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Effects of hypnosis, cognitive therapy, hypnotic cognitive therapy, and pain education in adults with chronic pain: a randomized clinical trial

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Abstract

Chronic pain is a significant health problem worldwide with limited pharmacological treatment options. This study evaluated the relative efficacy of four treatment sessions each of four non-pharmacological treatments: (1) hypnotic cognitive therapy (using hypnosis to alter the meaning of pain); (2) standard cognitive therapy; (3) hypnosis focused on pain reduction, and (4) pain education. One hundred seventy-three individuals with chronic pain were randomly assigned to receive four sessions of one of the four treatments. Primary (pain intensity) and secondary outcome measures were administered by assessors unaware of treatment allocation at pre-treatment, post-treatment, and 3-, 6- and 12-month follow-up. Treatment effects were evaluated using ANOVA, a generalized estimating equation approach, or a Fisher Exact Test, depending on the outcome domain examined. All four treatments were associated with medium to large effect size improvements in pain intensity that maintained up to 12 months post-treatment. Pre- to post-treatment improvements were observed across the four treatment conditions on the secondary outcomes of pain interference and depressive symptoms, with some return towards pre-treatment levels at 12-months follow-up. No significant between group differences emerged in omnibus analyses, and few statistically significant between-group differences emerged in the planned pairwise analyses, although the two significant effects that did emerge favored hypnotic cognitive therapy. Future research is needed to determine if the significant differences that emerged are reliable.

Keywords

Chronic pain; Hypnosis; Hypnotic cognitive therapy; Randomized controlled trial

1. Introduction

Chronic pain is a significant health problem worldwide, with prevalence from 9% to 64% [77]. Low back pain is one of the most common chronic pain problems [39; 40; 62], and chronic pain is also highly prevalent as a secondary condition in individuals with chronic physical conditions, including those with spinal cord injury [10] and multiple sclerosis [31].

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Given the significant psychological and financial costs of chronic pain to both individuals and society [26], as well as the need to develop viable alternatives to chronic use of opioids and other harmful drugs [3; 9], there is an urgent need to identify effective treatments for chronic pain.

Cognitive behavioral therapy (CBT) is a well-established psychosocial treatment for chronic pain, with demonstrated efficacy for a variety of chronic pain conditions [25; 74]. However, the effect sizes for CBT treatment on pain and pain-related outcomes tend to be only small to medium [25]. Hypnosis has been shown in a number of studies to result in reductions in pain intensity in individuals with chronic pain [1; 4; 7; 66]. In addition, preliminary evidence suggests that adding hypnosis to other treatments – including CBT – may enhance the effects of the latter [51; 68].

We performed a pilot study to evaluate the possibility that hypnosis could be used to target changes in thoughts about pain (i.e., Hypnotic Cognitive Therapy or HYP-CT; [46]). The study also evaluated potential differences in efficacy between HYP-CT, traditional cognitive therapy (CT), a hypnosis treatment focused on pain reduction (HYP). The pilot study compared four sessions each of CT, HYP-CT, HYP, and pain education (ED; the control condition) using a repeated measures design (i.e., all participants received all four treatments, but in different orders) in a sample of 15 individuals with multiple sclerosis. The participants reported minimal pre- to post-treatment changes in pain intensity with CT or ED. Greater pain reductions were reported following HYP than CT. The largest benefits, however, were reported following HYP-CT. Based on these pilot findings, as well as findings from other studies suggesting that hypnosis may enhance the beneficial effects of other treatments [51], we determined that a full clinical trial was warranted.

The primary purpose of the study was to evaluate the efficacy of HYP-CT, relative to pain education (ED) and to both CT and HYP. We hypothesized that four sessions of HYP-CT, CT, and HYP would result in larger pre- to post-treatment (primary endpoint) decreases in daily pain intensity than four sessions of ED, and that four sessions of HYP-CT would result in larger decreases in daily pain intensity than four sessions of CT or HYP. We also planned secondary analyses to evaluate the relative efficacy of the four treatments on the secondary outcome variables of depressive symptom severity, pain interference, opioid medication use, and global satisfaction with treatment. Further, we evaluated the maintenance of benefits of the treatments, relative to each other, for up to 12 months following treatment.

2. Methods

2.1. Trial design, randomization procedures, and study overview

The study used a single-site, four-group parallel randomized controlled trial design. Research staff enrolled participants into the study prior to treatment assignment. One research staff member who was pre-specified to not be blind to treatment allocation (i.e., not among the research staff who performed the outcome assessment interviews) assigned participants to the interventions based on the assignment provided to them by the study biostatistician. Randomization was stratified such that each treatment arm was balanced relative to (a) primary diagnosis and (b) pain intensity using the random function (RAND) in

Excel to control for the potential effects of each of these variables on treatment response. The pain intensity stratum was separated into two pain groups - mild/moderate (<7 NRS) or severe (7–10 NRS) - using the average across the four pre-treatment NRS measurements (see average pain intensity in Measures section).

Treatments (described in more depth below) were manualized, and included an education control intervention (ED), hypnosis intervention (HYP), cognitive therapy intervention (CT), and a hypnotic cognitive therapy intervention (HYP-CT). All participants were offered four individual 60-minute sessions of their respective treatment interventions after randomization, administered in-person in a clinic setting by clinical psychologists, each with at least four years' clinical experience in the study interventions. Participants in all four treatment arms were provided workbooks that included a summary of session content and home practice materials that were tailored to the particular intervention. They were instructed to engage in home practice using these materials on a daily basis. Audio recordings (either a live recording of each treatment session or a pre-recording of the treatment session content, depending on the intervention) were also provided to participants to listen to at home.

2.2. Participants

Participants were adults with chronic low back pain (LBP) or chronic pain secondary to one of the following chronic conditions: multiple sclerosis (MS), spinal cord injury (SCI), acquired amputation (AMP), or muscular dystrophy (MD). Study inclusion criteria included: (a) being at least 18 years of age, (b) having a diagnosis of chronic LBP or one of the primary physical conditions (confirmed by medical record review or physician confirmation), (c) endorsing pain that had either started or became worse following the onset of the primary physical condition (if they had MS, SCI, AMP, or MD) and pain that had been present for at least 6 months, (d) having an average pain intensity in the past week ≥ 4 on a 0 to 10 numerical rating scale (NRS), (e) having pain at least half of the days in the past 4 weeks (6 months for participants with LBP, in accordance with the National Institutes of Health task force on research standards for chronic low back pain [22]), and (f) being able to read, speak, and understand English. Exclusion criteria were (a) the presence of electroencephalography (EEG) confounders (EEG measures were included as potential mediators and moderators of treatment efficacy; analyses to identify moderators and mediators of treatment outcome are planned for future papers and are therefore not performed here); (b) having received at least four sessions of, or currently receiving, a psychological treatment for pain (including relaxation training, self-hypnosis, cognitive, or cognitive behavioral therapy); (c) past or current participation in a treatment study that significantly overlapped with the current study's treatments; (d) severe cognitive impairment (defined as a > 1 error on the 6-item cognitive screener; [12]), and (e) current or recent (within the last year) psychiatric instability (active suicidal ideation, active delusional or psychotic thinking) that could interfere with participation, as assessed by a licensed clinical psychologist (MPJ or DME).

