Clinical Pain Research

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Prolonged exposure for pain and comorbid PTSD: a single-case experimental study of a treatment supplement to multiprofessional pain rehabilitation

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Abstract

Objectives: It is unclear how to address PTSD in the context of chronic pain management. Here we examine the potential benefits of an addition of prolonged exposure (PE) therapy for PTSD for adults attending multidisciplinary CBT for chronic pain.

Methods: Four adults seeking treatment for chronic pain from a specialized pain rehabilitation service were offered PE for PTSD using a replicated, randomized, single-case experimental phase design, prior to commencing a 5-week multidisciplinary CBT program for chronic pain. Pre-, post-, follow-up, and daily measures allowed examination of PTSD and pain outcomes, potential mediators, and the trajectory of these outcomes and potential mediators during the subsequent pain-focused CBT program.

Results: Visual inspection of the daily data demonstrated changes in all outcome variables and potential mediators during the PE phase. Changes came at different times and at different rates for the four participants, highlighting the individual nature of putative change mechanisms. Consistent with expectation, PE produced reliable change in the severity of PTSD symptoms and trauma-related beliefs for all four participants, either by the end of the PE phase or the PE follow-up, with these gains maintained by the end of the 5-week pain-focused CBT program. However, few reductions in pain intensity or pain interference were seen either during the PE phase or after.

Conclusions: Although “disorder specific” approaches have dominated the conceptualising, study, and treatment of conditions like PTSD and chronic pain, such approaches may not be optimal. It may be better instead to approach cases in an individual and process-focused fashion.

Ethical committee number: 2013/381.

Keywords: CBT; chronic pain; mediators; prolonged exposure; PTSD.

Introduction

In comparison to the general population, individuals seeking treatment for chronic pain are at significantly increased risk of comorbid mental health conditions [1]. Among the most common comorbid conditions is Post-traumatic Stress Disorder (PTSD), where the self-reported prevalence is estimated at 20.5%, nearly four times higher than the general population [2, 3]. PTSD occurs in response to a traumatic event and involves symptoms from four symptom clusters: intrusion (persistent re-experiencing of the trauma), avoidance of traumatic reminders, negative alterations in cognitions and mood, and negative alterations in arousal and reactivity [4]. Similar experiences and psychological processes involved in PTSD and chronic pain may create a situation where they mutually exacerbate or maintain each other [3, 5–8].

The most widely disseminated evidence-based treatment for chronic pain is cognitive behavioral therapy (CBT) [9]. However, CBT for chronic pain typically does not include the core (active) components in all evidence-based treatments for PTSD, namely a combination of therapist and
patient-led exposure to traumatic reminders [10]. A recent study from our research group found that individuals with chronic pain and self-reported PTSD experience significant reductions in pain, mood, and anxiety symptoms, but no changes in PTSD in response to a standard, multidisciplinary, CBT program for chronic pain [11]. In fact, while pain-focused CBT programs consistently yield moderate effects on comorbid mood and anxiety symptoms [9], the addition of PTSD-focused interventions may be required to improve outcomes for both the PTSD and chronic pain symptoms [7, 11, 12].

Currently there is a gap in the literature with respect to whether adding evidence-based interventions for PTSD, such as prolonged exposure (PE) [13], to standard pain-focused CBT programs will yield improvements in both PTSD and pain. In addition, pain researchers have called for a greater use of designs that permit the researcher to identify treatment processes that may underpin (mediate) changes in symptoms and overall functioning [9, 14]. Over the past 20 years, mediation analyses have been carried out primarily in the context of Randomized Controlled Trials (RCTs). The least rigorous designs from the standpoint of mediation analyses, will involve assessments of (usually) a single mediator and multiple outcome measures at pre-randomization, post-treatment, and 1–2 follow-ups. Methodologically stronger RCTs may include monthly/weekly measures of both 1–2 mediators and a single outcome measure during the treatment phase. There is widespread agreement that such designs measure too few mediators and outcome variables, and lack the number of measurement points necessary to estimate whether change in the mediator(s) precedes changes in the outcome variables, an important assumption of mediation [15]. Thus, researchers have begun to call for increased use of N-of-1 or single case experimental designs that include weekly or daily assessments of multiple mediators and outcomes during the baseline, treatment, and follow-up phases [14]. Such designs can accommodate interaction of multiple factors and within-person variations [14, 16] and are therefore particularly suited to identifying potential therapeutic change processes (mediators). While the N-of-1 design is recognized as having advantages over RCTs in relation to mediation analyses, there is as yet no consensus in the literature how best (statistically) to estimate mediators in single case designs [17].

The aim of this study was to apply N-of-1 methods to examine outcomes and potential mediators around the addition of exposure therapy for PTSD in the context of CBT for chronic pain. Four adults seeking treatment for chronic pain from a specialized pain rehabilitation service were offered PE for PTSD using a replicated, randomized, single-case experimental phase design, prior to commencing a 5-week multidisciplinary CBT program for chronic pain. We hypothesized that PE would decrease PTSD symptoms compared to the no treatment phase, and this decline in would be associated with improvements in un-targeted symptoms of pain intensity and interference during the PTSD-focused treatment. In an exploratory fashion, we undertook analyses with several potential mediators, with special attention being paid to the time dimension, i.e. to assess whether changes in the mediator occurred before changes in outcomes. Based on theory and earlier research on mediators of the relationship between PTSD and chronic pain, we assessed pain-related acceptance, anxiety and depression, and trauma-related beliefs as well as PTSD and pain outcomes on a daily basis throughout the baseline and treatment phases [13, 18–21]. We also examined the trajectory of residual PTSD symptoms, pain symptoms, and the proposed mediators through the subsequent pain-focused CBT program.

