



# Overcoming placebo-related challenges in manual therapy trials: The ‘whats and hows’ and the ‘touch equality assumption’ proposals

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## ABSTRACT

Due to the significant increase in interest in placebos, biomedical scientists have incorporated placebo innovations into a modern methodological research scenario in order to increase the quality of clinical studies. Indeed, the randomised-controlled trial design has changed dramatically, and these changes have had an impact on manual therapy research as well. The present paper outlines the main difficulties that placebo-controlled trials pose for research in manual therapy, for example, designing ineffective sham protocols, the role of touch in triggering neurobiological responses, or the unique specificity of manual therapies. The paper then offers suggestions on how to overcome such challenges, for example by providing a definition of ‘specificity’ in the context of manual therapies, and specifically osteopathy, suggesting how to design adequate sham procedures, and by introducing the so-called ‘touch equality assumption’.

Over time the evolving conceptualization of the placebo effect and its mechanisms has highlighted several challenges in both clinical and research fields. The placebo controlled randomised-controlled trial (RCT) evolved to overcome those challenges [1]. Manual therapy RCTs that use a placebo manual control present some interesting manual therapy-related issues that remain unaddressed. The present paper outlines the main difficulties that placebo-controlled trials pose for research in manual therapy and offers suggestions on how to overcome them.

Defining the concept of placebo treatment is surprisingly challenging [2–7]. This may be due to the tumultuous history of the placebo construct itself [8], the multiple frameworks (e.g. neurobiological, clinical, etc. [9, 10]), and the different contexts in which placebos are used (pharmacology, psychotherapy, complementary and alternative medicine). For instance, the dichotomies active/inactive and effective/ineffective have been commonly used to underline the difference between a treatment and a placebo. However, such dichotomies do not adequately reflect the placebo phenomenon. Indeed, it is misleading to define placebo drugs as inactive, ineffective, or inert, because even a lactose pill, often chosen as a placebo, has measurable effects [11]. The more recent specific/nonspecific lexical dichotomy [12–14] better reflects the underlying

paradigm of a clinical trial: the term specific refers to the therapeutic component included only in the intervention arm of the trial. In this way, what the trial is measuring is methodologically clear: a specific therapeutic modality, included only in the intervention arm. The placebo intervention therefore does not constitute a control lacking any biological activity, but rather “lacks the biological activity of interest” [15].

As far as manual therapy trials are concerned, several placebo approaches have been proposed over the years; examples from osteopathy include detuned ultrasound [16], placebo pills [17], random slight touch [18], and others [19]. Applying the specific/nonspecific paradigm clarifies four issues that have long characterized the placebo controls in manual therapy randomized controlled trials (mtRCTs) (Fig. 1).

- (1) Firstly, some authors argued that it is difficult to design an ineffective sham protocol [17,20]. Others proposed to define a standard manual procedure as placebo if it demonstrates the inability to modify objective outcome measures, like heart rate variability [21], or pressure pain threshold [22]. In contrast, the specific/nonspecific paradigm suggests that it is not important whether the sham protocol is ineffective: it matters that it is nonspecific [23,24].

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**List of abbreviations**

RCT	Randomized Controlled Trial
mtRCTs	manual therapy Randomized Controlled Trials
ASE	Assumption of Specific Efficacy
TEA	Touch Equality Assumption
OMT	Osteopathic Manipulative Treatment

(2) Several studies demonstrated that touch alone could significantly contribute to placebo effects in manual therapy [2,25–27]. However, touching is not a manual technique per se, due to its non-specificity [23,28]. Multiple studies applied non-therapeutic manual approaches in a very different fashion compared to the technique used, for example using i.e. “*functional sham technique*”, characterized by soft touch, or simple gentle touch as controls for high velocity low amplitude techniques [22]. Others used sham therapies with non-manual components [29], for example detuned ultrasound machines [22], that do not match the non-specific features of inter-human physical contact. In order to highlight the contribution of specific aspects of touch, it has instead been suggested that the sham therapy should “*mimic*

the real intervention” [19], especially the non-specific features of touch (e.g., time of manual contact, targeted anatomical areas, and type of movement).