Figure 1 shows participant flow through study procedures. A total of 2,349 potential participants were approached between February 2013 and November 2016. Recruitment sources included a coding list of patients seen in University of Washington's medical system

who had a relevant diagnosis (n = 1,721), a registry of individuals who had participated in past studies and indicated an interest in being contacted about future research opportunities (n = 444), and other sources, such as ClinicalTrials.gov, referral by a University of Washington researcher or provider, or in-clinic flyer advertisements (n = 184). Potential participants were mailed recruitment brochures and a cover letter. Research staff called potential participants about two weeks after the recruitment brochures were mailed to provide an overview of the study and to screen those who expressed interest. We were able to contact by telephone 1,542 of 2,349 potential participants identified. Six hundred and fifty-three of these declined to participate before screening, leaving 889 possible participants who were assessed for eligibility. Of these 889, we were unable to re-contact 53, 76 declined to participate, and 4 withdrew after being consented, but prior to randomization. Of those who were fully screened and found ineligible (n = 583), 213 did not endorse having a pain problem, 152 did not have sufficiently high pain intensity, 42 did not experience pain at least half of the time in the past 4 weeks (6 months for participants with LBP), 40 were currently receiving or had received psychological treatment for pain in the past, 30 did not have a verified diagnosis, 21 had an EEG confounder, 21 did not have pain related to their primary diagnosis, 18 had participated in a previous clinical trial conducted by one of the study investigators, 11 failed the cognitive screener, 6 could not read, speak, and understand English, 3 did not have chronic pain for at least six months or longer, 3 failed the psychological screening, and 23 were found ineligible for other reasons. A total of 173 individuals were deemed eligible, consented in-person by study staff, and randomized to one of the four treatment conditions.

2.3. Interventions

2.3.1. Hypnosis intervention (HYP)—Hypnosis has been defined as a "…state of consciousness involving focused attention and a reduced peripheral awareness characterized by an enhanced capacity for response to suggestion" (p. 6 [29]). Hypnosis treatment usually involves two steps [41; 93]. First is the hypnotic induction ("A procedure designed to induce hypnosis", p. 6 [29]). Hypnotic inductions usually invite the subject to focus his or her attention on and become absorbed by a single object (e.g., spot on a wall) or experience (e.g., their breathing, feelings of relaxation, or an experience of being in a "favorite place;" [42]). The induction is then followed by suggestions that are designed to result in "changes in subjective experience, alterations in perception, sensation, emotion, thought, or behavior" (p. 143 [33]). In the same way that "medication" and "surgery" represent types or categories of treatments that can target a large variety of mechanism variables and that can be found to vary in efficacy depending on the specific type of medication or surgery being evaluated and condition being treated, "hypnosis" should not be viewed as a single treatment. Instead, hypnosis is a type of treatment that can vary a great deal in terms of specific content (i.e., the specific wording of the suggestions and the mechanism variables targeted). When using hypnosis for chronic pain treatment, for example, the suggestions could focus on pain reduction, changes in pain-related thoughts, increases in activity, or improvement in sleep quality, among many other outcomes [41].

The HYP intervention used in the current study focused on using hypnosis to reduce pain intensity and awareness of pain. Each HYP session began with a relaxation and "favorite

place" hypnotic induction followed by suggestions for pain reduction, reductions in the bothersomeness of pain, and an increased ability to ignore pain. Posthypnotic suggestions were (a) that the benefits of each session would last beyond the session "for minutes, hours, days, and years," and that these benefits would increase in duration with practice, and (b) that participants would to be able to enter a state of hypnosis using a cue (in this case taking a deep breath, and letting it go) in order to experience an immediate reduction in pain intensity and pain bothersomeness. Each HYP session was audio recorded, and recordings were provided to the participant to take home at the conclusion of each session. Participants were instructed to listen to the recordings at least once every day (or more often, if the participant found it helpful), and to practice self-hypnosis without the audio recordings by using the established cue several times throughout each day. The HYP intervention for this study was adapted from an existing protocol utilized in a series of trials of self-hypnosis for chronic pain, including the pilot study that formed the basis of this trial [43; 44; 46; 47; 78; 80].

2.3.2. Cognitive Therapy intervention (CT)—The primary aim of the CT intervention was to teach participants skills to monitor and evaluate their pain-related thoughts, and to challenge and replace any unhelpful thoughts with thoughts that were more helpful, accurate, and balanced. Participants were educated about the role of unhelpful cognitions (particularly catastrophizing) in chronic pain, pain related distress, and function. They were also taught specific cognitive restructuring techniques to help them to evaluate and change/replace unhelpful cognitions about pain. Home practice for the CT intervention consisted of completing detailed thought records recounting situations, automatic thoughts, emotional responses, and physical reactions that arose between sessions, and practice in cognitive restructuring. Participants were also provided with pre-recorded audio material that covered the content presented in each session and told that they could listen to the recordings as often as helpful as a way to "enhance the benefits of treatment." The CT intervention for this study was adapted from treatment protocols used in other studies conducted by our group [28; 46] and influenced by other CT interventions for chronic pain [8; 81; 84].

2.3.3. Hypnotic Cognitive Therapy intervention (HYP-CT)—The HYP-CT intervention was designed to use hypnosis to enhance the efficacy and extend the duration of the positive effects of cognitive restructuring. Whereas the hypnotic suggestions for the HYP intervention used suggestions to achieve reductions in pain intensity and pain awareness, the hypnotic suggestions in the HYP-CT protocol focused on changing the meaning of pain, based on the cognitive restructuring principals of the CT intervention. Specifically, hypnotic suggestions encouraged the participants to (a) increase their tolerance of a sense of ambiguity about the meaning of pain sensations, (b) increase their sense of control over their pain and its impact, (c) increase the time spent thinking adaptive and reassuring thoughts about pain, and (d) automatize the process of cognitive restructuring, such that any alarming or catastrophizing cognitions were automatically noticed (even before the participants are consciously aware of them), evaluated, and adjusted as needed into more adaptive ones. Home practice involved a combination of skills used in both the HYP and CT interventions. As with the HYP intervention, participants were asked to listen to the audio recordings of

the treatment sessions at least once a day, and to practice self-hypnosis on their own without the recordings several times a day. Participants were also asked to complete thought records after sessions one and two, and to select adaptive thoughts from these records to include in hypnotic suggestions in later sessions. The HYP-CT intervention was developed based on a synthesis of available protocols and literature used for both the HYP and CT conditions, and was the same intervention described in the pilot trial [46].

2.3.4. Pain Education intervention (ED)—The ED intervention was the active control condition against which the other interventions could be compared. It was designed to control for both the effects of time and repeated measurement of outcomes, as well as for non-specific and expectancy factors associated with receiving an active treatment (including the presence of a therapeutic relationship, treatment dosing, and participation in a manualized intervention). ED involved educating the participants about pain, including its costs, neurophysiology, nature, and impact. The ED condition included both general pain information as well as information tailored to the participant's particular medical condition (based on what is known about pain in MS, SCI, AMP, MD, and LBP). The ED intervention was also interactive; the therapist elicited discussion of the educational content and its relevance to participants' lives. The home practice for the ED condition consisted of encouraging participants to read educational handouts and to think about what they learned between sessions. Participants also completed a form with questions about the material they learned from the sessions and the readings. They were provided with pre-recorded compact discs that covered the content presented in each session, and encouraged to listen to these recordings daily or "as often as you would like as a way to enhance the benefits of treatment." The ED intervention for this study protocol was adapted from a protocol used in previous research [28], including the pilot study that informed the procedures used in the current clinical trial [46]. We should emphasize that, although the ED intervention was offered as an active control condition, to control for the effects of time (i.e., regression to the mean) and therapist attention, it can also be viewed as a treatment in and of itself.

2.4. Outcome assessment

Outcome data were collected at pre-treatment, mid-treatment, and post-treatment (primary endpoint), as well as at 3-, 6-, and 12-month follow-up. All outcome data were collected over the phone by study staff members that were blind to treatment group allocation. Each telephone assessment consisted of one "longer" telephone assessment which included all study outcome measures (see Measures section for more details) and took approximately 45 minutes to an hour to complete, as well as four "short" telephone assessments. The "short" telephone assessments were brief (1–3 minutes) and assessed pain intensity only (see Measures section).

The mid-treatment assessments were performed to identify mediators of treatment outcome. These included measures of pain intensity, additional psychosocial domains (e.g., pain related beliefs, coping responses, catastrophizing, hypnotizability) as well as measures of brain oscillation patterns as determined by electroencephalogram (EEG). However, these variables are not included in the current analysis, which focuses on primary and secondary

treatment outcomes. Participants were compensated $30.00 for each telephone assessment period, and received a bonus of $50.00 for completing all six telephone assessment periods.

