

**Official Title:**

Efficacy of Chiropractic Spinal Manipulative Therapy in Patients With  
Primary Chronic Low Back Pain: a Mechanistic Randomized Controlled  
Trial

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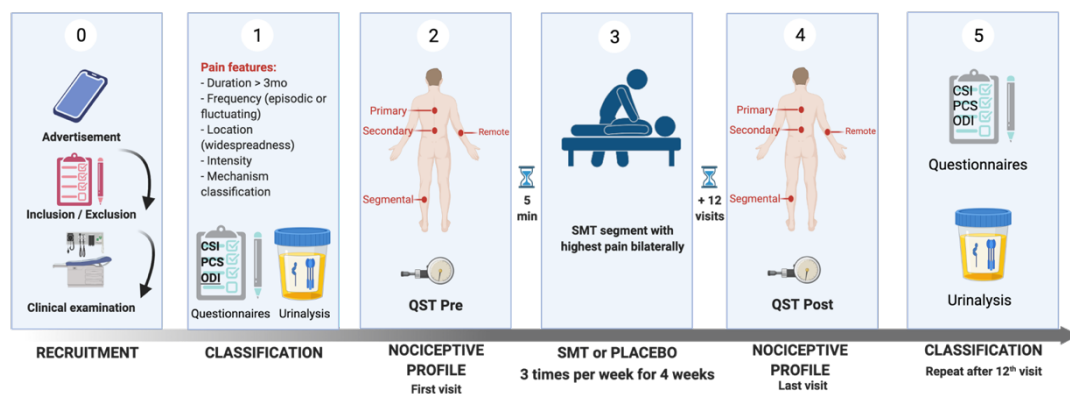
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## Project Protocol

### Experimental design

The study consists of a mechanistic randomized placebo-controlled clinical trial with a mixed experimental design, whose objective is to assess which variables that have been linked to central sensitization (CS) in chronic pain patients can predict the response of chronic low back pain (CLBP) patients to spinal manipulative therapy (SMT). In order to do this, clinical, psychophysical and inflammatory variables will be measured in CLBP patients, which will be exposed to either SMT or a placebo SMT for 12 visits over a 4-week period. Another group made up of healthy volunteers will be used to determine the reference values of the same variables in a healthy population and compare them with the clinical population, before and after exposure. The primary outcome measures and main clinical variables are pain intensity and disability. All variables will be measured before the first SMT session, as well as at the end of the twelfth and last session, except for pain intensity, which will be measured at the start of each session for exploratory reasons.



**Figure 1.** Study protocol for the clinical trial

### Patient sample

For this study, participants will be recruited through the network of contacts of MCC and the Chiropractic Research Network. To be included in the study, patient participants must be of legal age (18-70 years old), receive a diagnosis of primary CLBP of at least 3-month duration, with or without leg pain (according to a clinical examination carried out at the Madrid College of Chiropractic – MCC). If pain affecting the low back or lower limb is suspected to be predominantly of neuropathic origin, the patient will be excluded (Kosek et al., 2021). Additionally, patients will be excluded from the study if they present any of the following criteria: evidence of specific pathology as the cause of their CLBP, diagnosis of mental illness or pain of equal or higher intensity affecting the hand / thumb or regions near the lumbar spine, use of corticosteroids, opiates or anti-cytokine medication, pregnancy, lumbar fusion surgery or recent laminectomy, having received SMT in the 12 months prior to the beginning of the study (Gerhardt et al., 2017; Klyne et al., 2019; Smart et al., 2012). The only exception to this will be patients with a diagnosis of anxiety and depression, as these conditions are very frequently comorbid with CLBP (Gore et al., 2012; Wong et al., 2021) and may also suggest a CS phenotype (Aoyagi et al., 2019; Smart, et al., 2012). Candidates interested in participating in the study will initially complete a questionnaire with the selection criteria, either in person at the MCC or online. If the criteria are met, patients will be scheduled an appointment where they will be provided with an information sheet so that they can read all the information in detail and ask any questions they see fit, before signing the informed consent. Subsequently, they will be referred for a clinical examination (consisting of a case history and physical examination) that will confirm the diagnosis of primary CLBP (see Figure 1–0).