- (3) The specific active agents of manual therapy have not been fully identified. It is therefore important to ensure that the sham treatment does not possess the same attributes as the intervention, which could result in a “*misclassification error*” [30]. Even among experts in the field, beliefs about what constitutes an appropriate placebo in manual therapy are very diverse. Some authors conclude that as long as the biological basis for spinal manipulative therapy remains unclear, the issues regarding sham procedures in manual therapy trials will not be solved [25]. The mechanism through which a technique works is not, however, the primary aspect defining its specificity: it is unnecessary to know how a technique works to know that it elicits a certain effect. Indeed, the scope of the trial is to test efficacy, not the mechanism of action [31].
- (4) Licciardone [32] questioned whether it is possible or not to identify the specificity of the osteopathic treatment because osteopaths “*have long embraced an approach to patient care that optimizes patient-physician rapport and focuses on an array of psychosocial and individual health factors*”. We agree, even more so when considering the latest updates in manual therapy related to

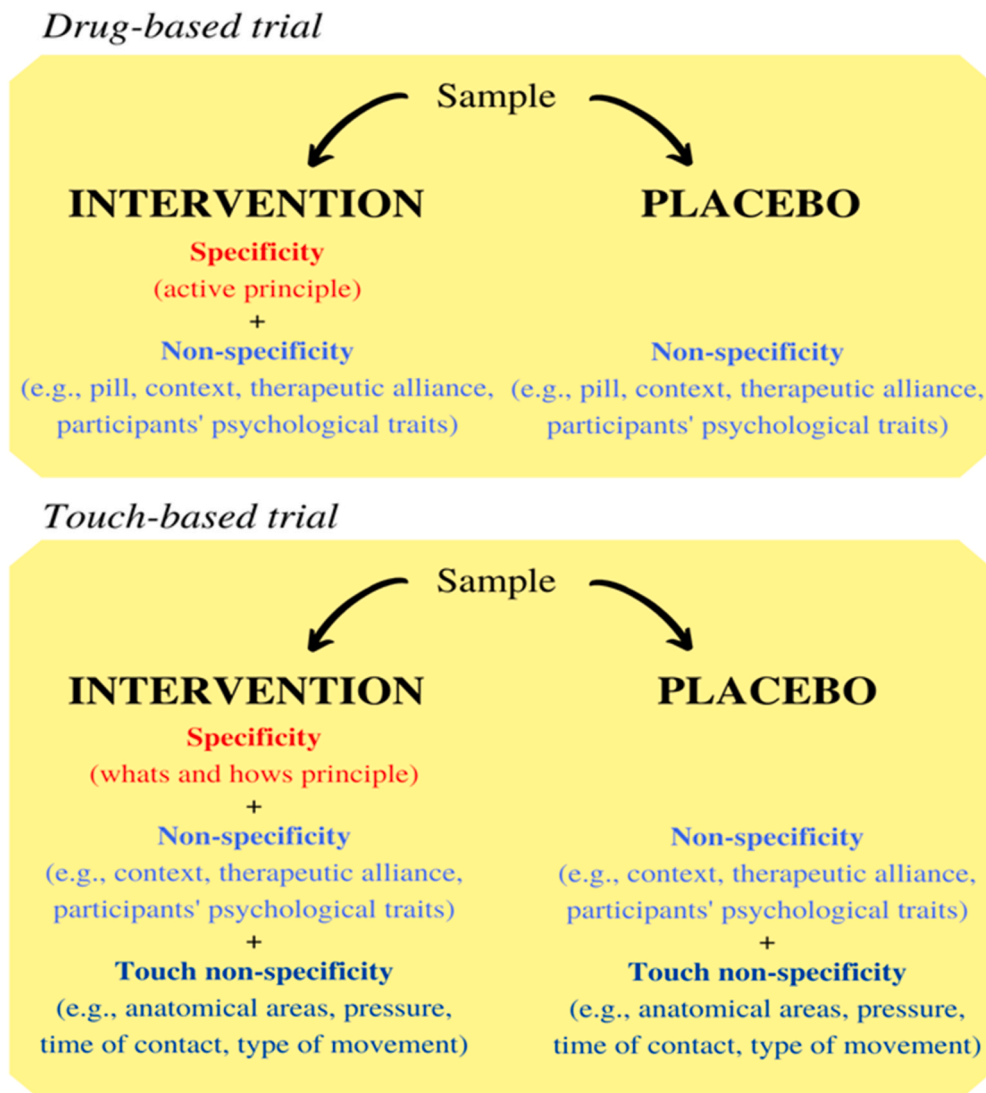


Fig. 1. Specificity and non-specificity in drug-based and touch-based research trial.

the biopsychosocial model [33,34], the role of placebo effect [35] and the concepts of therapeutic alliance and shared clinical decision-making process [36]. But the equivalent happens in pharmacological research. In pharmacological trials, as in everyday clinical practice, the active therapeutic component is not administered in a sensory vacuum [37,38]. While the contextual, or non-specific, factors are fundamental in eliciting the clinical response [39], the specific component is nevertheless known. Similarly, an osteopathic treatment, like other manual approaches [11,39], cannot be administered in a sensory vacuum, but identifying the specificity of osteopathy becomes relevant in designing appropriate clinical trials.

