What Works? Processes of Change in a Transdiagnostic Exposure Treatment for Patients With Chronic Pain and Emotional Problems

Martin Södermark, MSc, Steven J. Linton, PhD,† Hugo Hesser, PhD,†‡ Ida Flink, PhD,† Björn Gerdle, MD, PhD,* and Katja Boersma, PhD†*

Objectives: We recently developed a transdiagnostic exposure treatment (the hybrid treatment) for chronic pain patients with concurrent emotional difficulties. This paper investigates the hypothesized treatment processes, specifically: (1) if changes on pain-related dysregulation (catastrophizing, fear-avoidance, and nonacceptance of pain) and general emotion dysregulation (difficulties to regulate a broad spectrum of emotional responses) mediate effects on outcomes; and (2) if mediation is more pronounced for patients who score higher on these processes pretreatment.

Materials and Methods: Structural equation modeling for longitudinal data using the full intention-to-treat sample was used to test whether proposed variables mediated the effect of the hybrid treatment (n = 58) compared with a guided internet-delivered pain management treatment based on cognitive-behavioral principles (n = 57) on pain interference and depressive symptoms at the 9-month follow-up. To make full use of the multiple process measures collected in the trial, we modeled mediators as 2 continuous latent variables: pain-related dysregulation and general emotion dysregulation.

Results: Reduced pain-related dysregulation mediated the effects of treatment on both outcomes, whereas reduced general emotion dysregulation mediated the effects on depressive symptoms only. In the hybrid treatment, the mediated effect was more pronounced for participants who scored higher on pain-related dysregulation pretreatment relative to those who scored lower.

Discussion: Our findings provide initial support for the transdiagnostic theoretical underpinnings of the hybrid treatment model. Using a hybrid treatment approach that centers on teaching patients emotion-regulation skills before commencing broad exposure successfully influenced both pain-related dysregulation and general emotion dysregulation, which in turn was associated with better treatment outcomes. It appears central to address these processes in pain patients with comorbid emotional problems, especially among patients scoring high on measures of catastrophizing, fear-avoidance, and nonacceptance of pain.

Key Words: chronic pain, depression, cognitive-behavioral therapy, emotion regulation

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Cognitive-behavioral therapy (CBT) has substantial empirical support based on a vast number of clinical trials and systematic reviews evaluating the effects on chronic pain[1] and on emotional disturbances.[2] However, for the large number of patients with *concurrent* pain and emotional problems, CBT treatments have shown to be less effective.[3–8] As comorbid pain and emotional problems entail a great deal of suffering, marginalization, and societal costs, there is an urgent need for developing more effective treatments.[9–11]

One way to improve outcome for patients with comorbidities is to target transdiagnostic processes, underlying in this case both pain and emotional problems.[12] One potential transdiagnostic process is difficulties with emotion regulation, or emotion dysregulation. This has been conceptualized as involving (1) lack of awareness and understanding of emotions; (2) nonacceptance of emotions; (3) difficulties in controlling impulsive behaviors and behave in accordance with desired goals when experiencing emotions; and (4) difficulties in using situationally appropriate emotion-regulation strategies flexibly to meet individual goals and situational demands.[13] Emotion dysregulation has been pinpointed as central in both psychiatric disorders[14,15] and in chronic pain.[16] Several forms of recent CBT approach explicitly this mechanism with the assumption that this might improve important outcomes such as well-being, health, and disability.[17,18] Building on these efforts, we developed a transdiagnostic exposure treatment (the hybrid treatment) for patients with concurrent pain and emotional problems, integrating exposure methods based on the fear-avoidance model[19] with an explicit emotion-regulation approach informed by procedures in dialectical behavior therapy.[20] Hence, the hybrid treatment rational and protocol[21] target transdiagnostic treatment processes, such as general skill deficits in coping with difficult emotions as well as pain-specific fears and catastrophizing thoughts. Hence, the protocol explicitly addresses both pain-related dysregulation and general emotion-regulation difficulties.

After piloting the protocol in a controlled single case series,[22] we tested the hybrid treatment in a randomized-controlled

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From the *Pain and Rehabilitation Center, Department of Medical and Health Sciences; ‡Department of Behavioural Sciences and Learning, Division of Psychology, Linköping University, Linköping; and †Center for Health and Medical Psychology, Örebro University, Örebro, Sweden.

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Reprints: Martin Södermark, MSc, Pain and Rehabilitation Centre, Linköping University Hospital, Linköping 581 85, Sweden (e-mail: martin.sodermark@liu.se).

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trial (RCT),[21] comparing it to a guided internet-delivered pain management treatment based on cognitive-behavioral therapy principles (iCBT). The hybrid treatment produced significantly better outcomes for depressive symptoms and pain interference at the 9-month follow-up. This initiates important follow-up questions on how the treatment exerted its effect. Specifically, there is a need to understand the *mediating variables* or processes by which change occurred.[23–25]