Methods

Study design

Four adults with comorbid PTSD and chronic pain who consecutively attended a specialized pain program based on CBT were sequentially randomized to baseline phases of varying lengths (6–17 days), using a random number generator, followed by seven weeks of PE for PTSD (treatment phase) in a replicated, single-case experimental phase design. The moment of the intervention start point was randomly determined. Baseline lengths were chosen to balance the need for establishing the stability of PTSD symptoms prior to commencing PE and the participant’s desire to get started with the PTSD treatment so they could move on to the CBT pain program. Approximately 7–9 weeks after completing the PE phase, the four participants began the standard five-week multidisciplinary CBT pain program to which they were originally referred. Patients completed a daily diary (described below) of outcomes and potential mediators throughout the baseline and PE phases, resulting in 64 daily measurements per participant. The participants also completed standardized self-report measures, described below, at baseline, post-PE, at the end of the 7–9 week wait for the next pain-focused CBT program to begin (follow-up from PE), and after completing the 5-week pain-focused CBT program (post pain CBT).

Participants

Participants were four adults with comorbid PTSD and chronic pain who were consecutively admitted for treatment at the Pain Rehabilitation Unit at Skåne University Hospital between July 2016 and September 2017. The unit is a government supported, regional specialist center focused on assessment and treatment of chronic pain and related disability. Admission criteria for the pain program are as follows: 1) between 18 and 67 years of age; 2) fluent in Swedish; 3) the
presence (for a minimum of 3 months) of persistent symptoms of chronic pain that significantly interfere with everyday life; 4) having been medically examined and received any medical treatment for pain if indicated; 5) the ability to function in a group setting and to take part in a 5-week program, consisting of 5–7 h per day of treatment for 2–4 days per week; 6) the ability to take an active part in the rehabilitation process and regain functioning in different areas of life; and 7) having goals that could be satisfied by the program. Patients are excluded from the program based on the following criteria: 1) presence of psychiatric disorders or symptoms that require more immediate treatment than pain, including suicidal ideation and symptoms of self-harm; 2) active abuse of analgesic medications, alcohol, or other drugs; 3) presence of medical conditions, or social or economic difficulties, expected to interfere with treatment; and 4) having already completed a similar treatment for pain. Patients treated at the unit suffer from one or more pain-related conditions including musculoskeletal pain conditions and fibromyalgia, but excluding headache and cancer-related pain. In addition to these inclusion and exclusion criteria, the participants had to: 1) meet the DSM-IV-TR criteria for PTSD [22]; 2) want treatment for their PTSD; 3) agree to a course of PE before (and therefore delaying their entry into) the 5-week chronic pain treatment program; and 4) refraining from any other PTSD treatment during the baseline and PE phase of this study. Table 1 provides an overview of the participant’s characteristics. Not reported in Table 1: participant 3 had comorbid symptoms of depression and generalized anxiety disorder, while participant 4 had comorbid symptoms of depression, generalized anxiety disorder, and panic disorder.

Procedure and study overview

As referrals to the specialist chronic pain unit, the four participants were initially assessed by a rehabilitation team consisting of a physician, physiotherapist, and a psychologist. This included physical examination, review of medical records, and an interview to evaluate the participant’s suitability for admission to the pain program. A separate interview based on the Mini International Neuropsychiatric Interview 5.0 (MINI [23]) was conducted by a clinical psychologist working in the pain unit, when patients scored above a clinical cutoff for PTSD on a self-report measure of PTSD (described below) and were considered to be at risk for having PTSD by the initial assessment team. Prior to study inclusion, the participants were provided verbal and written information about the study, and then gave written informed consent to participate. The four participants completed a baseline phase (A), the PE phase (B), and then waited several weeks before beginning the 5-week pain-focused CBT program. This study was approved by the regional ethics board at Lund University (Dnr: 2013/381).

Treatment

PE involved 10 individual treatment sessions lasting up to 90 min in length, occurring 1–2 times per week over 7 weeks. Treatment followed the standard PE manual published by Foa, Hembree, and Rothbaum [13]. Briefly, PE involves: 1) psychoeducation regarding common reactions to trauma and the treatment rationale; 2) breathing retraining as a form of relaxation; 3) approaching trauma-related but objectively safe activities, situations, or places that are otherwise avoided (in vivo exposure); and 4) imaginal exposure or repeated recounting of the traumatic memory out loud and in great detail. The therapist assists the patient in creating a fear and avoidance hierarchy that is used to guide progressively more difficult in vivo exposures as homework assignments. Imaginal exposures are audio recorded and the patient is asked to listen to these as homework. In this study, PE was provided by a licensed, clinical psychologist who worked in the chronic pain unit, had training in PE, and experience using PE to treat individuals with comorbid PTSD and chronic pain. Adherence to the protocol was maintained via regular supervision. No objective checks of treatment adherence and therapist competence were conducted during the PTSD treatment.