The scientific and the clinical community should agree about what constitutes the specificity of a manual approach (in our case, osteopathy). We propose that the specificity of osteopathy can pertain to both the techniques and the more comprehensive person-centered approach. The single osteopathic technique or approach can be defined as *the sequential procedure(s) applied by the practitioner in order to treat bodily areas with particular attention paid to the somatic dysfunction*. Expanding the definition, the clinical reasoning and the shared decision-making process should also be considered. Indeed, there are studies that investigate a certain technique [40] and studies using a person-centered approach [41].

Finally, to analyse the specific efficacy of a treatment, it is relevant to measure the effect on the experimental group minus the effect on the control group [42]. However, this assumption of specific efficacy (ASE) is strictly based on the so-called equality assumption (EA), which implies that the non-specific factors are matched between control and experimental group [43]. The concept is particularly relevant for the purpose of this discussion.

The EA is important for all the contextual aspects of a treatment (e.g., setting, patients' characteristics). Considerations of equality in manual therapy trials should take touch into account, as non-specific (or non-skilled) touch has shown to produce a plethora of neuro-biological

events, able to significantly modify the psycho-neuro-immune-endocrine response of the body [11,44–49], including inducing afferent stimulations [30,50] with potential autonomic consequences (see McGlone et al., 2014 for details on c-tactile fibers [51]; see D'Alessandro et al., 2016 for the interoceptive paradigm [52]). Several studies demonstrated that the touch variable could significantly contribute to placebo effects. For example, Cerritelli et al. [53] showed that sham-touch induced significant short-term effects on patient-reported outcome measures in a sample of chronic migraine patients compared to treatment-as-usual. However, the touch-sham group showed a significantly smaller response compared to the treatment group. It would therefore be useful to divide touch in two components: the specificity of the manual treatment and the non-specificity of touch itself. The EA in manual therapy could be accordingly adapted into a Touch Equality Assumption (TEA) [25,30,54], which should report all features of touch, including the bodily areas contacted and the style and type of treatment (e.g. passive/active role of the patient, light touch/thrust) (Fig. 2). To ensure an adequate comparison of the experimental and sham/placebo groups, it is necessary to design interventions and placebo-controls exposed to the same touch choreography. An example in which this condition has not been achieved comes from Antolinos-Campillo et al. [55]: regarding the intervention arm the authors report that *"The subject was in the supine position, and the therapist sat at the head of the table and placed both hands under the subject's head, contacting the space between the occipital condyles and the spinal process of the second cervical vertebra with the fingertips. Constant and painless pressure was exerted upward, towards the therapist"*. Regarding the sham arm the authors state that *"performing active movement of flexion/extension of the hip and knee joints on the opposite side to which the measurement was taken, according to the response to the ULNT-1"*. In this case, the sham approach does not incorporate the TEA, applying a different manual approach to different body areas. Researchers in the field of manual therapies should develop an adequate sham procedure for each approach and technique to be tested. In an osteopathic trial, for example, sham light touch could be an appropriate sham procedure for

## Touch Equality Assumption

Why is it important that the touch should be the same in both intervention and sham groups?

<p><b>Type of touch</b></p> <p>Different type of touch could differently influence the CNS: for example, light touch activate CT-fibers that have a homeostatic/emotional value.</p>
<p><b>Amount of pressure</b></p> <p>A greater pressure could be perceived more invasive; this in turn could be perceived as more effective</p>
<p><b>Type of movement + patient positioning</b></p> <p>Some techniques need the patient's active participation giving to the patient an immediate feeling of control/not control of a given part of body.</p>
<p><b>Areas of contact</b></p> <p>Some body areas (e.g., the head) could have a more powerful placebo significance. Furthermore there is a link with the type of touch since the CT-fibers are heterogeneously distributed</p>
<p><b>Time of contact</b></p> <p>A longer time of contact increases the non-specific effects of touch</p>
<p><b>Practitioners' characteristics</b></p> <p>Characteristics of practitioners (e.g., communication abilities, experience, empathy, appearance) could affect the way in which the subject perceives the touch itself.</p>

Fig. 2. Characteristics of the Touch Equality Assumption.

cranial osteopathy or balanced ligamentous tension techniques; whereas sham manipulation could control for structural approaches like high velocity low amplitude techniques. Clearly, the development of appropriate sham procedures comes after the identification of the specific characteristics of the tested technique. For example, if the operator's tactile attention is considered a specific and distinct characteristic of the technique, the selected sham procedure should exclude the operator tactile attention, while all the other elements are maintained equal [17, 56].