In accordance with the theoretical framework of the hybrid treatment, proposed mediators of change are as follows: (1) reductions in pain-related dysregulation, altering cognitive, emotional, and behavioral processes related to regulatory attempts to control and avoid pain, such as pain catastrophizing, nonacceptance, and fear-avoidance beliefs; and (2) reductions in general emotion dysregulation by improving emotion-regulation skills, such as awareness, understanding and acceptance of emotions, self-compassion, and ability to engage in goal-directed behavior. For the sake of brevity, these proposed mediators will be coined, respectively, "pain-related dysregulation" and "general emotion dysregulation." Earlier treatment studies suggest that these variables do play important roles as mediators of pain outcomes. Improvements on measures of pain-related dysregulation (such as the Pain Catastrophizing Scale, PCS[26]; the Tampa Scale of Kinesiophobia, TSK[27]; and the Chronic Pain Acceptance Questionnaire, CPAQ[28]) have been shown to mediate effects on pain interference and disability in both CBT treatments and physical therapy for patients with chronic pain,[26–28] and reductions in emotion dysregulation (including several measures of difficulties in emotion regulation, rumination, and experiential avoidance) have been shown to correlate with effects on emotional problems such as depressive symptoms in multiple psychological treatments for psychiatric disorders.[14]

In the current study, we used several measures to capture our proposed mediators. When exploring mediation in such a context, it is important to use a methodology that specifically addresses the overlap among variables, for both conceptual and methodological reasons.[29,30] One such approach, which we will apply in this study, is to reduce the number of overlapping observed variables to a smaller set of latent dimensions (ie, latent variables) within the framework of structured equation modeling (SEM).[31,32] This approach will also allow us to test important methodological assumptions of longitudinal mediation analysis (eg, longitudinal measurement invariance)[33] and overcome other problems associated with testing mediators with observed variables (eg, measurement error).[32]

The other important question that we will address is whether the hybrid treatment exerts its effect through the same mechanism for all participants. Specifically, effects of treatments are often stronger for participants scoring worse on mediating variables before treatment (so-called baseline-moderated mediation).[34] Therefore, we suggest that pretreatment levels on pain-related dysregulation and general emotion dysregulation might moderate the mediated effect. By testing moderated mediation, we can determine for whom, and under what conditions, specific processes operate.[35] Information gained from such theory-driven analyses may further improve the effectiveness of the hybrid treatment by identifying individuals who will benefit most from the treatment and by pointing out treatment techniques that change specific mediators for subgroups of individuals.

To summarize, in this study, we focus on 3 hypotheses. First, we hypothesize that the hybrid treatment has a more pronounced effect than iCBT on the 2 latent process variables labeled pain-related dysregulation and general emotion dysregulation. Second, we hypothesize that effects on the latent variables at posttreatment mediate the effectiveness of the hybrid treatment on depressive symptoms and pain interference at follow-up. Our third hypothesis is that patients scoring worse on the mediator pretreatment will have more pronounced indirect effects through that mediator.

MATERIALS AND METHODS

This study is based on a multicenter parallel-group study in which 115 chronic pain patients with emotional problems were randomized to either the hybrid treatment (n = 58) or an active control condition receiving a guided iCBT (n = 57). The current paper presents secondary analyses of the original RCT, the main results of which are reported elsewhere.[21] The study was carried out between 2016 and 2018 at 2 sites in Sweden (Örebro and Linköping). The Ethics Review Board in Uppsala approved the study (2015/479) and the trial was preregistered at Clinicaltrails.gov (NCT02808286).

Inclusion Criteria

We recruited individuals with chronic pain aged 18 to 70 years via advertisements in local newspapers, social media, and through clinical departments of pain rehabilitation. Inclusion criteria were as follows: (1) chronic musculoskeletal pain (> 6 mo duration); (2) functional problems in daily life due to pain (≥ 11 points on items 21 to 24 of the Örebro Musculoskeletal Pain Questionnaire[36]); (3) emotional problems (≥ 8 on either subscale of the Hospital Anxiety and Depression Scale[37]); (4) access to a computer or a tablet; and (5) sufficient mastery of the Swedish language. In addition, we excluded participants with (1) severe psychiatric disorders that may have required immediate or other treatment (alcohol abuse, psychotic disorders, or at risk of suicide); (2) ongoing psychological treatment elsewhere; and (3) recently started, or changed, psychopharmacological treatment (cutoff criterion: <3 mo before planned treatment start). We provide a more detailed description of the recruitment process in the original article presenting the results of the RCT.[21]

Sample

Table 1 provides the clinical and demographic characteristics of the included participants.

Patient-reported Outcome Measures

Participants filled out assessment batteries electronically in their own environment at pretreatment before randomization, at posttreatment (after median = 21 wk, interquartile range = 17 to 26 wk), and at the 9-month follow-up (after median = 60 wk, interquartile range = 56 to 64 wk). All measures have been used, and most of them validated, in a Swedish context.[38–46]

Figure 1 shows the flow chart of the study procedure. The retention rate to posttreatment assessment was 81% for the hybrid treatment and 75% for iCBT, and 79% and 84%, respectively, at follow-up. In this report, we analyze assessment of mediators at pretreatment and posttreatment, and outcome measures at pretreatment and follow-up.