2.5. Measures

Table 1 lists the outcome measures that were administered at each assessment point. As can be seen, outcomes were assessed at pre-treatment, mid-treatment, post-treatment, and at 3-, 6-, and 12-month follow-up. The mid-treatment assessments were made to allow for mediation analyses to evaluate potential treatment mechanisms. The results of these analyses will be presented in a future paper.

2.5.1. Descriptive variables—Descriptive variables were assessed in-person by research staff following the informed consent process approved by the institutional human subject committee. Basic demographic variables included age, sex, race, ethnicity, educational level, employment status, marital status, and whether or not the participants were taking medications for pain management. Hypnotizability was assessed using the Stanford Hypnotic Clinical Scale [63] as a descriptive variable in the current paper (although hypnotizability will be examined as a potential treatment moderator in a planned future paper).

2.5.2. Average pain intensity (primary outcome)—Average pain intensity was selected as the primary outcome for several reasons. First, it is the outcome domain most often assessed in chronic pain clinical trials (e.g., [32]). Second, it is one of the core outcome domains that consensus groups recommend be assessed in clinical trials [17; 86]. In addition, it was the primary outcome variable used in the pilot study that was conducted to determine if the current trial was warranted [45]. Average pain intensity was assessed at each telephone assessment period. Participants were asked to rate their average pain in the past 24 hours on four different days during a 7-day assessment period, using a 0 to 10 numerical rating scale (NRS) ranging from 0 *"No pain"* to 10 *"Pain as bad as you can imagine."* Pain intensity NRSs scales have substantial empirical evidence supporting their accuracy and reliability [48]. The four ratings were averaged into a single composite score representing average characteristic pain. The Cronbach's alpha of this composite score was 0.92, indicating excellent internal consistency.

2.5.3. Depressive symptom severity (secondary outcome)—Depressive symptom severity was assessed once at each telephone assessment period using the 8-item Patient Health Questionnaire (PHQ-8; [52]). With the PHQ-8, respondents are asked to indicate how often they had been bothered by each of 8 symptoms of depression (e.g., "Little interest or pleasure in doing things" and "Feeling down, depressed, or hopeless") in the past two weeks using a 0 to 3 scale, where 0 indicates "*Not at all*" and 3 indicates "*Nearly every day*." Items are summed, resulting in a depressive symptom severity score. The PHQ-8 is a modified version of the PHQ-9, and both have been extensively validated for use in various clinical populations, including among individuals with the chronic physical conditions [27; 53; 56; 73]. The Cronbach's alpha of the PHQ-8 items at pre-treatment in the current sample was 0.81, indicating good reliability.

2.5.4. Pain interference (secondary outcome)—Pain interference was assessed once at each telephone assessment period using seven pain interference items from the Brief Pain Inventory (BPI; [19]). With the BPI Interference subscale, respondent are asked to indicate how much pain interfered with seven different activity and response domains (e.g., "general activity," "mood," "relations with other people") in the past week using a 0 to 10 NRS, ranging from 0 (*"Pain does not interfere with that activity"*) to 10 (*"Pain completely interferes."*) The BPI Pain Interference scale has a great deal of evidence supporting its reliability and validity in populations of individuals with chronic pain [59; 60; 79]. The internal consistency (Cronbach's alpha) of the BPI Pain Interference scale in the current sample at pre-treatment was 0.88, indicating good reliability.

2.5.5. Change in opioid medication use (secondary outcome)—Participants were asked to indicate all of the medications they were taking at each assessment point, and to indicate whether or not they were taking the medication(s) for pain. If they were taking opioids or any medications containing opioids, they were asked to report their use (dosage and frequency) of these medications during the past week. We then converted these values into an average daily morphine equivalent dose (MED) using conversion factors recommended by the Washington State Agency Medical Directors' Group [34; 55]. Subsequently, we created a four-category variable for change in opioid use (i.e., no opioid use at pre- or post-treatment, increase in dose from pre- to post-treatment, decrease in dose from pre- to post-treatment, no change in dose from pre- to post-treatment) based on the pre- and post-treatment values.

2.5.6. Global Impression of Change and treatment satisfaction (secondary outcomes)—Global impression of change was assessed at post-treatment only using the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines [24]. The three domains of change assessed were (1) change in pain, (2) change in ability to manage pain, and (3) change in pain interference. Participants were asked to describe their change in each domain since they began the treatment program using a 7-point scale ranging from 1 ("*Very much improved*") to 7 ("*Very much worse*"). Participant global satisfaction with treatment (PGATS) was also assessed once at post-treatment. Participants were asked to rate their satisfaction with treatment ("How satisfied are you overall with the study treatment?") on a 5-point categorical scale (0 = "very dissatisfied"; 1 = "dissatisfied"; 2 = "no preference"; 3 = "satisfied"; 4 = "very satisfied"). This single item PGATS measure has been validated for use in heterogeneous chronic pain populations, including those with pain conditions studied here [23].

2.6. Treatment participation, fidelity assessment and therapist training

Participation was monitored by recording the number of sessions attended. Regarding treatment fidelity, all participants were asked if they were willing to have their sessions audio recorded for fidelity review. One-hundred and sixty-nine participants (98%) provided this permission. One of the four recorded sessions from each of these participants was then randomly selected in stratified blocks for fidelity monitoring (i.e., 25% of the sessions), such that an equal number of each of the four sessions from each treatment was coded. A subset of research staff not involved in data collection were trained in methods to code the

recordings using a pre-established checklist of the key elements of each treatment. These included both required and proscribed elements of treatment (e.g., participants in the HYP group, and only the HYP group, should be provided hypnosis with suggestions for reducing pain and increasing pleasant sensations; participants in the CT group, and only the CT group, should be taught the cognitive skill of evidence gathering, etc.). Each item on the checklist of required and proscribed elements was coded as being present or absent during the session. All of the randomly selected audio recordings were coded by two reviewers. When the coders were not in agreement for any treatment element for any recording, one of the study investigators coded the discrepant item independently to resolve the discrepancy (i.e., whichever code the third coder agreed with for the item in question was the code used). A total score (possible range, 0 to 100) represented the percent of required items that were present and proscribed items being absent (e.g., a session that was coded as having all of the required items present and all of the proscribed items absent received a score of 100).

Study clinicians were doctoral level clinical psychologists with at least four years' experience in pain treatment in general and the four categories of interventions evaluated here. In addition, they were trained in the specific study procedures by the study investigators. Clinicians utilized detailed therapist manuals to enhance treatment fidelity. Any study clinician whose fidelity coding dropped below 90% for any one session was given corrective feedback regarding his or her adherence to the established protocols to ensure high treatment fidelity throughout treatment.

2.7. Safety monitoring

Safety monitoring procedures were followed per University of Washington Human Subjects Division procedures and included (a) monitoring for possible adverse events, (b) managing any adverse events that were identified, and (c) reporting adverse events to the principal investigator, Human Subjects Division, and study sponsor, as appropriate.

2.8. Ethics approval and trial registration

All study procedures were approved by the University of Washington's Institutional Review Board. All participants signed informed consent forms before data were collected. The study was also registered before data were collected at clinicaltrials.gov (Identifier: NCT01800604).

2.9. Sample size determination

A power analysis to determine the sample size needed for the current study was based on the results of the pilot study [46]. In the pilot study, and for the control, CT, HYP, and HYP-CT interventions, the mean changes in pain intensity scores from pre-treatment to post-treatment were 0.06 (SD=0.70), 0.38 (SD=1.41), 0.92 (SD=1.45), and 1.58 (SD=1.50) for each of these treatments, respectively. Using the software PASS [38], we calculated the power of an ANOVA to find differences between these means, with an alpha of 0.05, and varying the standard deviation (SD) from 1.2 to 1.5 (to cover values observed in the pilot study). We found that sample sizes of 36 individuals per condition (total = 144) would have 99% power to detect these differences.

