	37.5	31.25	31.25	
3	18.24	48.39	35.48	16.13	
4	71.18	20.66	56.2	23.14	
Clinical diagnosis of depression (%)	42.5 (*n*=85)	20	41	24	ns
Depression symptoms (BDI-FS)	5.31 + 3.95	4.38 + 4.04	5.35 + 3.85	7.31 + 3.84	*0.018***, 0.06
Body Mass Index (BMI)	29.96 + 5.56	30.30 + 5.12	29.89 + 5.83	29.67 + 5.66	ns
Opioid use (%)	30 (*n*=60)	23.33	46.67	30	ns
Use of psychoactive drugs (%)	43.3 (*n*=82)	25.33	50.67	24	ns.
Previous IMPT's (%)	41 (*n*=82)	28.05	42.68	29.27	ns
1 previous IMPT	31.71	30.77	38.46	30.77	
2 previous IMPT's	20.73	29.41	41.18	29.41	
3 previous IMPT's	19.51	43.75	37.5	18.75	
4 or more previous IMPT's	28.05	13.04	52.17	34.78	

Data are given as mean + standard deviation or %. *p* values from independent sample t-tests or Pearson Chi²-tests comparing subgroups. * $p < .05$, ** $p < .01$. CPGS = Chronic Pain Grade Scale. BDI FS = Beck's Depression Inventory Fast Screen. IMPT = Interdisciplinary multimodal pain therapy. [a] The Chronic Pain Grade is the result of disability points and pain intensity, measured with the Chronic Pain Grade Scale.

Table 2. Results of multiple regression analyses.

Dependent Variable	**Predictor variable**	**B**	***robust standard error***	**t**	***p***	**adj. R^2**	**f^2**	**AIC**
Pain intensity T2	depression	1.344	0.303	4.433	< 0.001	0.124	0.149	757.77
	treatment expectations	-3.332	1.295	-2.573	0.011	0.162	0.212	752.62
	constant	78.771		8.452				
			β					
Disability T2	pain intensity T0	0.677	0.372	4.654	< 0.001	0.132	0.160	830.925
	depression	1.967	0.352	4.611	< 0.001	0.245	0.344	812.752

	treatment expectations	-4.610	-0.227	-3.068	0.003	0.290	0.439	805.385
	constant	42.225		2.881				

Results of multiple linear regression analyses with pain intensity and disability as dependent variables, treatment expectation as predictor, adjusted for depression (both models) and for pain intensity (model for disability). Table provides regression coefficient (B), robust standard error or standardized coefficients (β), t-score, exact p value (p), adjusted multiple determined coefficient (R^2), Cohen's effect size (f^2), and Akaike Information Criterion (AIC).

Table 3. Results of analyses of variance of TEX-Q-subscales and therapy expectation subgroups

Treatment expectation subscales	**total**	**high**	**moderate**	**low**	***p***	**single contrasts**
Treatment benefit	6.50 + 1.83	8.23 + 1.27	6.22 + 1.36	4.77 + 1.40	< 0.001	*all groups*
Positive impact	6.40 + 2.03	8.35 + 1.24	6.11 + 1.58	4.49 + 1.51	< 0.001	*all groups*
Adverse events	2.86 + 1.68	2.10 + 1.46	2.91 + 1.63	3.84 + 1.48	< 0.001	low > high $p < 0.001$ low > moderate $p = 0.002$ moderate > high $p = 0.02$
Negative impact	3.26 + 2.32	2.25 + 2.12	3.28 + 2.27	4.42 + 1.99	< 0.001	low > high $p < 0.001$ low > moderate $p = 0.08$ moderate > high $p = 0.02$
Process	7.49 + 1.57	8.50 + 1.25	7.62 + 1.12	5.97 + 1.63	< 0.001	*all groups*
Behavioural control	7.83 + 1.60	8.65 + 1.36	7.94 + 1.31	6.62 + 1.63	< 0.001	low > high $p < 0.001$ low > moderate $p < 0.001$ moderate > high $p = 0.008$

Data are given as mean + standard deviation. *p*-values refer to Bonferroni-corrected post-hoc tests. TEX-Q = Therapy expectation Questionnaire.

Highlights

- Treatment expectations predict outcomes in the treatment of chronic low back pain
- High treatment expectations were associated with better outcomes
- Consideration of treatment expectations should be made in conjunction with depression
- Treatment expectations partially mediate the depression-outcome relationship