Applying these concepts to manual therapy trials, every paper should report:

- 1) the 'whats' of the intervention, defining its characterising elements (i. e., patients' need-based treatment/treatment protocol, the concept of barrier/neutral point, the haptic level of attention, the somatic dysfunction addressed).
- 2) the 'hows', describing how the operator performs the techniques, for how long or until when (e.g., until tension's release) how the operator maintains the tactile attention, how the operator tailors the clinical reasoning to the patients involved in the trial.
- 3) the 'how not to', highlighting the description of strategy used by the researchers to avoid the specificity in the sham technique, maintaining the EA and the TEA (Fig. 3).

If we apply this distinction to clinical trials, it is possible to critically appraise the *whats* and *hows* as presented in the following examples.

1. **'What' Not specified, 'How' Not specified, 'How-not-to' Not specified** - An example is Hubert et al. [56]. The authors only list the techniques performed without explaining the principles guiding them or indicating how to perform them. Regarding the sham group, the authors only state: "Patients in the sham OMT group received light touch at the skull and at the sacrum" with no indication about 'how not to' reach the specificity.

- 2 **'What' Specified, 'How' Not specified, 'How not to' Not specified** - For example, Florance et al. [57] described the principles of direct and indirect techniques, therefore exploring the 'whats', but did not report how the techniques were performed, not even through external references, and did not give any indication on how to avoid the specificity in the sham therapy.

- 3 **'What' Specified, 'How' Specified, 'How not to', Not specified** - Rolle et al. [58] listed the performed techniques. Although no description of technique is present, they provided references, and so we can assume that the entire specificity has been reported (what + how). In the sham arm they only stated "assessing the patient's cranial rhythmic impulse, spending a similar amount of time as used for OMTh techniques in the treatment group". Please, note that the 'how not to' implement the specificity is missing, and paradoxically, the authors included a specific feature of cranial osteopathy in the sham group (i. e testing the cranial system for a long time). The strategy to disturb the attention or the intention of the operator should be described.

- 4 **'What' Specified, 'How' Specified, 'How not to' Specified** - Giles et al. [59] stated that: "The OMT protocol involved the treatment of the subject's posterior cervical musculature by using the two soft tissue techniques of kneading and stretching. Kneading is a technique in which a force is applied perpendicular to the long axis of the muscle, whereas stretching is a separation of the origin and insertion of a muscle. This soft tissue treatment was performed for approximately 5 minutes. Following this, the treatment provider performed a suboccipital (O-A) decompression for 2–3 minutes. To achieve the O-A decompression, the treatment provider used his or her index fingers to contact the occiput as near to the occipital condyles as possible. The index fingers were reinforced with the middle fingers. Tension was then applied toward the orbits to make firm contact with the occiput and constant traction was directed superiorly. Minor adjustments in all three planes of motion (flexion/extension, sidebending, and rotation) were made as needed to maintain ligamentous balance". Regarding the sham intervention the authors indicate that: "A sham treatment protocol involved the placement of fingers near the