Following the PE phase, all participants took part in the standard, 5-week, outpatient, group-based, multi-disciplinary, pain-focused CBT program. The program was delivered by three multi-disciplinary teams consisting of a physician, social worker, occupational therapist, physiotherapist, and clinical psychologist. The groups included approximately 10 participants, each working according to an individual treatment plan formulated with team members during the first week of the group. Treatment consistency/adherence during the pain-focused program was maintained through weekly team meetings and co-leading of some group sessions by more than one team member. The program consisted of 18 active treatment days over five weeks followed by a two-month ‘homework’ phase wherein participants work on their individual goals at home with support from the treatment team. This was followed by two additional days of group treatment at the unit in which progress towards the patient’s individualized treatment goals, any ongoing difficulties, and future goals were addressed.

Table 1: Participant characteristics.

| Participant | Demographics | Work situation | Pain duration | Pain diagnosis | Traumatic experience |
|-------------|---------------|----------------|---------------|----------------|---------------------|
| 1           | Woman, 36 years, single, 1 child, born in Sweden | In full-time work | 11 months | Cervicobrachial syndrome | Motor vehicle accident, emotional abuse |
| 2           | Man, 27 years, single, no children, born in Sweden | In full-time work | 55 months | Cervicocranial syndrome | Motor vehicle accident |
| 3           | Woman, 43 years, married, 3 children, born outside of Sweden | On full sick leave | 14 months | Cervicocranial syndrome | Sexual assault, repeated physical and sexual threats, motor vehicle accident |
| 4           | Woman, 40 years, living with partner, 1 child, born outside of Sweden | On full sick leave | 30 months | Fibromyalgia | Repeated physical and sexual abuse, sexual assault in her immediate social network |
Outcome measures

Participants were assessed using a mixture of standardized self-report questionnaires and a 13-item daily diary designed for the purposes of this study. The questionnaires were administered at the start of the baseline, after PE, at the end of the 7–9 week wait for the next pain-focused CBT program to begin (follow-up from PE), and after the pain-focused CBT program (post pain CBT). The daily diary was completed during the baseline and PE phases. The primary outcome was the severity of self-reported PTSD. Secondary outcomes included pain intensity and pain interference. The putative mediators were pain-related acceptance, anxiety and depression, and trauma-related beliefs, also measured on a daily basis during the baseline and PE phases. In addition, diagnostic status (PTSD) was assessed.

PTSD diagnostic status

The presence of a DSM-IV-TR diagnosis of PTSD (and comorbid psychiatric disorders) was established with the Mini International Neuropsychiatric Interview 6.0 (MINI) [23] carried out by a licensed clinical psychologist with experience of the MINI and PTSD. The interview was conducted at the start of the baseline, after PE, at follow-up from PE, and after the pain-focused CBT program. Diagnostic remission was defined as no longer meeting the DSM-IV-TR criteria for a PTSD diagnosis.

PTSD symptom severity

PTSD symptom severity was measured with the 49-item, self-report Posttraumatic Diagnostic Scale (PDS) [24]. This version of the PDS was designed to assess the DSM-IV-TR criteria for PTSD [22]. The later, DSM-5 compliant version of the PDS was not available in a Swedish-language validated version at the time of this study. The PDS is comprised of a trauma checklist to establish whether the person meets the A criterion (traumatic exposure), items assessing the frequency of re-experiencing, avoidance, and arousal symptoms over the past month (in relation to a specific trauma), and items assessing the impact of the current PTSD symptoms on different aspects of everyday life. The 17 symptom items are used to calculate a total severity score, ranging from 0 to 51 with severity ranges defined as follows: 1–10=mild; 11–20=moderate; 21–35=moderate to severe; ≥36=severe. The original scale and the Swedish version used in this study have acceptable psychometric properties for the total scale [18, 26].

Subjective distress during in vivo exposures

Following the PE protocol, participants were instructed in the use of a Subjective Units of Distress Scale (SUDS) with anchor points of 0 (no distress) and 100 (extreme distress). Participants were then asked to use this scale to rate their degree of distress in relation to stimuli or situations associated with the trauma or their PTSD symptoms, and that were avoided or endured with distress. These trauma-related stimuli were then listed in written format in a hierarchy of increasing distress/avoidance. A mean SUDS score was calculated for all stimuli/situations on the hierarchy at the start of the baseline phase, after the PE phase, and at the follow-up several weeks later. The daily diary did not include SUDS ratings.

Trauma-related beliefs

Beliefs that develop during or in the aftermath of a trauma, and that have been found to be associated with the severity and persistence of PTSD symptoms, were assessed with the 36-item Posttraumatic Cognitions Inventory (PTCI) [18]. The items assess negative cognitions about the self (21 items), the world (7 items), and self-blame (5 items). Three items are experimental and not included in the scoring. Each item is rated on a seven-point scale (1=totally disagree; 7=totally agree). Only the total score (33 items) was used in this study; higher scores indicating greater endorsement of negative posttraumatic cognitions. The English and Swedish versions of the PTCI have been shown to have acceptable psychometric properties for the total scale [18, 26].