2.10. Data analyses

To describe demographic and clinical variables at pre-treatment (pre-treatment) and to assess the effectiveness of treatment randomization, we computed means and standard deviations (for continuous variables) and numbers and percentages (for categorical variables), and compared these demographic variables by treatment group using analysis of variance (ANOVA, for continuous variables) or the Fisher exact test (for categorical variables). We also computed the average treatment fidelity score for each intervention separately.

To answer the question, “Are the mean effects across treatments equal?”, the primary outcome, change in average pain from pre- to post-treatment, was analyzed using an analysis of covariance (ANCOVA), with change in average pain from pre- to post-treatment as the response variable, the pre-treatment average pain as the covariate for adjustment (see [6], Chapter 5), and treatment group as the factor of interest. We first tested the interaction of the intervention group with the pre-treatment measure, and if not statistically significant, we removed it and left only the main factors in the model. Simple contrasts comparing each intervention with the ED group was performed in the final model. Significance level was set to 0.05. We calculated three effect sizes for descriptive purposes. The effect size from pre- to post-treatment within each treatment group was defined as the mean of the individual changes in pain intensity divided by the standard deviation of the change. The absolute effect size of each treatment relative to the ED group as mean change from a treatment group minus the mean change of ED group. The relative effect size of each treatment was calculated by Cohen’s *d*, which is the difference between the means of the ED and treatment group divided by the pooled standard deviation, and for which we also calculated the 95% confidence interval [21]. In addition, we calculated the proportion of individuals in each group that had an improvement of at least 2 points in the pain score, which is considered as a clinically significant improvement [30]. Difference in proportions who reported meaningful improvements in pain among the four groups was tested using the Chi-square test. We used an intent-to-treat approach [18], such that any participant who was randomized and provided the necessary pre- and post-treatment data for calculating a change score was included in the analysis.

Change in the secondary outcomes of pain interference (as measured by BPI) and depressive symptoms (as measured by the PHQ-8) were analyzed similarly to the primary outcome. We still kept the significance level at 0.05 for each secondary analysis test, but interpreted the results with caution as we powered the study for the primary outcome only.

As planned *a priori*, we also explored the extent to which the change in pain intensity differed among treatments during follow-up assessment points. This was accomplished by using a Generalized Estimating Equations (GEE) approach, with the identity link (equivalent to assuming normal distribution). The GEE accounts for the correlated nature of the data due to the multiple observations of the same person over time by incorporating a matrix of correlations between observations at different time points, and does not require complete data for every person. Response variables over time were the change from pre-treatment to post-treatment, 3-, 6- and 12-months follow-ups, with intervention group and follow-up time as the main factors of interest (including a Group × Time interaction), and the pre-treatment value as the covariate. For the correlation matrix, we assumed an unstructured format, since

there was no *a priori* reason to use a more structured matrix format. We repeated these analyses for the secondary outcome measures assessing pain interference and depressive symptoms.

To examine the effects of the treatments on the secondary outcome of opioid medication use, we first calculated the morphine dose-equivalent per day of the person's opioids prescription at pre- and post-treatment. Using the morphine-equivalence, we classified the individuals in four categories: no prescription of opioids at either pre- or post-treatment, increase in dosage from pre- to post-treatment, decrease in dosage from pre- to post-treatment, and no change in dosage from pre- to post-treatment. We tested if the final distribution into those four categories was independent of the intervention group using a Fisher Exact Test with p-value based on the Monte Carlo method (with 10000 sampled tables), and shown as the estimated p-value and its 95% confidence interval (CI).

To analyze the secondary outcomes of global impression of change (PGIC, using ratings of pain level, pain management, and pain interference) and global satisfaction (PGATS) from pre- to post-treatment, we tested if the distributions were the same for all four groups, using a Fisher Exact Test with Monte Carlo method (estimated p-value and 95% CI). Data analyses were performed using SPSS version 25 for Mac.

3. Results

3.1. Participant enrollment and pre-treatment (demographic and descriptive) characteristics

The first participant for this study was enrolled on February 2013, and the final follow-up assessment was performed on January 2018. As shown in Figure 1, of the 889 individuals screened for eligibility, 173 (19%) of these were enrolled and randomized. At pre-treatment, sample sizes for the groups were 42 for ED, 44 for CT, 43 for HYP, and 44 for HYP-CT. There was minimal loss to follow-up in all groups, for post-treatment assessment (3 losses for ED, 4 for CT, 2 for HYP, and 0 for HYP-CT). As expected, at 12-month follow-up, there were more losses to follow-up (5 for ED, 5 for CT, 6 for HYP, and 3 for HYP-CT). Outcome assessment retention rates for all four groups were 88% or higher at all assessment time-points.

Table 2 shows the demographic characteristics, hypnotizability score means, and the means and standard deviations of pre-treatment measures of pain intensity, pain interference, and depressive symptoms of the study participants, by randomization group. The groups did not differ statistically in the means or distributions of any of the descriptive variables or the outcome measures at pre-treatment.

3.2. Treatment participation

Of the 173 subjects who were randomized, the great majority (157, 91%) participated in all four treatment sessions of the treatment to which they were assigned. Two (1%) participated in three sessions, seven (4%) participated in two sessions, five (3%) participated in one session, and two (1%) did not end up participating in treatment. However, regardless of the number of sessions they participated in, we attempted to collect data from all of the

randomized participants at each assessment point in order to perform the planned intention-to-treat analyses. No treatment-related serious adverse events were reported.

3.3. Treatment fidelity

One hundred sixty-three treatment sessions from 163 participants (i.e., one session per participant) were coded for treatment fidelity. Sessions from 10 randomized participants were not coded because (1) they did not grant permission to record their sessions (four participants); (3) they did not end up receiving any treatment after randomization due to repeated failed attendance (one participant) or becoming unable to contact (one participant); or (3) there were technical difficulties with the recordings (four participants). One hundred and thirty-two (81%) of the 163 coded sessions were coded with 100% level of agreement between the two primary coders. The 31 sessions that had one or more items of disagreement between the two primary coders were then coded a third time by one of the investigators to resolve the discrepancies. Treatment fidelity was very high for each intervention (ED, 97%; CT, 96%; HYP, 96%; and HYP-CT, 95%).

3.4. Primary outcome: Change in average pain intensity from pre- to post-treatment

Table 3 shows the descriptive analysis of the observed changes in average pain intensity (API) from pre- to post-treatment by intervention group. There were few individuals that were lost to follow-up in three of the groups: three individuals in the ED, four in the CT, and two in the HYP groups. None were lost to follow-up in the HYP-CT group. There was no evidence that the missing values in these few individuals who were lost to follow-up were related to the interventions; we therefore determined that it was unlikely that the analyses were biased due to the exclusion of those individuals. The last column of Table 3 shows the p-values for the final ANCOVA model, with the interaction removed since it was not statistically significant. The largest mean changes from pre- to post-treatment occurred in the HYP-CT group, followed by CT, with less change for the HYP and ED groups. However, after adjusting for the pre-treatment average pain intensity ($p<0.001$), the omnibus intervention group main effect was not statistically significant ($p=0.13$). Pairwise contrast comparisons of the means of intervention groups (after adjusting for the pre-treatment values) with the mean of the ED group were not statistically significant for the CT and the HYP groups, but were statistically significant for the HYP-CT group ($p=0.048$). Relative effect sizes (ES) relative to the ED group were moderate for the CT (ES = −0.36; Note: the negative values indicates a pre- to post-treatment decrease in the outcome variable) and HYP-CT (ES = −0.47) groups, with almost non-existent effect for the HYP group (ES = −0.02). Our initial plan was to adjust the model for use of any pain medication use (yes or no, as reported by individual), but the four treatment groups were not statistically different in the proportion of use ($p = 0.60$, see Table 2) and the proportions were very high for all groups (ranging from 88% to 96%). Therefore, the models did not include use of medications as a covariate.