Outcomes

To assess depressive symptoms, we used the Montgomery-Åsberg Depression Rating Scale—Self-report[47] (9 items, range: 0 to 60; test-retest reliability $r = 0.78$[48]; Cronbach $\alpha = 0.78$). To assess pain interference, we used the subscale from the Swedish version of the West Haven-Yale Multidimensional Pain

TABLE 1. Baseline Description of Participants' Demographic and Clinical Characteristics

	Hybrid (N = 58)	iCBT (N = 57)
Sex, n (% women)	52 (89.7)	44 (77.2)
Age, mean (SD)	45 (12)	44 (12)
Screening measures, mean (SD)		
ÖMPSQ function (0-40)	21 (7.5)	21.7 (7.3)
HADS anxiety (0-21)	12.2 (4.0)	11.2 (4.1)
HADS depression (0-21)	11.4 (3.8)	11.8 (4.3)
Occupational status, n (%)		
Working	33 (56.9)	34 (59.6)
Unemployed	3 (5.2)	4 (7)
Student	3 (5.2)	4 (7)
Pensioner	9 (15.5)	6 (10.5)
Other	10 (17.2)	9 (15.8)
Sick leave, n (% during last year) (d)		
0-14	25 (43.1)	25 (43.9)
15-180	8 (13.8)	11 (19.3)
181-365	25 (43.1)	21 (36.8)

These data are also presented elsewhere.[1]

HADS indicates Hospital Anxiety and Depression Scale; Hybrid, the hybrid treatment; iCBT, internet-delivered pain management treatment based on cognitive-behavioral principles; ÖMPSQ, Örebro Musculoskeletal Pain Screening Questionnaire, items 21 to 24.

Inventory—Interference[49] (11 items, range: 0 to 66; test-retest reliability $r = 0.85$[39]; Cronbach $\alpha = 0.87$). We replaced missing values for the item "interference with work" due to the participant not working, with the mean of the other items on the interference scale.

Mediators

As indicators for the latent variable *pain-related dysregulation,* we used (1) the PCS (13 items, range: 0 to 52; test-retest reliability $r = 0.75$[50]; Cronbach $\alpha = 0.91$) assessing negative thinking related to actual or anticipated pain experiences[50]; (2) the TSK-11 (11 items, range: 11 to 44; test-retest reliability $r = 0.81$[51]; Cronbach $\alpha = 0.80$.) assessing fear of reinjury or worsening of pain due to movements and activities[52]; and (3) the CPAQ-8 (8 items, range: 0 to 48; Cronbach $\alpha = 0.78$) assessing the ability to engage in activities in the presence of pain, willingness to experience pain, and attempts to avoid or control pain.[53]

As indicators of the latent variable *general emotion dysregulation* we used (1) the Difficulties in Emotion Regulation Scale (DERS; 36 items, range: 36 to 180; test-retest reliability $r = 0.88$[13]; Cronbach $\alpha = 0.93$) assessing a broad range of emotion-regulation strategies including awareness of emotions, control of impulses, acceptance of emotions, access to functional regulation strategies, and ability to

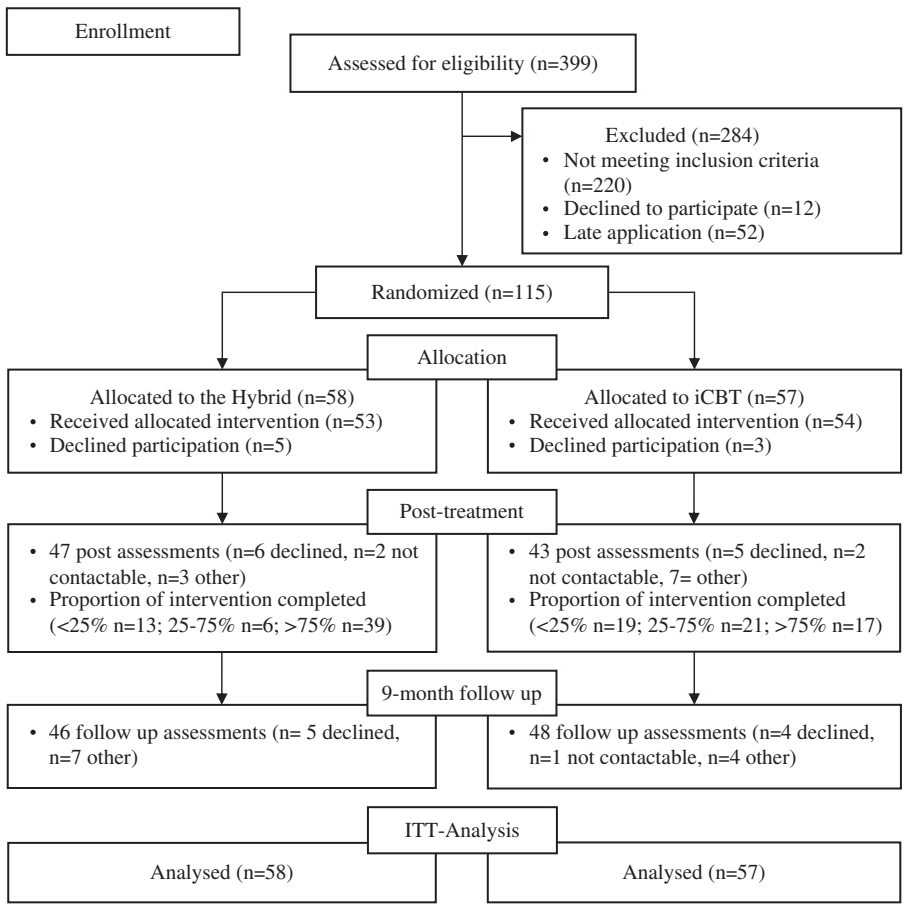

FIGURE 1. Flow chart of the study procedure. Hybrid indicates the hybrid treatment; iCBT, internet-delivered pain management treatment based on cognitive-behavioral principles; ITT, intention-to-treat.