Pain intensity

Pain intensity over the past week (0=no pain; 10=worst possible pain) was assessed using the single-item Numerical Rating Scale (NRS). The NRS is widely used in pain research and has been found to be a valid measure of pain intensity and sensitive to changes in pain in different contexts [27, 28].

Pain interference

Pain interference was measured with the 11-item subscale from the Multidimensional Pain Inventory Version 2 (MPI) [29]. The items assess interference from pain in everyday life, including family and marital functioning, work and work-related activities, and social and leisure activities. Respondents rate impairment in each area on a seven-point scale (0=never; 6=very often) and an overall mean is computed for the 11 items. The psychometric properties of the MPI are well established [30]. The Swedish version used in this study has been shown to be sensitive to the effects of treatment for chronic pain and to positively correlate with other measures of pain-related functioning [31].

Anxiety and depression

Anxiety and depression were assessed using the 14-item Hospital Anxiety and Depression Scale (HADS) [32]. Respondents use a 0–3 scale to rate the frequency/severity (past week) of depression (seven items) and anxiety symptoms (seven items). Separate depression and anxiety subscale scores are calculated from the respective items with both subscales ranging from 0 to 21; scores ≥8 on either subscale evidence clinical caseness. The English and Swedish versions have satisfactory psychometric properties for the total, anxiety, and depression scales [32, 33].

Pain-related acceptance

Pain-related acceptance was assessed using the 8-item version of the Chronic Pain Acceptance Questionnaire (CPAQ-8) [34]. The items reflect two components referred to as activity engagement and pain willingness. Each item is rated on a seven-point scale (0=never true; 6=always true) and summed to produce a total score; higher scores indicate greater acceptance of pain. The English and Swedish
versions have been found to possess satisfactory psychometric properties [34, 35].

**Daily (diary) measures**

A 13-item daily diary of the mediators and outcomes was designed for the purposes of this study. The first four items come from the PDS and measure PTSD symptom severity: “Having upsetting thoughts or images about the traumatic event that came into your head when you didn’t want them to” (re-experiencing); “Trying to avoid activities, people, or places that remind you of the traumatic event” (avoidance); “Feeling distant or cut off from people around you” (numbing); and “Having trouble concentrating” (for example drifting in and out of conversations), losing track of a story on television, forgetting what you read” (hyper-arousal). These items were chosen to represent the four-factor solution for the PDS, corresponding to the four PTSD symptom clusters in DSM-5 in a previous study by King et al. [36]. The next three items come from the PTMJ and measure trauma-related beliefs: “I will never be able to feel normal emotions again” (negative cognitions about self); “The world is a dangerous place” (negative cognitions about the world); “The event happened because of the way I acted” (self-blame for the trauma). The next two items come from the HADS and measure levels of anxiety and depression: “I look forward with enjoyment to things” (depression scale); “Worrying thoughts go through my mind” (anxiety scale). The next two items come from the CPAQ and measure pain-related acceptance: “Although things have changed, I am living a normal life despite my chronic pain” (activity engagement); “Before I can make any serious plans, I have to get some control over my pain” (pain willingness). The next item comes from the NRS and is a single-item question about pain intensity (Average pain intensity). The final item comes from the pain interference scale from the MPI: “Affects ability to participate in social activities”. These items were chosen based on previous studies that have shown them to explain the most unique variance in their respective factors [18, 25, 30, 33, 34]. The original scoring system for the items was modified to harmonize them in the diary so that each item was rated using a 0 (totally disagree; never) to 10 (totally agree; always) scale for the previous 24 h. Participants were instructed to complete the paper diary at the same time each day throughout the duration of the baseline and PE treatment phases of the study and it was handed in weekly.

**Statistical analyses**

**Daily measures:** Mediators are treatment processes through which a treatment might reach its effects [37]. Mediation analyses explore the underlying mechanism by which an independent variable (treatment) influences a dependent variable (PTSD symptom severity, pain intensity, pain interference) via a mediating variable (pain-related acceptance, anxiety/depression, and trauma-related beliefs). Change in the mediator should temporally precede the change in outcome and we focus on the time dimension in these analyses. Graphical inspection and randomization tests for single-case experimental phase designs were conducted to analyze the data from the daily diaries. In addition, we investigated variability using range lines, the mean for each condition, mean level change, and trend using the split middle technique for the primary outcome PTSD symptom severity.