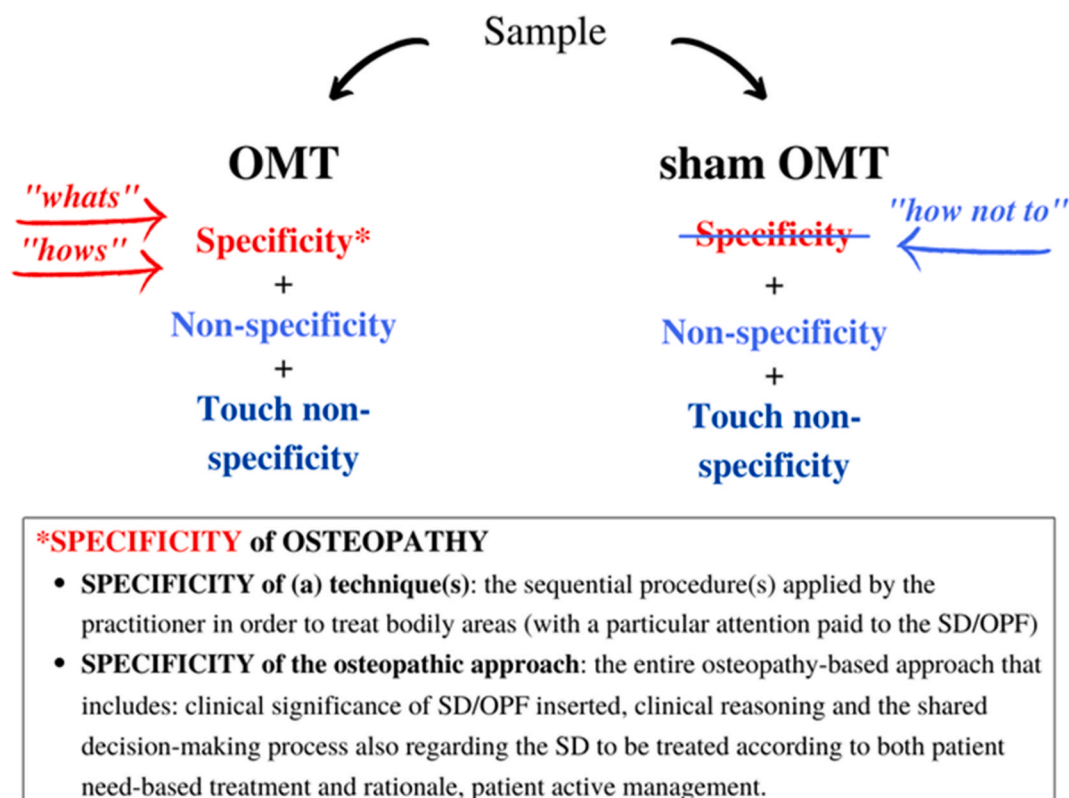


Fig. 3. Elements of the Touch Equality Assumption: whats, hows and how not to.



occipital condyles. However, no tension was applied in any direction, the subject's head was simply held in the treatment provider's hands". In this case, all aspects of the intervention and sham therapy were clearly reported.

The above mentioned possibilities have three important consequences. Firstly, without a detailed description of such elements, researchers might try to replicate sham procedures that were developed in and for a different methodological context. For instance, Ponzio et al. [60] replicated the same sham procedure used in Ruffini et al. [61], but the two studies tested different approaches (direct/indirect techniques versus only indirect techniques, respectively). Secondly, researchers may use different sham procedures to control for the same treatment. Examples are Catro-Sanchez et al. [62] and Haller et al. [63]: both studies tested the fourth ventricle compression technique but used different sham/placebo procedures (disconnected magnetotherapy, and light touch applied on standardized anatomic areas, equivalent to those treated with craniosacral therapy, for 2 mins each time, respectively). This might yield different or even opposite trial results preventing the possibility to perform meta-analysis [20]. Thirdly, the TEA indirectly addresses the issue of the credibility of the sham treatment, already questioned by some authors [17,23,25,64,65]. We recommend, however, to assess the blinding success and the credibility of the interventions, as several mRCTs have already done [17,61,66].

The TIDieR-Placebo checklist [67] could be a useful tool for manual therapy trials, as it guides the description of placebo and sham controls. The what and how of the TIDieR-Placebo are not meant for manual therapy trials. In our proposal, 'whats', 'hows', and 'how-not-tos' are strictly relative to the manual-based scenario, and specifically adapted for osteopathy.

## Conclusions

A comprehensive reporting of 'whats', 'hows' and 'how-not-tos' would allow for a more coherent methodological paradigm in osteopathic research, increasing the internal validity of the trial. This would, in return, clarify the peculiar contribution of osteopathy to the treatment and management of a given clinical condition, which is crucial in the multidisciplinary context of modern healthcare.

Designing the methodology of appropriate sham procedures begins with a shared consensus about the specificity of its counterpart. Reflecting and reporting on placebo procedures would help highlight the distinctive characteristics of a given manual approach, and to differentiate it from other similar therapies.

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## Declaration of competing interest

The authors declare that they have no competing interests.