pursue goals regardless of emotions[13]; (2) the Self-Compassion Scale-12 (SCS-12; 12 items, range: 12 to 60, test-retest reliability $r = 0.89$[54]; Cronbach $\alpha = 0.87$) assessing emotion-regulation strategies such as cognitive reappraisal, self-compassion, and acceptance[55]; and (3) the Behavioral Activation for Depression Scale (BADS; 25 items, range: 0 to 150; test-retest reliability $r = 0.74$[56]; Cronbach $\alpha = 0.85$) assessing difficulties with goal pursuit, avoidance behaviors, social withdrawal, and rumination.[56]

The latent constructs aim to represent 2 relevant and theoretically distinct higher order factors: pain symptom-specific coping and general emotion-regulation abilities. The TSK, PCS, and CPAQ, grouped under the first latent construct, all assess pain-specific cognitive-behavioral processes. Although each instrument is associated with somewhat different theories, they have clear commonalities and overlap. Specifically, they all share the notion that pain triggers emotions and is associated with cognitions and behaviors that can be conceptualized as regulatory attempts to control and avoid pain.[51,53,57] The DERS, BADS, and SCS, grouped under the second latent construct, all assess cognitive and behavioral attempts to regulate emotional responses.[13,17,55,56]

Hybrid Treatment

The hybrid treatment is principle based and presented in 5 different treatment stages: (1) building a working relationship and developing relevant goals, (2) developing emotion-regulation skills, (3) exposure for emotions and movements, (4) applying skills in tune with environment, and (5) maintaining and refining learned skills. A target of 10 to 15 weekly sessions was set, but because the stages allow for tailoring to the patients' needs, no specific formulations of session content, number of sessions per stage, or detailed step-by-step methods were provided. The treatment was conducted by licensed clinical psychologists (n = 5) and clinical psychologists in their postgraduate year of supervised professional training for accreditation (n = 2).

iCBT

The iCBT intervention included 8 treatment modules consisting of educational texts, pictures, case examples, audio-files, and 2 to 3 homework assignments per module. The content consisted of common cognitive-behavioral interventions in pain management such as graded exercise, pacing and activity planning, applied relaxation, coping with negative thoughts, mindfulness exercises, stress management, sleep hygiene, and developing a maintenance plan. During treatment, participants were guided via the chat function of the internet platform by licensed clinical psychologists (n = 2), psychology students in their final stage of clinical training (n = 4), and clinical psychologists in their postacademic year of supervised professional training for accreditation (n = 2).

Statistical Methods

All primary data models were estimated within the framework of SEM and fitted with full information maximum likelihood estimation with non-normality robust SEs (MLR or Bootstrap) using Mplus, version 8.2.[58]

To make full use of multiple measures collected in the trial, we modeled mediators as 2 continuous latent variables. Indicators for the latent variable *pain-related dysregulation* were the total scores on TSK-11, PCS, and CPAQ-8. Indicators for the latent variable *general emotion dysregulation* were the total scores on DERS, SCS-12, and BADS. We reversed CPAQ-8, SCS-12, and BADS before analyses so that factor loadings were all positive, and higher scores on the factors were indicative of more dysfunction.

In addition to the advantages of using latent factors stated in the introduction (ie, handling measurement error, empirical overlap among variables, test of measurement invariance), this approach also limited the number of tests required for testing mediation and thus prevented inflated type-1 error rates. Furthermore, by retaining information from all indicators and time points irrespective of missing data for any individual, all randomized individuals were included in the primary models following the intention-to-treat principle using full information maximum likelihood, 1 of 2 recommended methods for handling missing data.[59]

We used the following procedures. First, to determine the adequacy of the proposed 2-factor structure, we started by constructing confirmatory factor analysis (CFA) models, one at each time point (pretreatment and posttreatment). The cross-sectional CFA models were then combined into a longitudinal CFA model.[60] We evaluated the fit of the models using the χ^2 test, where a good fitted model should not be rejected by the data as indicated by a nonstatistically significant test. In addition, we used the root mean square error of approximation, the Comparative Fit Index, and the standardized root mean square residual with values <0.06,[61,62] >0.95,[61,63] and <0.08[61] as benchmarks for a good fitted model.

Second, we proceeded to test longitudinal measurement invariance for each latent variable (the 2 suggested mediators). Measurement invariance was constructed by constraining measurement intercepts and factor loadings for indicator variables for each latent factor to be equal across measurement points.[60,64] To test whether the constraints significantly worsened model fit, we compared the global fit of the constrained model with a configural model in which these constraints were removed using a scaled χ^2 difference test.[58,65] The more constrained model (null model) was deemed to fit worse than an alternative less restrictive model if the increase in χ^2 statistics was statistically significant at the level of P-value <0.05 (with degrees of freedom equal to the difference in free parameters between models). If this test was not statistically significant, we assumed longitudinal measurement invariance (ie, scalar invariance) to be established. Following recommendations for longitudinal SEMs,[60,64] residual errors were correlated for the same indicators across time to avoid model misspecifications.