Randomization tests are based on random determination of the moments of phase change, for example the change between the baseline (A) and active treatment phases (B). More details on randomization tests can be found in Onghena and Edgington [38]. By design, the duration of the baseline phases was unequal for all participants as they were randomized to baselines with a predetermined length of 6–17 days duration. A directional test statistic (difference between phase means) was used to test the treatment effects in this randomized experiment. The null hypothesis of a randomization test is that the observed scores are independent of the phase in which they were observed, indicating no effect of the treatment [38]. We expected a reduction in the summed (total) scores for the items measuring the primary outcome (PTSD symptom severity), as well as on items measuring the secondary outcomes (pain intensity and interference), and the putative mediators (pain-related acceptance, anxiety/depression, and trauma-related beliefs) during the treatment phase (B) as compared to the baseline phase (A). The scoring of the CPAQ and HADS items were adapted to be in line with the items from the other measures such that a reduction in scores over time could be interpreted as an improvement. Hence, we used the difference between the phase means (mean of Phase A – mean of Phase B) as our test statistic for all measures. Analyses of delayed effect were also conducted since group-level data suggest that symptom reduction is often delayed until the fourth session in PE (which corresponds to the third week of treatment in this study) [39]. The tests were repeated to determine whether a delayed effect could be detected, following a similar analytical approach described by de Jong et al. [40] in a N-of-1 study examining treatment mechanisms in CBT for chronic pain. Specifically, we carried out separate test sequences using the raw data from all observations by assuming increasing delays of one day (one observation or one lag) at a time until the minimal empirical p-value (p < 0.05) was reached with one observation per phase. This test allows for detection of effects at differing delays for each person and each outcome. In other words, a test statistic that takes into account progressively increasing delays, for each case and variable, was computed repeatedly until the minimal empirical p-values was first reached. When it was reached this was regarded as support for a delayed effect. The Shiny SCDA computer software provided by the University of Leuven, Belgium was used for the analyses [41].

**Non-daily measures**

Reliable change between the baseline, post PE, follow-up from PE, and post CBT pain program were investigated based on the criteria by Jacobson and Truax [42]. Reliable change detects the amount of change needed on a measure to exceed change that could be attributed to measurement error and is one aspect of clinical significance. A reliable change index was calculated and scores <1.96 were considered to be reliable for all measures except for CPAQ where a score ≥1.96 was expected. For the SUDS during in vivo exposures, 50% improvement from baseline was considered to be a reliable change.

**Results**

**Daily symptom measures during baseline and PE treatment phases**

Figure 1 presents a graphical representation of the daily diary (total) scores for the items assessing PTSD severity
including trend lines using the split middle technique. Visual inspection revealed trend changes for each participant during the active treatment phase, suggesting that PE was successful in reducing PTSD severity (primary outcome). For participants 1, 2, and 4 the declines were similarly steep although the end state PTSD score for participant 4 was not as low as the other two. Participant 3 had a slow rate of decline in symptoms with the end state PTSD score being relatively high. For participant 1, the mean for the baseline phase was 7.07 and scores varied between 5 and 9. The mean for the treatment phase was 5.35 (range=3–10), resulting in a mean level change of 1.72. For participant 2, the mean for the baseline phase was 8.86 (range=8–10). The mean for the treatment phase was 5.18 (range=2–10), resulting in a mean level change of 3.68. For participant 3, the mean for the baseline phase was 9.62 (range=9–10). The mean for the treatment phase was 8.61 (range=8–10), resulting in a mean level change of 1.01. For participant 4, the mean for the baseline phase was 8.91 (range=8–9). The mean for the treatment phase was 7.00 (range=5–10), resulting in a mean level change of 1.91. Taken together, all mean values were reduced from the baseline phase to the treatment phase indicating a positive treatment effect.

Figure 2 presents the graphical representations for the secondary outcomes (pain intensity and interference) and putative mediators (pain-related acceptance, anxiety/depression, and trauma-related beliefs). Visual inspection revealed trend changes for the participants during the active treatment phase, suggesting that PE was successful in reducing pain intensity and interference, depression/anxiety, the strength of (negative) trauma-related beliefs, and increasing acceptance of pain. Taken together, the largest changes were observed for the severity of PTSD symptoms and trauma-related beliefs.

Participant 1 demonstrated variability in her response overall, both in the baseline and the treatment phase. For her, the largest changes were seen on PTSD severity and trauma-related beliefs. Participant 2 showed large improvements when considering all the measures together. Participant 2 had a relatively fast response with changes already after the first treatment sessions. He had distinct changes for all measures, with the largest changes seen for PTSD severity, trauma-related beliefs, and pain interference. Participant 3 had a gradual response with small changes throughout treatment for pain interference, pain-related acceptance, anxiety/depression, and trauma-related beliefs. The largest change was seen for PTSD severity, while her pain intensity remained high throughout treatment. Participant 4 had a clear response on PTSD severity, trauma-related beliefs, and pain interference. The changes in the first two variables came about rather quickly, while the changes for pain interference were most noticeable at the end of

![Figure 1: Daily measures of PTSD symptom severity including trend lines using the split middle technique.](image-url)
treatment. Her pain intensity remained high throughout treatment. Before taking the possibility of delayed treatment effects into account, we note that most of the p values were non-significant for the individual participants in the initial analyses at the smallest possible p-value level.

Table 2 shows the effect delay in days during the treatment phase. This is the point in days following the initiation of treatment at which the empirical minimum p-value for the randomization test was first obtained using the raw data on all observations (64 days) with one observation per phase. This is calculated for each participant on measures of PTSD severity, pain intensity, pain interference, pain-related acceptance, anxiety/depression, and trauma-related beliefs. The results support the conclusions drawn during the visual inspection. The range in days for significant change for the severity of PTSD and anxiety/depression symptoms was similar (range=11–35 vs. 17–35 days, respectively). Significant reductions in pain intensity usually occurred later in the treatment phase (range=29–39 days). The range for the other measures were highly variable (pain-related acceptance range=18–48 days; trauma-related beliefs range=18–49 days; pain interference range=10–48 days).