## References

- Enck P, Klosterhalfen S. Placebos and the placebo effect in drug trials. *Handb Exp Pharmacol* 2019;260:399–431.
- Ernst E. Placebo: new insights into an old enigma. *Drug Discov Today* 2007;12(9–10):413–8.
- Grünbaum A. The placebo concept in medicine and psychiatry. *Psychol Med* 1986;16(1):19–38.
- Hernández A, Baños J-E, Llop C, Farré M. The definition of placebo in the informed consent forms of clinical trials. *PLoS One* 2014;9(11):e113654.
- Howick J, Friedemann C, Tsakok M, Watson R, Tsakok T, Thomas J, et al. Are treatments more effective than placebos? A systematic review and meta-analysis. *PLoS One* 2013;8(5):e62599.
- Hróbjartsson A. What are the main methodological problems in the estimation of placebo effects? *J Clin Epidemiol* 2002;55(5):430–5.
- Moerman DE, Jonas WB. Deconstructing the placebo effect and finding the meaning response. *Ann Intern Med* 2002;136(6):471.
- Macedo A, Farré M, Banos J-E. Placebo effect and placebos: what are we talking about? Some conceptual and historical considerations. *Eur J Clin Pharmacol* 2003;59(4):337–42.
- Annoni M. Better than nothing: a historical account of placebos and placebo effects from modern to contemporary medicine. *International Review of Neurobiology*. Elsevier; 2020. p. 3–26.
- Benedetti F. Placebo effects: from the neurobiological paradigm to translational implications. *Neuron* 2014;84(3):623–37.
- Rossetti G, Testa M. Manual therapy RCTs: should we control placebo in placebo control? *Eur J Phys Rehabil Med* 2018;54(3):500–1.
- Clifford V. The placebo mystique: implications for clinical trial methodology: placebo use in clinical trials. *J Paediatr Child Health* 2011;47(6):361–6.
- Kampermann L, Nestoriuc Y, Shedden-Mora MC. Physicians' beliefs about placebo and nocebo effects in antidepressants – an online survey among German practitioners. *PLoS One* 2017;12(5):e0178719.
- Leckridge RW. Human effect is important. *BMJ (Clin Res ed)* 2008;336(7653):1087.2.
- Silva MA, Duarte GS, Camara R, Rodrigues FB, Fernandes RM, Abreu D, et al. Placebo and nocebo responses in restless legs syndrome: a systematic review and meta-analysis. *Neurology* 2017;88(23):2216–24.
- Hensel KL, Pacchia CF, Smith ML. Acute improvement in hemodynamic control after osteopathic manipulative treatment in the third trimester of pregnancy. *Compl Ther Med* 2013;21(6):618–26.
- Wynne MM, Burns JM, Eland DC, Conatser RR, Howell JN. Effect of counterstrain on stretch reflexes, hoffmann reflexes, and clinical outcomes in subjects with plantar fasciitis. *J Am Osteopath Assoc* 2006;106(9):547–56.
- Cardoso-de-Mello-E-Mello-Ribeiro AP, Rodríguez-Blanco C, Riquelme-Agulló I, Heredia-Rizo AM, Ricard F, Oliva-Pascual-Vaca Á. Effects of the fourth ventricle compression in the Regulation of the autonomic Nervous system: a randomized control trial. *Evidence-based complementary and alternative Medicine*, vol. 2015. eCAM; 2015. p. 148285.
- Cerritelli F, Verzella M, Cicchitti L, D'Alessandro G, Vanacore N. The paradox of sham therapy and placebo effect in osteopathy: a systematic review. *Medicine* 2016;95(35):e4728.
- Barral P, Klouche S, Barral N, Lemoulec Y-P, Thés A, Bauer T. Preoperative osteopathic manipulative therapy improves postoperative pain and reduces opioid consumption after total knee arthroplasty: a prospective comparative study. *J Am Osteopath Assoc* 2020;120(7):436.