Third, once factorial invariance was established, we could test for mediation using the latent variables as mediators in a path model. The associations between (X) treatment condition, (M) the latent variables as measured at posttreatment, and (Y) the observed outcomes symptoms of depression and pain interference at the 9-month follow-up assessment were modeled using regression among these continuous latent and observed variables. Specifically, the latent mediator variables posttreatment were regressed on the treatment condition (*a*-path) as an observed binary coded variable (1 = hybrid treatment, 0 = iCBT) and the observed outcome at the 9-month follow-up was regressed on the latent mediator (*b*-path). To control for initial scores on both the latent mediator and the observed outcome in the model, the mediator and outcome measured at posttreatment and follow-up, respectively, were regressed on the latent mediator variable and the outcome assessed at pretreatment (similar to an analysis of covariance model). By regressing the posttreatment value on the pretreatment score, the net effect at posttreatment can be conceptualized as a change score between

TABLE 2. Means (SDs) at Assessment Points

Measure (Range), Treatment	Pretreatment	Posttreatment	9-mo Follow-up
Indicators for the latent variable pain-related dysregulation			
TSK-11 (11-44)			
Hybrid	24.34 (6.47)	19.48 (4.82)	NA
iCBT	24.96 (6.11)	24.0 (6.08)	NA
PCS (0-52)			
Hybrid	24.14 (10.21)	16.98 (9.97)	NA
iCBT	26.86 (10.54)	22.91 (11.83)	NA
CPAQ-8 (0-48)			
Hybrid	20.97 (7.34)	26.72 (6.07)	NA
iCBT	20.25 (7.98)	22.12 (7.59)	NA
Indicators for the latent variable general emotion dysregulation			
DERS (36-180)			
Hybrid	94.64 (25.85)	79.36 (21.26)	NA
iCBT	91.91 (21.39)	83.23 (24.98)	NA
SCS-12 (12-60)			
Hybrid	32.05 (9.89)	38.72 (8.96)	NA
iCBT	31.88 (8.23)	35.83 (10.66)	NA
BADS (0-150)			
Hybrid	75.17 (20.30)	93.77 (23.36)	NA
iCBT	79.04 (18.67)	92.08 (20.22)	NA
Outcomes*			
MADRS-S (0-60)			
Hybrid	23.72 (7.62)	NA	15.33 (9.63)
iCBT	23.11 (7.05)	NA	17.79 (9.28)
MPI-Interference (0-66)			
Hybrid	49.63 (10.46)	NA	36.39 (16.30)
iCBT	48.62 (12.09)	NA	41.32 (16.47)

Pretreatment N for Hybrid = 58, for iCBT N = 57; posttreatment N for Hybrid = 47, for iCBT N = 43; follow-up N for Hybrid = 46, for iCBT = 48.

*Data on outcomes also presented elsewhere.[1]

BADS indicates Behavioral Activation for Depression Scale; CPAQ-8, Chronic Pain Acceptance Questionnaire-8; DERS, Difficulties in Emotion Regulation Scale; Hybrid, the hybrid treatment; iCBT, internet-delivered pain management treatment based on cognitive-behavioral principles; MADRS-S, Montgomery-Åsberg Depression Rating Scale; MPI, West Haven-Yale Multidimensional Pain Inventory; NA, not applicable; PCS, Pain Catastrophizing Scale; SCS-12, Self-Compassion Scale-12; TSK-11, Tampa Scale for Kinesiophobia-11.

assessment points, and associations examined in mediator models can therefore be interpreted as predicting change in mediator and outcome (similar to how change is modeled in cross-lagged panel models[66]). This modeling approach also allowed us to control for bias due to regression toward the mean.

To formally evaluate mediation, we constructed bootstrapped confidence intervals (CIs) around the product of the *a*-path and *b*-path (*ab*-product) from 5000 samples drawn with replacements.[34] If this asymmetric 95% CI did not contain 0, mediation was assumed to be established at the specified α level (5%).

To test for moderated mediation by pretreatment levels on mediators, also known as mediated baseline by treatment moderation,[34,67] we created an interaction term between the latent variable measured at pretreatment and the treatment condition variable. Moderated mediation was assumed to be established if the product between this regression due to the interaction (moderated *a*-path) and the regression due to association between mediator and outcome (*b*-path) was statistically significant different from 0, as evaluated with the bootstrapped 95% asymmetric CI method. To determine the size and significance of the effect, following recommendations for moderated mediation,[67] we probed a statistically significant moderated effect by calculating the conditional effect for a range of values of the moderator (values between 2 SD above and below the mean). We then visualized the point estimate of the conditional effect along with a bootstrapped 95% CI for each value of the moderator.

RESULTS

Table 2 shows the observed means and SDs of the sample on the indicator measures for the proposed latent variables, pain-related dysregulation, and general emotional dysregulation, and on the outcome measures.

Factor Structure Invariance

In preparation of mediation analyses, we first determined the adequacy of the proposed 2-factor structure and tested longitudinal measurement invariance. Fit indices obtained from both the cross-sectional 2-factor CFA models and the longitudinal CFA model are presented in Table 3. Standardized factor loadings for indicators and correlation between latent factors are provided in the Supplementary Figure (Supplemental Digital Content 1, http://links.lww.com/CJP/A656). Fit indices indicated that the statistical models fitted the data well, and factor loadings for the indicators were all high (>0.62), supporting the use of latent factors. The estimated correlation between the latent factors, pain-related dysregulation and general emotion dysregulation, was moderate pretreatment ($r=0.30$) and large posttreatment ($r=0.67$).

Separate tests of longitudinal measurement invariance revealed that constraints on factor loadings and intercepts across measurement points did not significantly degrade model fit for the latent variables (pain-related dysregulation: $\Delta\chi^2_4=0.829$, $P=0.934$; general emotion dysregulation: $\Delta\chi^2_4=9.073$, $P=0.06$). This suggested that longitudinal measurement invariance was established, and we could proceed to test for mediation using the latent variables as mediators in a path model. Because the high correlation between latent factors at posttreatment could cause multicollinearity problems, we tested for mediation for each latent variable separately.