Within all groups, on average, there was a decrease in pain intensity from pre- to post-treatment. The effect sizes within each group (average change divided by standard deviation) were medium to large [20], with values of −0.60, −0.70, −0.76, and −0.80 for pain education, hypnosis, cognitive therapy, and hypnotic cognitive therapy, respectively. The

proportion of individuals with an improvement of at least 2 points from pre- to post-treatment in the pain scale was 0.15, 0.20, 0.22, and 0.39 for pain education, hypnosis, cognitive therapy, and hypnotic cognitive therapy, respectively. However, the differences in these proportions were not statistically different (p = 0.07).

3.5. Secondary outcomes: Change in pain interference, depressive symptoms, and opioid medication use from pre- to post-treatment

Table 3 also includes the ANCOVAS for the change in pain interference (as measured by the BPI) and change in depressive symptoms (as measured by the PHQ-8), and the Fisher test for changes in opioid use from pre- to post-treatment. For BPI, the largest mean change occurred in the HYP-CT group, followed by the CT and HYP groups, which had similar means, with the least change for the ED group. After adjusting for the pre-treatment BPI ($p<0.001$), the groups were not statistically different ($p=0.06$). Note that the standard deviation was largest in the HYP-CT group. Only the contrast comparison of HYP-CT with the ED group was statistically significant. Effect sizes for CT (ES = −0.08) and HYP (ES = −0.07), relative to ED were very low, but large for the HYP-CT (ES = −0.60).

For the PHQ-8, the largest mean change occurred for the HYP-CT group, followed by the CT and HYP groups, with the least change for the ED group. After adjusting for the pre-treatment PHQ-8 ($p<0.001$), the groups were not statistically different ($p=0.71$). Note that the standard deviation was high for each group. No contrast comparison was statistically significant. Effect sizes for CT (ES = −0.15) and HYP (ES = −0.18) were low, and only slightly larger for HYP-CT (ES = −0.23).

For opioid medication use, the categories of changes in dose (after calculating morphine-equivalent dose per day) are shown in Table 2. The treatment groups were not statistically associated with the changes in opioid medication.

3.6. Secondary data analysis: Change in primary and secondary outcomes over time

Table 4 shows the results of the GEE models that include changes from pre-treatment to post-treatment, 3-, 6-, and 12-months follow-ups. Estimated mean changes from pre-treatment (and their correspondent 95% confidence interval) using the models are shown by group and follow-up time. The last column reports Wald statistics, degrees of freedom, and p-values for each factor in the model. For change in pain intensity, treatment group ($p=0.35$), time ($p=0.18$), and their interaction ($p=0.44$) were not statistically significant, while the pre-treatment average pain intensity was ($p<0.001$).

We repeated the same analysis examining change over time up to the 12-month follow-up assessment for BPI pain interference and PHQ-8. For BPI, the HYP-CT group had a consistent lower mean over time than the other three groups. However, only the pre-treatment BPI was statistically significant in the model ($p<0.001$, Table 4). For PHQ-8, no consistent pattern was seen between or within groups, except that following the pre- to post-treatment improvements in depression across the four conditions, the depressive symptom severity scores tended to revert towards pre-treatment levels over time. Similar to the other two outcomes, only the pre-treatment PHQ-8 was statistically significant in the model ($p<0.001$, see Table 4).

3.7. Secondary outcomes: Global measures of change and treatment satisfaction

Table 5 shows the distributions of responses for the individuals' perception of change in pain, pain management, pain interference, and global satisfaction measured at post-treatment time. There were no statistically significant treatment group differences in distributions for change in pain (p=0.10, 95% CI: 0.09, 0.11), change in pain management (p=0.12, 95% CI: 0.11, 0.13), or change in pain interference (p=0.20, 95% CI: 0.19, 0.21). Although the groups were not statistically different, there are some patterns that deserve additional exploration. For change in pain, the proportion of individuals reporting no change or worsening was largest for the ED group (29%), followed by CT (20%), HYP-CT (16%) and HYP (10%). The largest proportion of "much improved or very much improved" for change in pain occurred for HYP-CT (59%), followed by HYP (46%), CT (43%), and ED (37%). For pain interference, the largest proportion of no change or worsening occurred for CT (50%), followed by ED and HYP-CT (37% each), and then HYP (32%). However, only two individuals actually reported some worsening (although no one selected "very much worse"), with all others reporting "no change." The largest proportion endorsing "much improved or very much improved" occurred for HYP-CT (45%), followed by ED (29%), HYP (24%), and CT (18%).

Table 5 also shows the results for a question on overall satisfaction with treatment. The distributions were statistically different (p=0.01, 95% CI: 0.009, 0.014). No individuals were dissatisfied in the HYP-CT and HYP groups, one person was dissatisfied in the CT group and five were dissatisfied in the ED group. In order, the rates of endorsement of "very satisfied" were 57% (HYP-CT), 49% (HYP), 40% (CT), and 32% (ED).

4. Discussion

The primary aim of this study was to compare the efficacy of four psychologically-based chronic pain treatments: (1) hypnotic cognitive therapy; (2) standard cognitive therapy; (3) hypnosis focused on pain reduction, and (4) pain education as a control condition. We hypothesized that the three experimental treatments would result in larger pre- to post-treatment decreases in daily pain intensity than the control (education only) condition, and that hypnotic cognitive therapy would result in larger decreases in pain intensity than the two other experimental treatment conditions.

We did not find statistically significant between-group differences on the omnibus test for pain intensity. Although not consistent with our hypotheses that were based on our pilot study [45], this finding is consistent with the results from other studies that have compared psychological interventions for pain with active control conditions similar to the pain education one we used here (e.g., [35; 69; 82; 87]; for an exception, see [88]). In addition, the lack of significant differences between the active treatments in the current study are consistent with those from other studies that have performed head-to-head comparisons between different pain treatments (e.g., [15; 49; 64; 65; 75; 89]).

The similarities in outcomes for different chronic pain treatments could have a variety of explanations. First, it is possible that the treatments are effective in part because of their similar effects on common factors such as therapeutic alliance [11; 13], patient motivation

[11; 13], and outcome expectancies [13]. Alternatively, it is possible that the treatments have different specific effects on mechanism variables (e.g., cognitive therapy may operate via its effects on pain-related beliefs and hypnosis may operate via its effects on brain activity related to the processing of nociception). Research to identify the shared and specific mechanisms of the different treatments that are available is needed to determine which mechanism or mechanisms play the most important role in beneficial outcomes, and which interventions most effectively impact each mechanism variable.

Although the omnibus test for group differences in the primary outcome measure was not statistically significant, in the planned pairwise comparisons between the education condition and each of the three experimental treatments, we did observe significantly greater reductions in pain intensity in the hypnotic cognitive therapy group than the education control condition. In contrast, neither hypnosis focused on pain reduction nor cognitive therapy alone evidenced significant improvements in pain intensity over pain education. Moreover, a significantly greater reduction in pain interference was observed for the hypnotic cognitive therapy than the education control condition. These findings suggest the possibility that hypnotic cognitive therapy may have specific beneficial effects for pain intensity and interference over and above those produced by pain education. These findings should be examined further in future research to evaluate their reliability.

The study findings regarding the long-term maintenance of treatment benefits are consistent with a number of other studies evaluating psychosocial pain treatments (e.g., [15; 54; 64; 82; 87]; see also review by Richmond et al [67]). Specifically, we found pre- to post-treatment improvements in pain intensity, pain interference, and depressive symptoms were generally maintained at 12 months following treatment, although depressive symptoms did evidence some return in the direction of pre-treatment levels over time. As noted by Cherkin and colleagues [15], the longer term maintenance of psychosocial pain treatments for pain contrasts with data from treatments that focus more on physiological processes, such as acupuncture, massage, and yoga [14; 16; 72]. Further research could determine whether the maintenance of treatment gains associated with skills-based approaches to pain are due to enduring changes in thought patterns that influence pain and function, the ongoing use of the skills learned by study participants, or some combination of these. In any case, the positive findings regarding benefit maintenance argues for the cost-effectiveness of these psychological skill-based treatments, in that additional “booster” treatments to help maintain treatment gains may not be needed.