### **Healthy population sample**

Additionally, a sample of healthy volunteers will be recruited to be used as a reference for the psychophysical and inflammatory variables collected in the sample of CLBP patients. The reference values obtained from this group will be compared to those of the patient population. To be included in the study, participants must be of legal age (18-70 years old), and present no current or chronic pain condition, as well as not having received any diagnosis of a systemic, inflammatory, neurological or psychiatric condition. They will age/sex matched to the patient group receiving SMT.

### **Sample size calculation**

To determine the ideal number of participants, we have considered our first aim, which is to identify the variables linked to the CS phenotype that could help predict the response to treatment based on SMT for CLBP. In order to do this, we will perform a multiple regression analysis, using five independent variables as predictors, in particular the score on the pain catastrophizing scale (PCS) and central sensitization inventory (CSI) questionnaires (indicators of catastrophism and CS), the pressure pain thresholds (PPTs) in the primary pain area (marker of primary hyperalgesia), the urinary levels of the cytokine Tumor Necrosis Factor Alpha (TNF- $\alpha$ ; marker of inflammation) and finally the expectations of relief for each patient (indicative of potential placebo effects). The baseline values of these variables will be included in the multiple regression model. For each predictor variable, it is recommended to estimate about ten sample elements, therefore we predict that a sample size of 50 patients per group will be necessary (Ortega Calvo and Cayuela Dominguez, 2002). Taking into account two groups, one that will receive real SMT and the other placebo SMT, we will need a sample of 100 patients. An additional group of age and sex-matched healthy individuals without CLBP of the same size (50 participants) will be recruited to be used as a reference group, to determine

reference values in a healthy population for the predictor variables (questionnaires, PPTs, cytokines only)

Regarding the two main outcome variables (pain intensity and disability related to low back pain), we expect a reduction in pain and disability after one month in patients who receive 12 sessions of SMT compared to placebo. We aim to detect small to moderate effects since it is a one-month intervention in patients with chronic pain unresolved by other treatments over at least 3 months. Therefore, based on an effect size of  $f = 0.175$ , an alpha of 0.05, a power of 0.8 for 2 groups and 2 repeated measures (baseline and session 12), and a correlation between the repeated measures of 0.5, the size of the necessary sample is 34 patients per group and a total of 68 patients to detect statistically significant changes in clinical pain and disability. Therefore, our analysis based on the regression model to predict the clinical course provides us with a large enough size for both the first and second aims of this study.

### **Dependent variables**

In order to discriminate pain mechanisms between groups of patients, including CS mechanisms, five topics have been identified: clinical examination, questionnaires, quantitative sensory testing, laboratory tests, and imaging tests (Shraim et al., 2021). In the present study, all categories will be taken into account except the last one (only in the case of suspected neuropathic pain)

#### *Clinical examination variables*

During the case history taken, data on the characteristics of the patients' CLBP will be collected. Pain intensity will be the main primary outcome. Patients will evaluate the intensity of their CLBP at the current time, as well as the mean, minimum and

maximum pain throughout the preceding seven days or since the time of the previous session, once the study is underway, according to the brief pain inventory (de Andres Ares et al., 2015; Tan et al., 2004). Pain intensity will be collected via an online questionnaire without the presence of any investigator in every visit for descriptive reasons, although only the baseline and the final values will be used for statistical analyses. The other primary outcome will be the degree of disability provoked by CLBP. Upon completing the case history, patients will fill out the Oswestry low back disability index questionnaire (Alcántara-Bumbiedro et al., 2006), which will also be completed at the end of the study.

Additionally, other pain variables will be recorded at baseline for exploratory purposes: CLBP trajectory (duration and frequency) and localization. For the later, patients will draw the area affected by their pain on a tablet, using an application (Symptom Mapper) that will allow the degree of widespreadness of their pain to be calculated (Ellingsen et al., 2021). They may also indicate any pain present of less intensity outside the low back region, as any symptom of higher intensity will necessarily exclude the patient from the study. Additionally, clinicians will determine whether the CLBP is proportionate or disproportionate to the degree or nature of the injury or pathology, with a discrete or rather diffuse distribution, according to criteria that have been defined in the literature (Nijs et al., 2015; Smart, et al., 2012). A diffuse rather than a discrete distribution has been identified as a key criterion suggesting a CS phenotype (Kosek, et al., 2021; Smart, et al., 2012).

Finally, other variables will be reported such as the intake of pain medication compatible with the selection criteria, both at baseline and at the end of treatment. Similarly, whether the patient regularly smokes will be reported at baseline, since smoking has been associated with increased serum levels of pro-inflammatory cytokines.

