Placebo response to manual therapy: something out of nothing?

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The mechanisms through which manual therapy inhibits musculoskeletal pain are likely multifaceted and related to the interaction between the intervention, the patient, the practitioner, and the environment. Placebo is traditionally considered an inert intervention; however, the pain research literature suggests that placebo is an active hypoalgesic agent. Placebo response likely plays a role in all interventions for pain and we suggest that the same is true for the treatment effects associated with manual therapy. The magnitude of a placebo response may be influenced by negative mood, expectation, and conditioning. We suggest that manual therapists conceptualize placebo not only as a comparative intervention, but also as a potential active mechanism to partially account for treatment effects associated with manual therapy. We are not suggesting manual therapists include known sham or ineffective interventions in their clinical practice, but take steps to maximize placebo responses to reduce pain.

Keywords: Placebo, Pain, Manual therapy

Introduction

Manual therapy is an effective intervention for some individuals experiencing musculoskeletal pain conditions.[1,2] Despite the clinical effectiveness, the mechanisms through which manual therapy influences clinical outcomes are unknown. Common clinical practices, including evaluative procedures, are intended to identify hypo-mobile or mal-aligned structures of interest and are followed by the application of specific techniques meant to 'correct' the observed dysfunction, suggesting a biomechanical mechanism. Manual therapists continue to follow this model of clinical practice[3,4] despite literature suggesting that these evaluative techniques are unreliable[5] and their findings do not affect clinical outcomes.[6] Neurophysiological responses accompany manual therapy interventions and are suggested as pertinent to the mechanisms.[7,8] Currently, neurophysiological responses to manual therapy have been studied primarily as an immediate within session response,[9–12] and the relevance of these findings to clinical outcomes is not well established. Consequently, the effectiveness of manual therapy may result from both biomechanical and neurophysiological mechanisms.

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Rehabilitation interventions such as manual therapy are a 'structured experience'[13] rather than applied in isolation. Accordingly, the context of the treatment including the technique, the provider, the participant, the environment, and the interaction between these factors may contribute to patient outcomes. Therefore, the effects of manual therapy are likely related to multiple mechanisms. Placebo has a hypothesized role in all pain-related clinical outcomes including those associated with manual therapy[14,15] and has received less attention than other potential mechanisms. Interestingly, many of the neurophysiological responses associated with manual therapy and considered pertinent in the clinical outcomes are also observed in placebo studies unrelated to manual therapy.[7] Subsequently, placebo responses may account for some of the changes in clinical outcomes observed in response to manual therapy.

The traditional view of placebo is as an annoyance capable of confounding study results.[16,17] In fact, one of the highest levels of evidence, the randomized controlled trial, frequently bases the success of a studied intervention on the observed efficacy in comparison to placebo. The implication being not better than placebo is indicative of an ineffective intervention. Additionally, placebo is often defined as inert and a lack of a treatment effect has been suggested as a requirement for a valid placebo for manual therapy.[18,19] In contrast, recent literature

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suggests placebo is a psychologically and physiologically active process associated with a robust hypoalgesic response.[20] The current placebo literature suggests, 'The focus has shifted from the ''inert'' content of the placebo agent (e.g. starch capsules) to the concept of a simulation of an active therapy within a psychosocial context.'[21] Terms such as placebo effects,[22–24] placebo response,[22] and meaning response[24] refer to the context of the placebo experience as related to the patient, the clinician, the clinical environment, and the interaction of these factors.[23] For instance, the magnitude of a placebo response may vary depending on the participant–researcher interaction.[25] As a result, we will define placebo in this manuscript not as an inert agent, but as a mechanism likely accounting for some of the treatment effects of all interventions for pain including manual therapy. Additionally, placebo mechanisms of manual therapy will be operationally defined to include factors related to the patient, the clinician, and the clinical environment beyond the specific mechanical parameters of the intervention through which manual therapy may alter musculoskeletal pain conditions.