Looking at the individual participant’s results, significant changes in PTSD severity occurred before changes in pain intensity in participants 2, 3 and 4 (see Table 2), while significant change in PTSD and pain intensity happened simultaneously for participant 1. The significant changes in anxiety/depression happened at the same time or marginally after the changes in PTSD severity. The changes on trauma-related beliefs came after the changes of the PTSD severity and the anxiety/depression symptoms for all participants with significant changes on these measures. The changes in pain-related acceptance and pain interference happened roughly at the same and before the changes on pain-related acceptance and pain interference.

Non-daily measures

Table 3 presents the means for each participant on the full-length, standardized measures of PTSD severity, pain intensity, pain interference, pain-related acceptance, anxiety, depression, and trauma-related beliefs at the start of baseline, after the PE phase, after the PE follow-up, and after completion of the CBT pain program. Table 3 also presents the average SUDS score for the in vivo exposures to traumatic reminders at the start of baseline, end of PE, and at the end of the PE follow-up period. Based on Jacobson and Truax criteria [42], participants 1, 2, and 3 demonstrated reliable changes, relative to baseline, on the measure of PTSD at the end of the PE phase, and these gains (relative to
baseline) were maintained at the end of the PE follow-up and the end of the CBT pain program. Participant 4 only experienced a reliable change in PTSD symptoms by the end of the PE follow-up, but with this gain maintained at the end of the CBT pain program. By the end of the PE phase, average SUDS scores relative to baseline, reliably changed for participants 1 and 2. However, by the end of the PE follow-up, all four participants had achieved reliable change on this outcome. SUDS ratings were not assessed again after the CBT pain program. The pattern for trauma-related beliefs was similar to that for PTSD, i.e. all four participants had achieved reliable change on this measure relative to baseline by either the end of the PE phase (participants 1, 2 and 3) or by the end of the PE follow-up (participant 4). Again, these gains were maintained at the end of the CBT pain program.

The pattern for anxiety was similar to that for the PTSD-related outcomes. By way of contrast, only one of the four participants experienced reliable change in their depression scores relative to baseline at the further assessments. With respect to pain intensity and pain interference, only participant 2 experienced a reliable change by the end of the PE phase, with these gains maintained at the two further assessments for pain intensity and at one further assessment for pain interference. The pattern for pain-related acceptance was quite mixed; reliable change on this measure was observed at each post-baseline assessment only for participant 2.

## PTSD diagnostic status

All four participants met the DSM-IV-TR PTSD criteria at the start of the baseline phase. At the end of the PE phase, participants 1 and 2 no longer met the PTSD criteria and participants 3 and 4 did. However, at the time of the post-CBT pain program assessment, participants 3 and 4 also no longer met diagnostic criteria for PTSD. Again, diagnostic status at all assessments was based on structured interviews employing the MINI.

## Discussion

The aim of this study was to address a gap in the literature with respect to whether adding an evidence-based intervention for PTSD to standard pain-focused CBT programs would yield improvements in both PTSD and pain outcomes. In this study, four individuals seeking treatment for chronic pain underwent PE for PTSD in a replicated, randomized, single-case experimental phase design, prior to commencing CBT for chronic pain. We hypothesized that PE would decrease PTSD symptoms compared to the no treatment phase, and this decrease would be associated with improvements in un-targeted symptoms of pain during the PTSD-focused treatment. Even though the offered PTSD treatment had an effect on a broad range of outcome

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Table 3: Scores of PTSD symptoms, pain intensity, pain interference, pain-related acceptance, anxiety, depression, trauma-related beliefs, and SUDS during the in vivo exposure situations at baseline, post PE, follow-up from PE, and post pain CBT for the four participants.