Although the focus of this study was to test hypotheses regarding the relative efficacy of the four treatment conditions, some additional findings from the study are worth noting. For example, we found that there were individuals in every treatment group who reported clinically meaningful (i.e., 2 points or more on a 0–10 scale) pre- to post-treatment decreases in pain, ranging from 15% for the pain education condition to 39% for the hypnotic cognitive therapy condition. Moreover, treatment adherence was high. These findings support each of the treatments as potentially viable for reducing pain and improving other outcomes. That said, it should be noted that there were more participants who were dissatisfied with the education condition (13.2%) than the cognitive therapy (2.5%), hypnosis (0.0%), or hypnotic cognitive therapy (0.0%) conditions. To the extent that a lack

of treatment satisfaction could impact patient engagement with treatment [50; 91], especially given the importance of treatment engagement to psychosocial pain treatments [49], this finding suggests the possibility that the three active treatments have the potential to be more effective in the long run than pain education. The finding also underscores the importance of assessing treatment satisfaction as a key secondary outcome in pain treatment clinical trials.

Another design feature of the current study that warrants discussion is the brevity of the treatments that were examined. The number of treatment sessions (or treatment "dose") provided in psychosocial chronic pain interventions varies widely from as few as two or three (e.g., [2; 61; 80]) to as many as 12 (e.g., [71]). However, researchers tend to most often evaluate the efficacy of six to 10 psychological pain treatments sessions, with eight sessions being the most common (e.g., [5; 15; 37; 43; 83; 85; 90; 94]). Here we chose to evaluate the efficacy of four sessions of treatment. This choice was based in part on our clinical experience that four sessions is often enough to teach cognitive therapy and self-hypnosis skills, especially given the possibility that the amount of skill building with home practice may be a more important determinant of outcome than the number of treatment sessions. In addition, we found in our pilot study that four sessions of each active treatment resulted in detectable improvements in the primary and secondary outcome domains evaluated in the current study [45], and we have found four sessions of these treatments to result in significant improvements in other trials (e.g., [47; 58]). Thus, we reasoned that if the current study found benefits from four sessions of these treatments, this might provide even greater support for the use of these treatments by both (often busy) patients, and support for these treatment by third-party payers, relative to longer (e.g., eight session) treatments.

This study has a number of limitations that should be considered. First, the control condition we elected to use for this study – pain education – was an active control condition that was associated with pre- to post-treatment improvements in all study outcomes. Future researchers in this area should consider a usual care condition instead of an active control condition to control for the effects of time alone (e.g., regression to the mean). This would allow for a more accurate estimate of the effects of the active treatments. Second, although the effects we found in this study were in the same direction as found in the pilot study – that is, the pattern of findings favored HYP-CT over the other three condition for all outcomes [45] – the effect sizes found in the current study were smaller than those found in the pilot study. Thus, it is possible that the current study was not adequately powered to detect significant benefits of HYP-CT over HYP and CT. Future researchers should examine these effects in larger samples, if possible (cf. [76]). Finally, as previously noted, the number of treatment sessions (four) tested was low relative to the number of sessions often tested in clinical trials of psychosocial chronic pain interventions (e.g., [36; 57; 70; 71; 92]). It is possible that the efficacy of one or more of the treatments might have been found to be greater had more treatment sessions been provided. We are aware of only one study that has compared the relative effects of different numbers of hypnosis sessions [80], and know of no studies that have compared the relative efficacy of different numbers of sessions of cognitive therapy. Addressing questions of the impact of dose on outcomes remains an important issue in this field.

Despite the study's limitations, the findings provide important new information regarding the relative benefits of four non-pharmacological chronic pain treatments. First, for the most part, the four treatments evidenced similar beneficial effects on the primary and secondary outcome variables. Second, the results of planned pairwise comparisons indicated that hypnotic cognitive therapy was more effective than pain education for pain intensity and pain interference. The extent to which these findings replicate and generalize to other pain populations, and the identification of factors that moderate treatment outcome, will need to be examined in future analyses and research studies.

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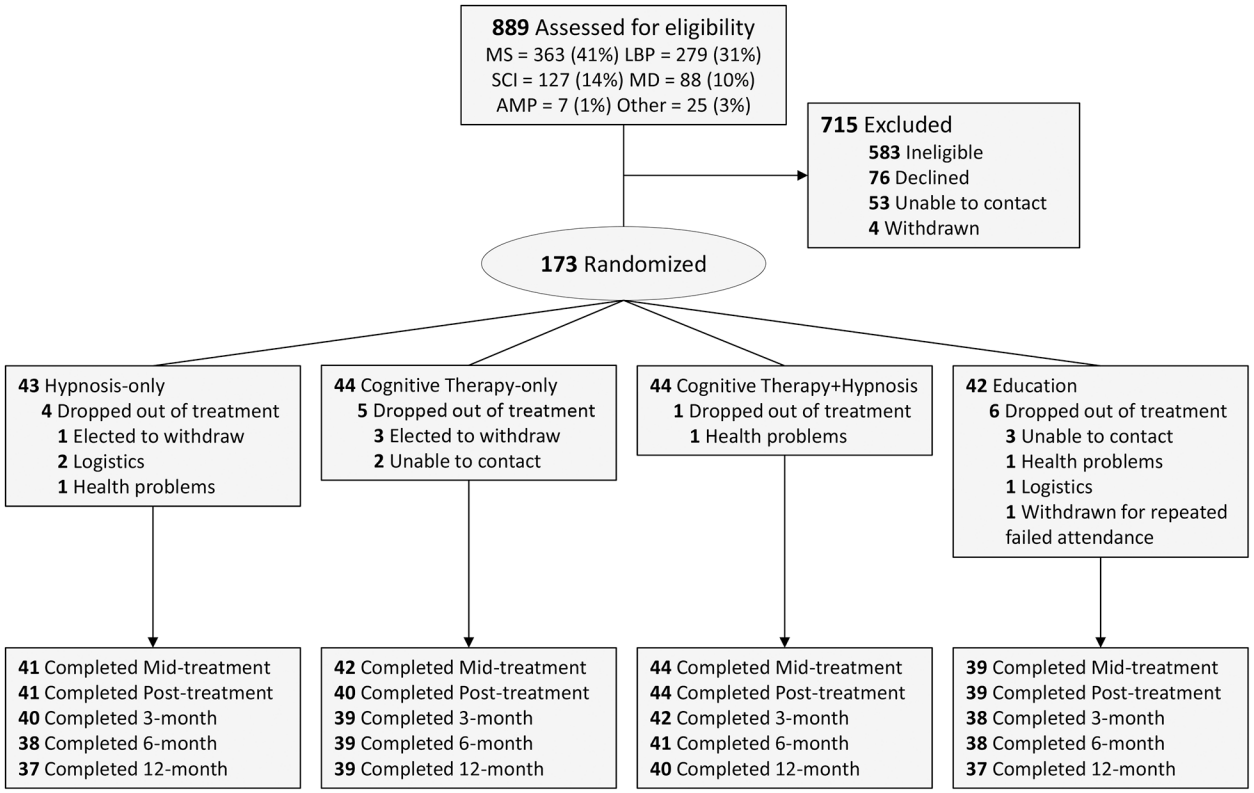

Figure 1.
CONSORT Flow Chart of the study participants through the trial.

Table 1.

Outcome domains collected at each assessment point.