TABLE 3. Fit Indices for Estimated Confirmatory Factor Analysis Models for Evaluating Latent Variables Cross-sectionally and Longitudinally

Model	χ^2	*df*	CFI	SRMR	RMSEA	90% CI
Two-factor model pretreatment	6.03 (NS)	8	1.00	0.04	0.000	0.000, 0.09
Two-factor model posttreatment	7.77 (NS)	8	1.00	0.034	0.000	0.000, 0.12
Longitudinal 2-factor model	58.93 (NS)	50	0.99	0.079	0.039	0.000, 0.075

The longitudinal 2-factor model constrained factor loadings and intercepts to be equal across measurement points (scalar invariance).

CFI indicates Comparative Fit Index; CI, confidence interval; NS, nonsignificant; RMSEA, root mean square error of approximation; SRMR, standardized root mean residual.

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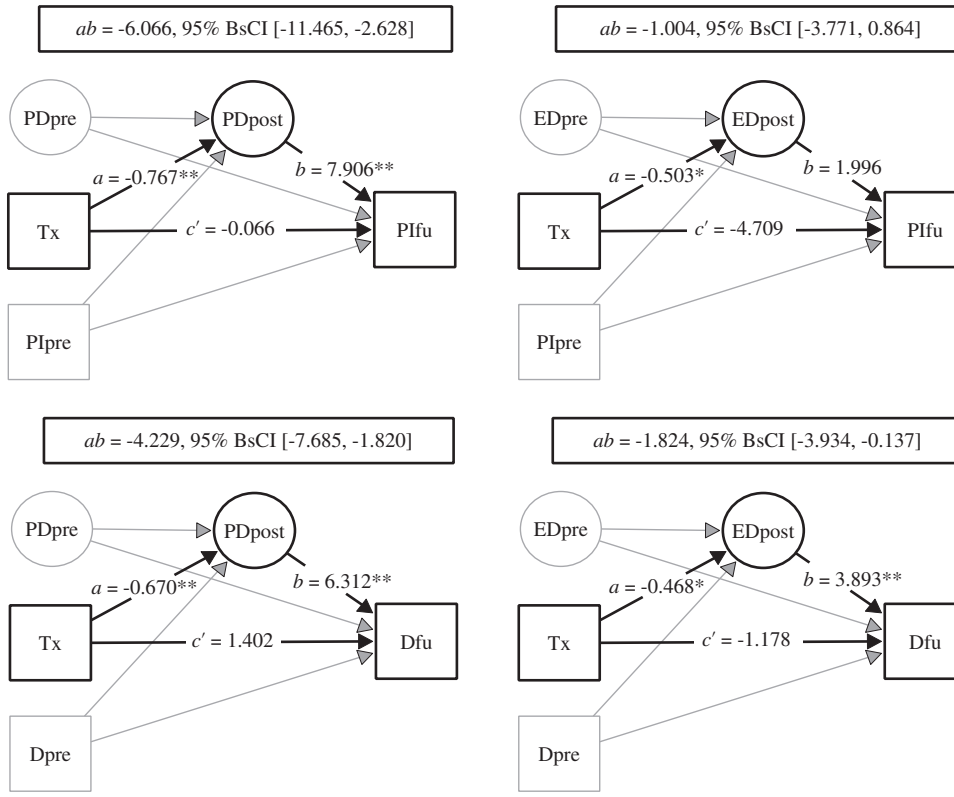

FIGURE 2. Estimated mediation models with robust maximum likelihood parameter estimates, β coefficients for the associations among treatment condition, latent mediators, and outcomes, along with tests of indirect effects (*ab*-product with 95% asymmetric bootstrap confidence intervals). Observed indicators for latent variables (circles) and residual covariance are not shown. BsCI indicates bootstrap confidence interval; Dfu, depressive symptoms at 9-month follow-up; Dpre, depressive symptoms pretreatment; EDpost, general emotion dysregulation posttreatment; EDpre, general emotion dysregulation pretreatment; Hybrid, the hybrid treatment; iCBT, internet-delivered pain management treatment based on cognitive-behavioral principles; PDpost, pain-related dysregulation posttreatment; PDpre, pain-related dysregulation pretreatment; PIfu, pain interference at 9-month follow-up; PIpre, pain interference pretreatment; Tx, binary treatment variable (1 = Hybrid, 0 = iCBT). *$P < 0.05$, **$P < 0.01$.

Mediation

Figure 2 shows the results from the estimated mediation models. There was a statistically significant effect of treatment condition on posttreatment pain-related dysregulation and general emotion dysregulation (covarying pretreatment scores on the mediator and outcome). This indicates that the hybrid treatment, on average, reduced pain-related dysregulation and general emotion dysregulation relative to iCBT (*a*-path). There were also statistically significant effects of pain-related dysregulation (*b*-path) on depressive symptoms and pain interference at the 9-month follow-up (primary endpoint), and for general emotion dysregulation (*b*-path) on depressive symptoms, but not on pain interference at the 9-month follow-up (primary endpoint). This indicates that larger treatment effects on pain-related dysregulation posttreatment were associated with reduced scores on pain interference and depressive symptoms at follow-up, and larger treatment effects on general emotion dysregulation were associated with reduced scores on depressive symptoms. Subsequently, pain-related dysregulation was a statistically significant mediator of the effect of the hybrid treatment on both depressive symptoms and pain interference, whereas general emotion dysregulation only mediated the hybrid treatment effect on depressive symptoms.