| Measure                        | Baseline | POST PE | FUP PE | POST pain CBT |
|-------------------------------|----------|---------|--------|---------------|
| PTSD severity                 |          |         |        |               |
| Participant 1                 | 36.00    | 13.00   | 24.00  | 21.00          |
| Participant 2                 | 44.00    | 26.00   | 22.00  | 15.00          |
| Participant 3                 | 48.00    | 39.00   | 33.00  | 28.00          |
| Participant 4                 | 41.00    | 40.00   | 32.00  | 24.00          |
| Pain intensity                |          |         |        |               |
| Participant 1                 | 5.00     | 4.00    | 9.00   | 10.00          |
| Participant 2                 | 8.00     | 5.00    | 5.00   | 5.00           |
| Participant 3                 | 9.00     | 9.00    | 7.00   | 8.00           |
| Participant 4                 | 8.00     | 9.00    | 9.00   | 9.00           |
| Pain interference             |          |         |        |               |
| Participant 1                 | 2.64     | 2.64    | 2.64   | 2.00           |
| Participant 2                 | 5.82     | 3.91    | 3.91   | 4.36           |
| Participant 3                 | 5.64     | 5.27    | 4.36   | 5.00           |
| Participant 4                 | 5.27     | 5.36    | 4.36   | 4.36           |
| Pain acceptance               |          |         |        |               |
| Participant 1                 | 29.00    | 38.00   | 36.00  | 39.00          |
| Participant 2                 | 11.00    | 33.00   | 33.00  | 27.00          |
| Participant 3                 | 4.00     | 25.00   | 22.00  | 13.00          |
| Participant 4                 | 4.00     | 11.00   | 16.00  | 23.00          |
| Anxiety                       |          |         |        |               |
| Participant 1                 | 16.00    | 6.00    | 11.00  | 9.00           |
| Participant 2                 | 19.00    | 8.00    | 11.00  | 8.00           |
| Participant 3                 | 19.00    | 17.00   | 13.00  | 16.00          |
| Participant 4                 | 16.00    | 14.00   | 11.00  | 13.00          |
| Depression                    |          |         |        |               |
| Participant 1                 | 10.00    | 9.00    | 12.00  | 12.00          |
| Participant 2                 | 17.00    | 7.00    | 8.00   | 2.00           |
| Participant 3                 | 17.00    | 16.00   | 15.00  | 14.00          |
| Participant 4                 | 11.00    | 13.00   | 12.00  | 13.00          |
| Trauma-related beliefs        |          |         |        |               |
| Participant 1                 | 166.00   | 120.00  | 103.00 | 129.00         |
| Participant 2                 | 209.00   | 97.00   | 99.00  | 86.00          |
| Participant 3                 | 211.00   | 186.00  | 123.00 | 161.00         |
| Participant 4                 | 198.00   | 190.00  | 153.00 | 163.00         |
| SUDS during the in vivo exposures |        |         |        |               |
| Participant 1                 | 71.50    | 31.75   | 20.00  | 52.00          |
| Participant 2                 | 70.95    | 7.86    | 11.67  | 8.00           |
| Participant 3                 | 89.38    | 65.63   | 26.88  | 51.00          |
| Participant 4                 | 65.00    | 42.86   | 22.50  | 50.00          |

*Reliable change from baseline to post PE, follow-up from PE, and post pain CBT based on Reliable Change Index and 50% improved from baseline for the SUDS during the in vivo exposures.
measures using the daily ratings, it seems like the core interventions used (imaginal exposure and \textit{in vivo} exposure) were most effective in relation to PTSD severity and trauma-related beliefs and had more modest effects on pain-related functioning. A corresponding and clearer pattern is seen when examining the trajectory of any PTSD and pain symptoms through the PTSD treatment and the subsequent pain-focused CBT program. Consistent with expectation, PE produced reliable change in the severity of PTSD symptoms and trauma-related beliefs for all four individuals. When explained to them, the four treated individuals indicated a willingness to proceed in the PTSD treatment. No adverse events were experienced and all four patients completed the treatment (no drop-outs). All four patients expressed a general level of satisfaction with the treatment. These findings, while based on a limited sample size comport with literature showing that exposure-based treatment for PTSD is acceptable to patients, including patients with comorbid PTSD and chronic pain [43]. Separate targeted treatment for comorbid PTSD in patients with chronic pain before or after receiving intensive treatment for pain is very resource demanding and seems to have rather modest effect on their pain outcomes. We recently published a study where we showed that participation in a pain-focused CBT program was associated with improvements in pain outcomes and symptoms of anxiety and depression, but was not associated with improvements in comorbid PTSD [11]. Even if disorder specific approaches have dominated the ways in which problems like PTSD and chronic pain have been conceptualized, studied, and treated in the past, such practices may be neither clinically effective nor cost-effective for individuals with comorbid PTSD and chronic pain. It may be better instead to approach cases in an individual and process-focused fashion. Also, in the last 10 years, transdiagnostic processes and treatment interventions that cut across diagnostic boundaries have gained more and more attention [44] and the application of such treatment strategies may be more successful for individuals with these combined problems.

As a secondary aim, we investigated putative mediators of outcomes. Following recommendations on the evaluation of mediation, we chose candidate mediator variables based on theory and earlier empirical findings, examining several mediators at the same time, and with validated measures [45, 46]. With the use of a daily diary involving assessment of symptoms and mediators during the baseline and PE phases, we were also able to address the issue of temporality, a condition of mediation where the change in the mediator should precede change in the relevant outcome measure. Visual inspection of the daily diary data revealed that changes came about in distinctive patterns, at different times, and at different rates for the participants, highlighting the potential complexity and individual nature of mechanisms of change. Looking at the result on an individual level, significant changes in PTSD severity were mostly seen before changes in pain intensity. Mutual maintenance models of PTSD and chronic pain have suggested that one mechanism of interaction between the two conditions might be increases in anxiety and depression, symptoms which are common in individuals with both PTSD and pain [5]. Significant changes in anxiety/depression happened roughly at the same time as changes in the PTSD severity for all four participants. Previous studies suggest that changes in trauma-related beliefs mediate PTSD outcomes in trauma-focused CBT for PTSD [20, 21]. Generally, changes in trauma-related beliefs followed changes in the severity of PTSD. Finally, previous studies have suggested that changes in acceptance of pain may partly mediate pain outcomes in pain-focused treatments [31]. We observed that changes in pain-related acceptance occurred roughly at the same time as changes in pain interference for all four participants, but mostly before changes in pain intensity. While significant changes in potential mediators occurred during PE, these changes were largely concomitant with or followed changes in PTSD and pain interference. Thus, the present findings do not support the view that treatment outcomes for PTSD or pain were dependent upon changes in these variables in this group of individuals with both PTSD and pain. These findings go against the general view on mechanisms of change and mediators, but is in accordance with a recent case series employing a similar design that found that changes in most of the proposed mediators (pain intensity, controllability, fear) occurred simultaneously to changes in disability in four individuals with low back pain receiving pain-focused CBT [14].