- Henley C, Wilson T. Use of beat-to-beat cardiovascular variability data to determine the validity of sham therapy as the placebo control in osteopathic manipulative medicine research. *J Am Osteopath Assoc* 2014;114(11):860–6.
- Lougee H, Johnston RG, Thomson OP. The suitability of sham treatments for use as placebo controls in trials of spinal manipulative therapy: a pilot study. *J Bodyw Mov Ther* 2013;17(1):59–68.
- Hawk C, Long CR, Rowell RM, Gudavalli MR, Jedlicka J. A randomized trial investigating a chiropractic manual placebo: a novel design using standardized forces in the delivery of active and control treatments. *J Alternative Compl Med* 2005;11(1):109–17.
- Manzotti A, Viganoni C, Lauritano D, Bernasconi S, Paparo A, Risso R, et al. Evaluation of the stomatognathic system before and after osteopathic manipulative treatment in 120 healthy people by using surface electromyography. *Int J Environ Res Publ Health* 2020;17(9).
- Hancock MJ, Maher CG, Latimer J, McAuley JH. Selecting an appropriate placebo for a trial of spinal manipulative therapy. *Aust J Physiother* 2006;52(2):135–8.
- Vernon H, MacAdam K, Marshall V, Pion M, Sadowska M. Validation of a sham manipulative procedure for the cervical spine for use in clinical trials. *J Manipul Physiol Therapeut* 2005;28(9):662–6.
- Vernon HT, Triano JJ, Ross JK, Tran SK, Soave DM, Dinulos MD. Validation of a novel sham cervical manipulation procedure. *Spine J* 2012;22(11):1021–8.
- Jamison JR. Nonspecific intervention in chiropractic care. *J Manipul Physiol Therapeut* 1998;21(6):423–5.
- Licciardone JC, Buchanan S, Hensel KL, King HH, Fulda KG, Stoll ST. Osteopathic manipulative treatment of back pain and related symptoms during pregnancy: a randomized controlled trial. *Am J Obstet Gynecol* 2010;202(1):e1–8. 43.
- Hawk C, Long CR, Reiter R, Davis CS, Cambron JA, Evans R. Issues in planning a placebo-controlled trial of manual methods: results of a pilot study. *J Alternative Compl Med* 2002;8(1):21–32.
- Benedetti F. *Nascita e sviluppo della medicina scientifica. Il cervello del paziente. Le neuroscienze della relazione medico-paziente*. Giovanni Fioriti Editore; 2012. p. 36.
- Licciardone JC, Russo DP. Blinding protocols, treatment credibility, and expectancy: methodologic issues in clinical trials of osteopathic manipulative treatment. *J Am Osteopath Assoc* 2006;106(8):457–63.
- Abrosimoff M, Rajendran D. 'Tell me your story' - how osteopaths apply the BPS model when managing low back pain - a qualitative study. *Int J Osteopath Med* 2020;35:13–21.
- Zegarar-Parodi R, Draper-Rodi J, Cerritelli F. Refining the biopsychosocial model for musculoskeletal practice by introducing religion and spirituality dimensions into the clinical scenario. *Int J Osteopath Med* 2019;32:44–8.
- Bialosky JE, Bishop MD, Penza CW. Placebo mechanisms of manual therapy: a sheep in Wolf's clothing? *J Orthop Sports Phys Ther* 2017;47(5):301–4.
- Baroni F, Ruffini N, D'Alessandro G, Consorti G, Lunghi C. The role of touch in osteopathic practice: a narrative review and integrative hypothesis. *Compl Ther Clin Pract* 2021;42:101277.