Baseline-moderated Mediation

As a final step, we tested whether the effect of the hybrid treatment was moderated by pretreatment levels on pain-related dysregulation and general emotion dysregulation (so-called baseline-moderated mediation). The model with depressive symptoms as outcome and pain-related dysregulation as mediator revealed a statistically significant interaction effect between treatment condition and pain-related dysregulation at pretreatment on the mediator, pain-related dysregulation, measured at posttreatment ($\beta = -0.479$, SE = 0.191, $z = 2.513$, $P = 0.012$). The moderated mediation effect, as evaluated by the product between this interaction term and the association between mediator and outcome, was also statistically significant ($\beta = -3.052$, 95% CI: −6.232, −0.621). Figure 3 visualizes the conditional treatment effect on the mediator, as a function of scores between 2 SDs above and below the grand mean of pain-related dysregulation measured at pretreatment. As can be seen, the difference between the hybrid treatment and iCBT increased as a function of higher scores on pain-related dysregulation at pretreatment. This means that higher scores on pain-related dysregulation at pretreatment were associated with a stronger positive effect of the hybrid treatment on the mediator pain-related dysregulation at posttreatment. For example, for participants scoring 1 SD above the mean at pretreatment (indicating more pain-related dysregulation), the effect was

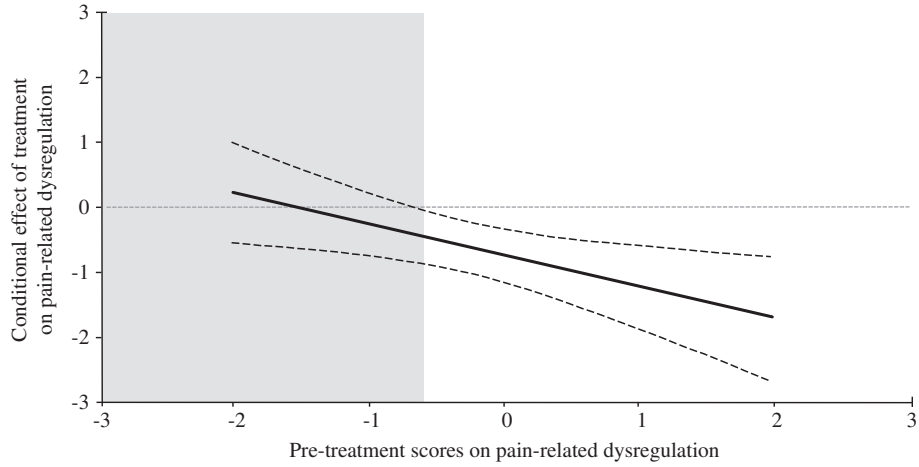

FIGURE 3. Conditional standardized treatment effect (*d*) on the latent mediator pain-related dysregulation at posttreatment as a function of pretreatment scores on the same latent variable. The solid line represents the point estimate and the dashed lines represent the lower and upper limits of bootstrapped 95% confidence intervals. The shaded gray area represents the region of nonsignificance.

statistically significant and of substantial magnitude, as indicated by a $d = 1.18$-point estimate of the standardized mean difference between treatment and control. However, for participants scoring ~0.7 SD below the mean at pretreatment (indicating less pain-related dysregulation), the difference between the hybrid treatment and iCBT was not statistically significant.

The same pattern of results was observed in the model examining moderated mediation with pain-related dysregulation as a mediator and pain interference as the outcome: the product term for testing moderated mediation was statistically significant ($\beta = -3.285$, 95% CI: −7.081, −0.298). This means that higher scores on pain-related dysregulation at pretreatment were associated with a stronger positive effect of the hybrid treatment on the mediator pain-related dysregulation at posttreatment, and the effects on pain-related dysregulation at posttreatment were subsequently correlated with pain interference at the 9-month follow-up.

The models with general emotion dysregulation as the mediator revealed no statistically significant interaction effects between treatment condition and general emotion dysregulation at pretreatment on general emotion dysregulation assessed at posttreatment ($P > 0.56$). Accordingly, the product for evaluating moderated mediation was not statistically significant in either of the models examining general emotion dysregulation as the mediator (pain interference model: $\beta = -0.295$, 95% CI: −2.389, 1.828; depressive symptoms model: $\beta = -0.621$ 95% CI: −2.982, 2.241). Thus, in contrast to pain-related dysregulation, the mediated effect of general emotional dysregulation was not dependent on pretreatment levels on general emotional dysregulation.

DISCUSSION

In this study, we tested the theoretical underpinnings of the hybrid treatment, using data from a previously published RCT comparing it to iCBT.[21] The results from our analysis were largely consistent with the theoretical model, supporting several of our hypotheses. First, and foremost, the hybrid treatment was more effective than iCBT in influencing both proposed mediators: pain-related dysregulation and general emotion dysregulation. Moreover, we found that both mediated effects on outcome. Specifically, improved pain-related dysregulation and general emotion dysregulation mediated effects on depressive symptoms, and improved pain-related dysregulation mediated effects on pain interference. Hence, we conclude that the previously reported effectiveness of this transdiagnostic exposure treatment for pain patients with concurrent emotional problems, at least partially, can be attributed to its effect on cognitive, emotional, and behavioral processes related to regulatory attempts to control and avoid pain, and general emotion dysregulation. These findings are in line with studies showing that improved catastrophizing and pain acceptance mediate effects on pain interference in similar cognitive-behavioral treatments focusing on exposure, values, and pain-coping.[26–28] In addition, these results add to the increasing empirical support for the theoretical assumption that pain interference, catastrophizing, inactivity, and lack of reinforcement are important factors in the development and maintenance of depression in the context of chronic pain.[8,68,69]