	Assessment point					
Outcome domain	**Pre-treatment**	**Mid-treatment***	**Post-treatment**	**3-month follow-up**	**6-month follow-up**	**12-mon follow-up**
Average pain intensity	X	X	X	X	X	X
Depressive symptoms	X	X	X	X	X	X
Pain interference	X	X	X	X	X	X
Opioid medication use	X	X	X	X	X	X
Global impression of change in…						
Pain			X			
Ability to manage pain			X			
Pain interference			X			
Treatment satisfaction			X			

*Mid-treatment outcomes were assessed for planned mediation analyses. Mid-treatment data were not used to address the study hypotheses tested in this paper.

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Table 2.

Demographic Characteristics and Clinical Measures at Pre-Treatment by Randomization Group.

Characteristic	Treatment Groups				P-value††
	Education	Cognitive Therapy	Hypnosis	Hypnotic Cognitive Therapy	
Sample Size	42	44	43	44	
Demographic Characteristics					
Age in years, mean (SD)	56.3 (12.1)	52.7 (13.1)	53.6 (12.9)	57.8 (12.5)	0.22
Median (Min, Max)	55.0 (28.0, 79.0)	53.5 (25.0, 75.0)	56.0 (25.0, 76.0)	60.0 (24.0, 81.0)	
Sex, %(n) females	59.5 (25)	56.8 (25)	58.1 (25)	61.4 (27)	0.98
Racial group, % (n) *					
Caucasian	73.2 (30)	79.5 (35)	76.2 (32)	86.4 (38)	0.68
Black or African-American	9.8 (4)	11.4 (5)	7.1 (3)	4.5 (2)	
Asian	7.3 (3)	0.0 (0)	7.1 (3)	2.3 (1)	
Other **	4.9 (2)	4.5 (2)	4.8 (2)	2.3 (1)	
More than one race	4.9 (2)	4.5 (2)	4.8 (2)	4.5 (2)	
Ethnicity, %(n) Hispanic/Latino ***	0.0 (0)	2.3 (1)	7.1 (3)	0.0 (0)	0.09
Education, % (n)					
Some high school or less	7.2 (3)	2.3 (1)	0.0 (0)	0.0 (0)	0.64
High School graduate or GED	9.5 (4)	18.2 (8)	14.0 (6)	11.4 (5)	
Vocational/Technical School or some College	23.8 (10)	25 (11)	37.2 (16)	34.1 (15)	
College Graduate	42.9 (18)	27.3 (12)	25.6 (11)	36.4 (16)	
Graduate school or Professional	16.7 (7)	27.3 (12)	23.3 (10)	18.2 (8)	
Employment, % (n)					
Unemployed †	38.1 (16)	29.5 (13)	44.2 (19)	47.7 (21)	0.65
Retired	23.8 (10)	27.3 (12)	20.9 (9)	31.8 (14)	
Employed full time	23.8 (10)	25.0 (11)	18.6 (8)	9.1 (4)	
Employed part time	11.9 (5)	11.4 (5)	14.0 (6)	6.8 (3)	
Homemaker	2.4 (1)	4.5 (2)	0.0 (0)	4.5 (2)	
School full time	0.0 (0)	2.3 (1)	2.3 (1)	0.0 (0)	
Marital Status, % (n)					
Married/With significant other	64.3 (27)	56.8 (25)	53.5 (23)	50.0 (22)	0.59

Characteristic	Treatment Groups				P-value††
	Education	Cognitive Therapy	Hypnosis	Hypnotic Cognitive Therapy	
Divorced, Separated, Widowed	28.6 (12)	31.8 (14)	30.2 (13)	34.1 (15)	
Never married	7.1 (3)	11.4 (5)	16.3 (7)	15.9 (7)	
Taking pain medications, % yes (n)	92.9 (39)	88.6 (39)	88.4 (38)	95.5 (42)	0.60
Hypnotizability (SHCS total score), mean (SD)	2.90 (1.36)	2.99 (1.30)	2.79 (1.04)	2.95 (1.10)	0.87
Clinical measures					
Average Pain Intensity					
Mean (SD)	4.63 (1.82)	4.91 (1.65)	4.47 (1.72)	4.91 (1.70)	0.56
Median (Min, Max)	5.00 (0.50, 8.50)	4.50 (1.50, 9.00)	4.31 (1.25, 8.00)	4.62 (2.00, 8.67)	
Pain interference					
Mean (SD)	4.75 (2.40)	4.41 (1.98)	4.26 (1.98)	4.98 (1.92)	0.37
Median (Min, Max)	4.71 (0.43, 9.00)	4.36 (0.57, 7.71)	4.43 (0.43, 8.29)	5.00 (1.00, 9.33)	
Depression					
Mean (SD)	8.83 (5.79)	9.23 (5.25)	8.98 (4.85)	8.34 (7.76)	0.88
Median (Min, Max)	8 (0, 23)	9 (1, 20)	8 (1, 20)	8.5 (1, 23)	

*One missing value in the Education and one in the Hypnosis groups.

**Includes American Indian, Alaskan Native, Native Hawaiian, Pacific Islander and other races.

***Two missing values in the Education and one in the Hypnosis groups.

†Unemployed due to various reasons related to condition, such as disability, pain, and other, and includes reports of being unemployed and homemaker.

††P-values based on ANOVA to test means for age, average pain intensity, pain interference, and depression; Fisher exact test for all other variables. For the Fisher test we collapsed: the last three categories of racial group; the last two categories for employment and marital status; and the first two categories of education.

Note: SHCS = Stanford Hypnotic Clinical Scale.

Table 3.

Changes in Primary and Secondary Outcomes from Pre- to Post-treatment by Intervention Group.

Change in clinical measures	Treatment Groups: Education	Cognitive Therapy	Hypnosis	Hypnotic Cognitive Therapy	P–value*
Sample size at post-treatment	39	40	41	44	
Change in average pain intensity					
Mean (SD)	−0.76 (1.26)	−1.32 (1.73)	−0.78 (1.12)	−1.54 (1.93)	Pre–treatment API: p < 0.001 Intervention group: p=0.13
Median (Min, Max)	−0.75 (−3.50, 1.63)	−1.00 (−8.00, 1.00)	−1.00 (−2.50, 2.00)	−1.00 (−8.42, 2.25)	
Contrast (p-value) **	--	−0.44 (p=0.20)	−0.03 (p=0.93)	−0.65 (p=0.05)	
Absolute effect size **	--	−0.55	−0.02	−0.78	
Relative effect size (95% CI) ††	--	−0.36 (−0.47, −0.26)	−0.02 (−0.12, 0.08)	−0.47 (−0.57, −0.37)	
Change in pain interference					
Mean (SD)	−0.90 (1.73)	−1.06 (1.99)	−1.03 (1.96)	−2.05 (2.04)	Pre–treatment BPI: p <0.001 Intervention group: p=0.06
Median (Min, Max)	−0.57 (−6.14, 2.86)	−0.64 (−6.57, 2.43)	−1.00 (−6.29, 2.86)	−2.00 (−6.43, 1.43)	
Contrast (p-value) **	--	−0.29 (p=0.45)	−0.26 (p=0.50)	−0.98 (p=0.01)	
Absolute effect size ***	--	−0.15	−0.12	−1.14	
Relative effect size (95% CI) ††	--	−0.08 (−0.18, 0.02)	−0.07 (−0.16, 0.03)	−0.60 (−0.70, −0.50)	
Change in depression					
Mean (SD)	−1.31 (3.11)	−1.82 (3.54)	−1.98 (4.15)	−2.11 (3.72)	Pre–treatment PHQ–8: p <0.001 Intervention group: p=0.71
Median (Min, Max)	−1 (−13, 5)	−1.5 (−10, 7)	−1 (−14, 6)	−2 (−10, 5)	
Contrast (p-value) **	--	−0.40 (p=0.60)	−0.51 (p=0.51)	−0.88 (0.24)	
Absolute effect size ***	--	−0.42	−0.67	−0.81	
Relative effect size (95% CI) ††	--	−0.15 (−0.25, −0.06)	−0.18 (−0.28, −0.08)	−0.23 (−0.33, −0.14)	
Opioid prescription in morphine-equivalent dose, % (n) ††					
No opioid prescription at pre- or post-treatment	59.5% (25)	65.9% (29)	74.4% (32)	63.6% (28)	
Increase in dose from pre- to post-treatment	14.3% (6)	13.6% (6)	9.3% (4)	4.5% (2)	p=0.56, 95% CI: 0.55, 0.57
Decrease in dose from pre- to post-treatment	14.3% (6)	13.6% (6)	14.0% (6)	22.7% (10)	

Change in clinical measures	Treatment Groups: Education	Cognitive Therapy	Hypnosis	Hypnotic Cognitive Therapy	P–value*
No change in dose from pre- to post-treatment	11.9% (5)	6.8% (3)	2.3% (1)	9.1% (4)	

*P-values from final ANCOVA model (except for opioid prescription - see note below), with change in API as the response variable, the intervention group as the factor of interest, and the measure at pre-treatment as the covariate. If a p-value is not shown for the interaction between the intervention and covariate, the final model does not include an interaction.