(Petrescu et al., 2010), and the average number of hours of sleep which may help predict pain patterns and will be used for exploratory purposes (Edwards et al., 2008). Additionally, the presence of any chronic conditions (including pain conditions) that is comorbid with the CLBP will be recorded for exploratory purposes.

### *Questionnaires variables*

The PCS and central CSI questionnaires will be completed before the beginning and upon completion of the study (Cuesta-Vargas et al., 2016; Garcia Campayo et al., 2008). Both these variables will be introduced as predictors in the regression model, due to their intrinsic association with a CS phenotype. The PCS will be used to identify specific pain cognitions that are usually present in patients with a CS phenotype, this measure will be used to evaluate the association of CLBP with psychosocial factors described by Smart et al. (Smart, et al., 2012). The CSI is an excellent tool to identify patients compatible with CS mechanisms, particularly when using the cut-off value of 40/100 (Scerbo et al., 2018). Pre and post reference values of these questionnaires will be taken from the healthy population sample in the same time-frame.

In addition, the Beck Depression Inventory II (BDI-II) and the Generalized Anxiety Disorder scale (GAD) questionnaires will be used to screen and quantify symptoms of depression and anxiety (García-Campayo et al., 2010; Sanz et al., 2005). The scores in these questionnaires will be measured both at baseline and follow-up for exploratory purposes and to determine whether significant correlations exist between any of these variables and the primary outcomes of pain and disability.

### *Quantitative sensory testing*

Once the clinical examination and questionnaires have been completed, quantitative sensory testing (QST) based on the German protocol (Rolke et al., 2006; Starkweather et al., 2016) will be performed with the aim of evaluating thresholds and sensitivity to pressure pain and PPTs (see Figure 1–2). QST will consist of the exploration of the PPTs in deep tissues, using an algometer (Wagner Force Dial FPX, Greenwich, CT, USA). In addition to examining the pain detection threshold, patients will assess the intensity of the first stimulus above threshold, using a numerical rating scale between 0 (no pain) and 100 (maximum pain imaginable) (Pfau et al., 2014). Two measurements will be taken twice bilaterally at a rate of about 50 kPa/s, and the arithmetic mean of both the thresholds and sensitivities reported will be calculated. Two repetitions of these measurements provide excellent reliability in a population with LBP (Balaguier et al., 2016), while performing two repetitions per side of the lower back has been proposed to optimize inter-session reliability (Liew et al., 2021). PPTs will be performed over muscle tissue in 4 different locations. The main one will be 2.5 cm lateral to the spinous process in the erector spinae (Pfau, et al., 2014) of the vertebral segment with the highest clinical pain indicated by the patient and verified by palpation. This will allow the local segmental sensitivity to be assessed, which will be used as the predictor in the multiple regression model. These variables have been extensively studied in relationship to CS mechanisms in a CLBP population (den Bandt et al., 2019; Shraim, et al., 2021). In addition, for exploratory reasons, PPTs will be measured in the erector spinae four to six segments cranial to the most painful lumbar segment (heterosegmental sensitivity in a non-symptomatic segment: secondary hyperalgesia), on both lower limbs in the dermatome corresponding to the segment of highest clinical pain (dermatomal sensitivity), and in a control zone in both thenar eminences (widespread sensitivity). PPTs will be assessed during the initial examination and at the end of the study (see Figure 1). Reference values



will be taken in healthy volunteers in the same locations (lumbar segmental, heterosegmental, dermatomal, widespread) and the same time frame.

#### *Laboratory tests: inflammatory biomarkers in urine*

Before initiating the first treatment session and on the day of the last one, urine samples will be collected from all patients (first morning micturition), which will be immediately stored at -20°C (see Figure 1–1). Additionally, the first morning micturition will be collected twice from healthy individuals in the same timeframe (two samples with a 4-week delay). Urine concentrations of tumor necrosis factor alpha (TNF- $\alpha$ ) will be measured. For each sample, the urine concentrations of each cytokine (in pg / ml) and creatinine (mg / dl) will be measured. The cytokine to creatinine ratio (in pg / mg) will be calculated to correct for differences in urine volumes (Ortega et al., 2019). TNF- $\alpha$  values will be used for the regression model, since it has been repeatedly found to be elevated in CLBP patients and may respond to a treatment based on SMT (Lim et al., 2020; Morris et al., 2020; Teodorczyk-Injeyan et al., 2006; Teodorczyk-Injeyan et al., 2021).