- [37] Benedetti F. Placebo and the new physiology of the doctor-patient relationship. *Physiol Rev* 2013;93(3):1207–46.
- [38] Frisaldi E, Piedimonte A, Benedetti F. Placebo and nocebo effects: a complex interplay between psychological factors and neurochemical networks. *Am J Clin Hypn* 2015;57(3):267–84.
- [39] Testa M, Rossetini G. Enhance placebo, avoid nocebo: how contextual factors affect physiotherapy outcomes. *Man Ther* 2016;24:65–74.
- [40] Abenavoli A, Badi F, Barbieri M, Bianchi M, Biglione G, Dealessi C, et al. Cranial osteopathic treatment and stress-related effects on autonomic nervous system measured by salivary markers: a pilot study. *J Bodyw Mov Ther* 2020;24(4): 215–21. Epub 2020/11/22.
- [41] Cerritelli F, Chiacchiarella P, Gambi F, Saggini R, Perrucci MG, Ferretti A. Osteopathy modulates brain-heart interaction in chronic pain patients: an ASL study. *Sci Rep* 2021;11(1):4556. Epub 2021/02/27.
- [42] Annoni M, Boniolo G. Learning by difference: placebo effects and specific efficacy in pharmacological RCTs. In: LaCaze A, Osimani B, editors. *Uncertainty in pharmacology: Epistemology, methods, and decisions*. Cham: Springer International Publishing; 2020. p. 211–30.
- [43] Rief W, Bingel U, Schedlowski M, Enck P. Mechanisms involved in placebo and nocebo responses and implications for drug trials. *Clin Pharmacol Ther* 2011;90(5): 722–6.
- [44] Feldman R, Singer M, Zagoory O. Touch attenuates infants' physiological reactivity to stress. *Dev Sci* 2010;13(2):271–8.
- [45] Gentsch A, Panagiotopoulou E, Fotopoulou A. Active interpersonal touch gives rise to the social softness illusion. *Curr Biol* 2015;25(18):2392–7.
- [46] Korosi A, Baram TZ. Plasticity of the stress response early in life: mechanisms and significance. *Dev Psychobiol* 2010;52(7):661–70.
- [47] Mancini F, Beaumont A-L, Hu L, Haggard P, Iannetti GDD. Touch inhibits subcortical and cortical nociceptive responses. *Pain* 2015;156(10):1936–44.
- [48] Paloyelis Y, Krahé C, Maltezos S, Williams SC, Howard MA, Fotopoulou A. The analgesic effect of oxytocin in humans: a double-blind, placebo-controlled cross-over study using laser-evoked potentials. *J Neuroendocrinol* 2016;28(4).
- [49] Uvnäs-Moberg K, Handlin L, Petersson M. Self-soothing behaviors with particular reference to oxytocin release induced by non-noxious sensory stimulation. *Front Psychol* 2015;5.
- [50] Chaibi A, Šaltytė Benth J, Bjørn Russell M. Validation of placebo in a manual therapy randomized controlled trial. *Sci Rep* 2015;5(1):11774.
- [51] McGlone F, Wessberg J, Olausson H. Discriminative and affective touch: sensing and feeling. *Neuron* 2014;82(4):737–55.
- [52] D'Alessandro G, Cerritelli F, Cortelli P. Sensitization and interoception as key neurological concepts in osteopathy and other manual medicines. *Front Neurosci* 2016;10:100.
- [53] Cerritelli F, Ginevri L, Messi G, Caprari E, Di Vincenzo M, Renzetti C, et al. Clinical effectiveness of osteopathic treatment in chronic migraine: 3-Armed randomized controlled trial. *Compl Ther Med* 2015;23(2):149–56.
- [54] Hawk C, Azad A, Phongphua C, Long CR. Preliminary study of the effects of a placebo chiropractic treatment with sham adjustments. *J Manipulat Physiol Therapeut* 1999;22(7):436–43.
- [55] Antolinos-Campillo PJ, Oliva-Pascual-Vaca A, Rodríguez-Blanco C, Heredia-Rizo AM, Espí-López GV, Ricard F. Short-term changes in median nerve neural tension after a suboccipital muscle inhibition technique in subjects with cervical whiplash: a randomised controlled trial. *Physiotherapy* 2014;100(3):249–55.
- [56] Hubert D, Soubeiran L, Gourmelon F, Grenet D, Serreau R, Perrodeau E, et al. Impact of osteopathic treatment on pain in adult patients with cystic fibrosis—a pilot randomized controlled study. *PLoS One* 2014;9(7):e102465–.
- [57] Florance BM, Frin G, Dainese R, Nébot-Vivinus MH, Marine Barjoan E, Marjoux S, et al. Osteopathy improves the severity of irritable bowel syndrome: a pilot randomized sham-controlled study. *Eur J Gastroenterol Hepatol* 2012;24(8): 944–9. Epub 2012/05/02.
- [58] Rolle G, Tremolizzo L, Somalvico F, Ferrarese C, Bressan LC. Pilot trial of osteopathic manipulative therapy for patients with frequent episodic tension-type headache. *J Am Osteopath Assoc* 2014;114(9):678–85.
- [59] Giles PD, Hensel KL, Pacchia CF, Smith ML. Suboccipital decompression enhances heart rate variability indices of cardiac control in healthy subjects. *J Alternative Compl Med* 2013;19(2):92–6. Epub 2012/09/22.
- [60] Ponzio V, Cinnera AM, Mommo F, Caltagirone C, Koch G, Tramontano M. Osteopathic manipulative therapy potentiates motor cortical plasticity. *J Am Osteopath Assoc* 2018;118(6):396–402.
- [61] Ruffini N, D'Alessandro G, Mariani N, Pollastrelli A, Cardinali L, Cerritelli F. Variations of high frequency parameter of heart rate variability following osteopathic manipulative treatment in healthy subjects compared to control group and sham therapy: randomized controlled trial. *Front Neurosci* 2015;9:272.
- [62] Castro-Sánchez AM, Matarán-Penarocha GA, Sánchez-Labraca N, Quesada-Rubio JM, Granero-Molina J, Moreno-Lorenzo C. A randomized controlled trial investigating the effects of craniosacral therapy on pain and heart rate variability in fibromyalgia patients. *Clin Rehabil* 2011;25(1):25–35.
- [63] Haller H, Lauche R, Cramer H, Rampp T, Saha FJ, Ostermann T, et al. Craniosacral therapy for the treatment of chronic neck pain: a randomized sham-controlled trial. *Clin J Pain* 2016;32(5):441–9.
- [64] Başoğlu M, Marks I, Livanou M, Swinson R. Double-blindness procedures, rater blindness, and ratings of outcome. Observations from a controlled trial. *Arch Gen Psychiatr* 1997;54(8):744–8.
- [65] Koes BW. How to evaluate manual therapy: value and pitfalls of randomized clinical trials. *Man Ther* 2004;9(4):183–4.
- [66] Tramontano M, Cerritelli F, Piras F, Spanò B, Tamburella F, Piras F, et al. Brain connectivity changes after osteopathic manipulative treatment: a randomized manual placebo-controlled trial. *Brain Sci* 2020;10(12):969.
- [67] Howick J, Webster RK, Rees JL, Turner R, Macdonald H, Price A, et al. TIDieR-Placebo: a guide and checklist for reporting placebo and sham controls. *PLoS Med* 2020;17(9):e1003294.