**Simple contrast defined by change in intervention group minus change in the Education group. P-value from constrast comparison using the final model with the adjustment for pre-treatment outcome value.

***Absolute effect size is the difference between the mean change in each group and the mean change in the Education group.

†Relative effect size compares the treatment group with the Education group, using pooled standard deviation in the denominator (Cohen's d) and present its 95% confidence interval (CI).

††P-value from Fisher exact test using Monte Carlo method; includes simulation estimate and 95% confidence interval (CI) for p-value.

Table 4.

Estimates and 95% Wald Confidence Interval of Changes (from Pre-treatment) in Average Pain Intensity, Pain Interference, and Depressive Symptoms by Treatment Group and Follow-up Time, from GEE Model.

	Treatment Groups				
Estimated Mean Change* at	**Education**	**Cognitive Therapy**	**Hypnosis**	**Hypnotic Cognitive Therapy**	**Results for GEE model****
Average Pain Intensity					
Post–treatment	−1.02 (−1.36, −0.69)	−1.17 (−1.54, −0.79)	−0.85 (−1.21, −.049)	−1.35 (−1.84, −0.86)	Group: W=3.26, df=3, p=0.35
3-Month Follow-up	−0.94 (−1.28, −0.59)	−1.08 (−1.46, −0.71)	−0.76 (−1.16, −0.36)	−1.27 (−1.76, −0.78)	Time: W=4.86, df=3, p=0.18
6-Month Follow-up	−1.08 (−1.49, −0.83)	−1.22 (−1.59, −0.85)	−0.90 (−1.29, −0.51)	−1.41 (−1.91, −0.90)	GxT: W=8.99, df=9, p=0.44
12-Month Follow-up	−1.16 (−1.49, −0.83)	−1.30 (−1.67, −0.94)	−0.99 (−1.37, −0.60)	−1.49 (−1.99, −0.99)	Cov: W=17.56, df=1, p<0.001
Pain Interference					
Post–treatment	−0.87 (−1.31, −0.43)	−1.12 (−1.66, −0.58)	−1.11 (−1.61, −0.62)	−1.86 (−2.40, −1.32)	Group: W=4.00, df=3, p=0.26
3-Month Follow-up	−0.84 (−1.29, −0.39)	−1.11 (−1.71, −0.51)	−0.76 (−1.37, −0.15)	−1.43 (−2.08, −0.77)	Time: W=3.65, df=3, p=0.30
6-Month Follow-up	−0.99 (−1.60, −0.38)	−0.81 (−1.41, −0.22)	−1.36 (−1.94, −0.79)	−1.33 (−1.99, −0.67)	GxT: W=14.88, df=9, p=0.09
12-Month Follow-up	−1.16 (−1.67, −0.66)	−0.77 (−1.28, −0.25)	−0.77 (−1.26, −0.30)	−1.54 (−2.09, −1.00)	Cov: W=62.26, df=1, p<0.001
Depressive Symptoms					
Post–treatment	−1.33 (−2.25, −0.41)	−1.79 (−2.82, −0.76)	−1.84 (−2.97, −0.70)	−2.21 (−3,21, −1,21)	Group: W=0.70, df=3, p=0.87
3-Month Follow-up	−0.80 (−1.87, 0.27)	−1.77 (−2.85, −0.69)	−1.26 (−2.33, −0.19)	−1.69 (−2.88, −0.51)	Time: W=7.18, df=3, p=0.07
6-Month Follow-up	−1.21 (−2.55, 0.13)	−0.63 (−1.72, 0.47)	−1.49 (−2.63, −0.35)	−1.03 (−2.18, 0.12)	GxT: W=7.84, df=9, p=0.55
12-Month Follow-up	−1.04 (−2.35, 0.27)	−1.21 (−2.28, −0.14)	−1.72 (−2.69, −0.75)	−1.28 (−2.41, −0.16)	Cov: W=30.21, df=1, p<0.001

*Estimates calculated for pre-treatment average pain intensity=4.67

**Includes Wald Chi-square statistics (W), degrees of freedom (df) and p-value (p) for each factor in the model. Group = randomization groups, Time = follow-up times, GxT= interaction between group and time, Cov = covariate measured at pre-treatment

Table 5.

Distribution of Perception of Global Change Measured at Post-treatment Time.

Change since treatment started for	Treatment Groups				P-value (95% CI)*
	Education	Cognitive Therapy	Hypnosis	Hypnotic Cognitive Therapy	
Pain, % (n)					
Very much improved	2.6 (1)	10.0 (4)	9.8 (4)	18.2 (8)	
Much Improved	34.2 (13)	32.5 (13)	36.6 (15)	40.9 (18)	
Minimally improved	34.2 (13)	37.5 (15)	43.9 (18)	25.0 (11)	0.10 (0.09, 0.11)
No change	28.9 (11)	20.0 (8)	4.9 (2)	13.6 (6)	
Minimally worse	0.0 (0)	0.0 (0)	2.4 (1)	2.3 (1)	
Much worse	0.0 (0)	0.0 (0)	2.4 (1)	0.0 (0)	
Pain Management, % (n)					
Very much improved	5.3 (2)	15.0 (6)	9.8 (4)	27.3 (12)	
Much Improved	34.2 (13)	45.0 (18)	39.0 (16)	40.9 (18)	
Minimally improved	52.6 (20)	32.5 (13)	46.3 (19)	27.3 (12)	0.12 (0.11, 0.13)
No change	7.9 (3)	7.5 (3)	2.4 (1)	4.5 (2)	
Minimally worse	0.0 (0)	0.0 (0)	2.4 (1)	0.0 (0)	
Much worse	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	
Pain Interference, % (n)					
Very much improved	5.3 (2)	5.0 (2)	0.0 (0)	14.0 (6)	
Much Improved	23.7 (9)	12.5 (5)	24.4 (10)	20.9 (9)	
Minimally improved	34.2 (13)	32.5 (13)	43.9 (18)	27.9 (12)	0.20 (0.19, 0.21)
No change	36.8 (14)	50.0 (20)	29.3 (12)	34.9 (15)	
Minimally worse	0.0 (0)	0.0 (0)	2.4 (1)	0.0 (0)	
Much worse	0.0 (0)	0.0 (0)	0.0 (0)	2.3 (1)	
Treatment Satisfaction, % (n)					
Dissatisfied	13.2 (5)	2.5 (1)	0.0 (0)	0.0 (0)	
No preference	13.2 (5)	2.5 (1)	12.2 (5)	2.3 (1)	0.01 (0.009, 0.014)
Satisfied	42.1 (16)	55.0 (22)	39.0 (16)	40.9 (18)	
Very satisfied	31.6 (12)	40.0 (16)	48.8 (20)	56.8 (25)	

*Estimated p-value from Fisher exact test using Monte Carlo method, based on 10000 sample tables, with respective 95% confidence interval (CI).