The other important hypothesis addressed in this study was that mediation effects would be moderated by patients' levels of pretreatment pain-related dysregulation and general emotion dysregulation. We found partial support for this idea. Individuals scoring higher on pain-related dysregulation showed a more pronounced change on the mediator relative to those scoring lower, thereby moderating the indirect effect of pain-related dysregulation on both depressive symptoms and pain interference. Not only does this finding provide further support for pain-related dysregulation as an important mediator of the hybrid treatment but it also gives prescriptive information that can guide further developments of tailored treatments and a direction for efforts to answer the clinical question: what works for whom? Specifically, it indicates that the hybrid treatment may be a superior treatment for pain patients with concurrent emotional problems who also have high levels of pain-related dysregulation and avoidance behaviors, a group of patients that was found to have suboptimal treatment results with standard exposure treatment.[4]

Contrary to our hypothesis, however, we found that mediation was not dependent on patients' pretreatment level of general emotion dysregulation. This may indicate that,

although change in depressive symptoms is mediated by improved emotion regulation, this process might be important irrespective of initial emotion-regulation problem levels. This result is in line with a recent review by Sloan et al,[14] noting that emotion dysregulation is an important process in several cognitive-behavioral treatments for patients with psychiatric disorders. However, the lack of moderated mediation could be a result of sample selection. As only patients with emotional problems were included, and as emotion dysregulation and depressive symptoms are closely connected, this may have restricted the variance in emotion dysregulation problems and thus influenced the results.

In our analyses, we chose to condense a total of 6 potential mediators under the umbrella of 2 latent variables that we labeled "pain-related dysregulation" and "general emotion dysregulation." With this, we aimed to capture, on the one hand, pain-specific cognitive, emotional, and behavioral processes and, on the other, general emotion-regulation skills. Although, arguably, nuances in psychological processes and specificity of constructs may be compromised, we did so for specific reasons. First, the 3 constructs and measures underlying each respective latent variable are conceptually interrelated and can as such represent 2 relevant and theoretically distinct higher order factors: 1 related to symptom pain-specific coping and the 1 related to general emotion-regulation abilities. By condensing constructs, we wanted to acknowledge the growing concern that seemingly different psychological constructs in fact capture the same behavioral patterns.[70,71] In addition, clustering process measures in 2 latent variables was determined to be statistically advantageous and we could confirm that the models fitted the data well, both cross-sectionally and longitudinally. Still, these choices do not imply that no other valid options are available, and several other models may have fitted the data well. For example, a high correlation was observed between the 2 latent factors at postassessment that suggests the existence of a higher order factor (eg, general dysfunctional coping strategies) that could potentially account for an additional amount of the shared variance among the latent factors. Although we deemed that the 2 latent constructs represented relevant and distinct theoretical entities, this finding reinforces the issue of the considerable empirical overlap in psychological constructs and that modeling each variable as a separate mediator would be more problematic.

The results of this study should be interpreted considering its limitations. Even though randomization strengthens claims of effects of treatment on mediators and outcomes, further research is warranted to confirm causality in terms of indirect effects in the association between mediators and outcomes (*b*-path). On a related note, although the time lag between mediators (assessed at posttreatment) and outcomes (assessed at follow-up) strengthens the findings from our mediation models, we cannot be certain that effects on mediators precede effects on outcomes as most of the improvements in outcomes had already occurred at postassessment.[34] Future studies may include repeated measures to establish the temporal relation between mediators and outcomes so that changes in mediators more reliably precede, and can be concluded to contribute to, subsequent changes in outcome. We also acknowledge that the sample size is in the lower range for the applied statistical models.[72] This may have influenced model fit statistics and stability of parameter estimates. However, we believe that the benefits of these models surpass their disadvantage. As detailed in the introduction and method section, this approach allowed us to overcome problems associated with measurement error, factorial noninvariance, type-1 error rates, and missing data. Indeed, the use of latent factors in SEM may be especially important in mediation analysis due to these reasons.[31,32] It is also important to remember that all variables rely on self-report instruments, which, although theoretically distinct, are empirically related to a natural overlap. For instance, catastrophizing might be regarded as a potential mediator, but it may also be one aspect of the outcome, for example a symptom of depression. Nevertheless, our study is based on a theoretical distinction between process variables and outcomes, and the findings should be interpreted keeping that in mind.

In conclusion, this study adds to the theoretical understanding of, and advancements in, developing treatments for chronic pain patients with concurrent emotional problems. One important finding is that using a hybrid treatment approach that centers on improving patients' emotion-regulation skills, combined with broad exposure in vivo, successfully influenced pain-related dysregulation and general emotion dysregulation and resulted in better treatment outcomes. Thus, addressing these processes appears central for pain patients with chronic pain and comorbid emotional problems. Another important finding points to a need to consider patients' baseline levels of pain-related dysregulation, such as catastrophizing, fear-avoidance, and nonacceptance of pain, to match treatment and optimize treatment results. Although further studies are warranted on the issue of moderation of outcomes, the results imply that the hybrid might have most added values for this subgroup of individuals.

Our study has tapped into the complex, but essential question of what works for whom, how, and in what context. This is a first step in discovering how we best target transdiagnostic processes to enhance treatment outcomes.

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