#### *Expectations and effectiveness of the blinding*

Before initiating treatment, each participant will be asked about their expectations of pain relief upon completion of the study. To do this, they will give a verbal evaluation using an analog scale with the descriptors -100, equivalent to "total pain relief," 0, equivalent to "no change," up to +100, equivalent to "maximum pain increase". Expectations of pain relief will be used as the fifth predictor in the regression model, allowing to identify the contribution of patients' expectations, which as an important part of the placebo effect and may predict the response to treatment for chronic pain (Cormier et al., 2016).

In addition, in order to confirm the efficacy of the placebo intervention, the participants will respond before the second, seventh and last (twelfth) sessions to the following question: “Do you think that the treatment you have received is a real chiropractic treatment for back pain?”. A second question will ask patients about the degree of certainty with respect to the previous question on a numerical rating scale of 0–10, with 0 being total uncertainty and 10 being absolute certainty (Chaibi et al., 2015). These questions will be answered in an online questionnaire without the presence or interference of any investigators. Potential differences to these questions between the two groups will be examined.

#### *Adverse events reporting*

At the beginning of any of the follow-up SMT or placebo sessions, each patient will complete an online questionnaire without the presence of the investigator, answering whether they have suffered any adverse effects that they feel could be related to the treatment received. A clinical trial identified the following adverse effects as those most commonly reported after chiropractic treatment based on lumbar SMT: muscle stiffness, increased pain, radiating discomfort, and others (Walker et al., 2013). Following the example of this study, adverse effects will be classified into these categories, in addition to indicating whether they were triggered immediately, up to 24 hours, or more than 24 hours after the previous session, whether their duration was of minutes, hours (< 24 hours), between 24 and 48 hours, or longer than 48 hours (Walker, et al., 2013), and according to their intensity (very mild, mild, moderate, severe, very severe). A 3-point increase in the NRS-11 or the reporting of moderate to severe adverse events in three consecutive visits will raise the alert and the patient will be interviewed to determine whether care should be interrupted.

## **Independent variables**

A computer application (random-number generator) will be used to generate a randomization sequence and thus assign each patient to one of the two groups. The SMT group will receive 3 times a week for 4 weeks a session (total of 12) based on SMT of the most painful vertebral segment (see Figure 1–3). The SMT will be performed by a chiropractor with twenty years of experience in the techniques. They will be performed with the patient positioned in the lateral decubitus position, and applying a high-speed, low-amplitude force on each side of the manipulated segment, with the aim of generating at least one joint cavitation (perceptible sound). For this, the chiropractor will use a contact with the hypothenar surface or the last phalanx of the 2<sup>nd</sup> and / or 3<sup>rd</sup> fingers of the hand with the spinous process in question. In case of not perceiving a cavitation or joint movement, the SMT will be repeated once at the corresponding side. For the placebo group, the sham SMT will be performed with the patient in the same position in the lateral decubitus position, with the lower leg extended and the upper leg flexed, and an unintended force will be applied to the gluteal region (Chaibi, et al., 2015), also bilaterally (Figure 1–3). Any cavitation perceived during both real and placebo SMT will be recorded. Healthy volunteers will not receive any intervention during the same time frame of 4 weeks.

## **Procedures**

The study will have a total estimated duration of one year, during which each patient will participate in 12 sessions divided into 3 weekly sessions for 4 weeks (see Figure 1). Once this phase of the study has been completed, patients who had been assigned to the placebo group will be offered the possibility of receiving the equivalent

“real” treatment at the MCC free of charge. Patients who received SMT may continue at their own cost. In addition, 4 weeks after the end of the study, patients will be contacted to request that they provide data on their pain intensity and disability, as described above, as well as responses to the questionnaires proposed as follow-up. Healthy volunteers will participate in two visits, baseline and follow-up after 4 weeks.

### **Safety protocols for COVID-19**

All participants will be treated at each visit in a properly ventilated and disinfected room, including the table on which measurements will be taken and SMT will be performed. The use of the mask will be mandatory for the patients, while the investigator and his assistants will use an N95 mask at all times. Before touching the patient, the latter will be obliged to disinfect their hands with hydroalcoholic gel. At the end of the session, all surfaces and instruments will be disinfected, and the room will be completely ventilated for a minimum of 5 minutes.

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