Consistent with previous literature, we found that PE is an effective treatment for PTSD with positive effects for comorbid anxiety symptoms [47], but with little clear impact on either pain intensity or pain interference in individuals with chronic pain and PTSD. Firm conclusions require further study but a few reflections are warranted.
First, effective treatments for chronic pain usually involve various cognitive behavioral interventions that have the aim of altering the functional “meaning” of pain sensations to the patient such that they increase behaviors whose aim is improved functioning (overall) rather than reducing their pain symptoms [48]. These approaches have small effects on pain intensity; rather the improvements accrue in terms of pain-related disability and can also include comorbid symptoms of anxiety and depression. On the other hand, in PE the therapist communicates to the patient at the start of treatment, that repeated therapeutic exposure to the trauma memory and reminders will produce a rapid and durable reduction in the frequency and intensity of their PTSD symptoms, as well as any accompanying, trauma-related experiences of anxiety, depression, shame, guilt (etc.) [13]. There is a large evidence base to support this claim [47]. It is possible that treatment incorporating standard interventions for both pain and PTSD, delivered simultaneously and using treatment rationales that are more compatible, or that has a broader focus on reducing avoidance to all unpleasant emotional/physical sensations might be more suited to patients with comorbid pain and PTSD. Again, firm conclusions await further, larger investigations.

A number of limitations should be noted in this study. First, visual inspection is subjective and requires judgement and methods for analyzing single subject data are still developing. Second, the reliance on self-report measures could potentially influence the results. For example, the possible effect of answering according to the participants’ expectations (that the treatment is effective and that the PTSD symptoms should be reduced). On the other hand, most studies within this research field rely on self-report measures, a broad range of validated measures were included in the study, and daily ratings as well as more detailed ratings at the start of the baseline, after the PE phase, after the PE follow-up, and after completion of the pain-focused CBT program were included. Third, as the participants were adults referred to a specialist pain clinic, the results might not generalize to individuals referred to treatment because of PTSD and who also suffered with chronic pain. Fourth, the treatment for PTSD was delivered in 10 sessions over seven weeks and results may differ in other delivery formats. Fifth, while the psychologist delivering treatment had training and experience of using PE for PTSD in adults with chronic pain, no therapist competence or adherence measures were employed. Sixth, blinding was not used during the diagnostic assessment and as a consequence the diagnoses could be compromised. Seventh, data collections of the frequency necessary to estimate mediation can be very burdensome to individuals with chronic pain and comorbid PTSD. For this reason, we prioritized daily measures and chose a relatively short baseline. However, a short and highly variable baseline can make it more difficult to detect subsequent change and attribute it to the intervention. Eighth, the term single case experimental design is typically used to describe this type of study, even if it could also be labelled as quasi-experimental. It is also important to note that N-of-1 methods, including analyses of delayed effects, are not entirely immune to threats to internal validity such as maturation, regression to the mean, history, and confirmation bias, but we tried to minimize these problems by assessing multiple variables, using daily measurements, and including baselines with multiple data points of varying lengths, randomly assigned. One of the aspects that has been highlighted in relation to delayed effects, is that they allow for inferring a causal relation between the intervention and the target behavior if the delay is expected and if it is consistent (in time and magnitude) across replications (e.g., participants) [49]. In this study the former condition was met. However, the change in the target behavior happened at unequal intervals with different magnitude for the participants. This is not surprising given that the clinical complexity between the participants differed. Still, more evidence is needed to infer causality and to have a greater degree of confidence that the change in the target behavior is not due to external factors. Lastly, we only calculated one aspect of clinical significance, reliable change [42], since the second aspect ideally requires normative data from a recovered or functional population which we have been unable to identify for posttraumatic stress disorder and comorbid chronic pain [50].

In summary, based on four single case series, PE therapy for PTSD resulted in improved trauma-specific outcomes in people with PTSD and chronic pain, but it resulted in few improvements in pain-related outcomes. A specialty multidisciplinary pain-focused CBT program following the PE did not substantially enhance the specific improvements achieved. These results suggest minimal if any positive spillover effects from these two treatment approaches. It appears that methods impact where they are targeted. Although “disorder specific” approaches have dominated the conceptualising, study, and treatment of conditions like PTSD and chronic pain, such approaches may not be optimal, due to this lack of beneficial side effects. These results might suggest in the context of
complex problems it is better to specifically target treatments to meet individual needs rather than to apply them according to the disorders identified.

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