The purpose of this manuscript is to present a non-systematic review of placebo-related hypoalgesia and the potential role of placebo as one of the mechanisms through which manual therapy alters musculoskeletal pain conditions. Functional improvements are also associated with placebo;[26,27] however, the focus of the current manuscript is on placebo as a mechanism of pain relief for manual therapy interventions in the treatment of individuals presenting with musculoskeletal pain conditions. First, we will consider the effectiveness of placebo in inhibiting pain from different clinical pain studies. Second, we will discuss the mechanisms of placebo-related hypoalgesia. Third, we will focus on identifying individual characteristics likely to influence the magnitude of a placebo response and ethical considerations in the use of placebo. Fourth, we will discuss factors which affect the magnitude of the placebo effect and how manual therapists may use this to their advantage. Finally, we will discuss limitations in the current manual therapy placebo literature for which manual therapists should be aware when reading and interpreting studies incorporating placebo. We will cite work from the pain research literature in order to accomplish these goals with the intention of translating this literature to manual therapy mechanisms and practice.

Effectiveness of the Placebo

Placebo is an active hypoalgesic agent; however, the effect is variable and dependent upon the context in which the placebo is administered. For example, a systematic review[28] and subsequent follow-up[29] concluded that placebo had a small, significant effect on clinical pain (mean reduction: 6.5 and 6 mm on a 100 mm visual analog scale respectively, Cohen's d=0.27 and 0.25 respectively). In contrast, Vase *et al.*[30] conducted separate meta-analyses of studies in which placebo was a comparative intervention and studies specifically of the placebo effect. These study designs differ in that participants in a placebo controlled study are instructed that they will receive either the studied intervention or a placebo. Conversely, in studies of placebo mechanisms, participants are provided with a placebo with an instructional set intended to enhance expectation for the effectiveness of the placebo ('the agent you have just received is known to powerfully reduce pain in some patients').[31] Vase *et al.*[30] noted a small effect size (Cohen's d=0.15) in studies of placebo as a comparative intervention; however, a large effect size (Cohen's d=0.95) in studies designed to specifically investigate placebo mechanisms.[30] Vase *et al.* further noted similar findings in a more recent follow-up to this study.[20]

Factors other than the study design (placebo as a control versus placebo as a mechanism) may also influence the magnitude of placebo hypoalgesia. The magnitude of placebo hypoalgesia may increase over time in a visceral pain model in participants presenting with irritable bowel syndrome,[31] increase with repeated exposure in healthy participants exposed to experimental pain,[32] and last up to a week following the initial application in healthy participants exposed to experimental pain.[33] However, the duration of the placebo effect is not established in studies of musculoskeletal pain.

Subsequently, the literature suggests a consistent hypoalgesic effect of placebo, although the related hypoalgesia is variable in magnitude and dependent upon the study design (placebo control versus placebo as a mechanism), and appears time and dose dependent.

Mechanisms of Placebo-related Hypoalgesia

Placebo hypoalgesia may result from a number of potential mechanisms. Nonetheless, expectation and conditioning are two of the primary mechanisms and will be the focus of this manuscript.

Expectation as a mechanism of placebo-related hypoalgesia

The magnitude of placebo-related hypoalgesia is dependent upon expectation or what the individual thinks will happen.[20,30] For example, Verne *et al.* found lidocaine gel to provide a superior hypoalgesic effect to placebo saline for visceral pain sensitivity in individuals with irritable bowel syndrome in a standard placebo controlled study.[34] Additionally,

placebo saline provided greater hypoalgesia than no intervention.[34] In a follow-up study, Vase *et al.* observed a similar hypoalgesic effect for visceral pain sensitivity between lidocaine and placebo saline provided with the instructions: 'The intervention you have received is known to significantly reduce pain in some people'.[35] In a study of clinical pain, Pollo *et al.* provided a saline intravenous therapy to three groups of patients following thoracotomy. One group received no instruction and served as the natural history group. One group was told the saline was either a 'powerful painkiller' or a placebo. The third group was told that the saline was 'potentially a potent painkiller'. Participants receiving the saline with the instructional set consistent with higher expectations for pain relief required less additional pain medication than those receiving the saline with the standard placebo-control instructional set. Both placebo groups required less additional pain medication than the natural history group. Interestingly, all three groups reported the same level of postoperative pain despite the differences in intake of 'actual pain medication'.[36] Finally, Charron *et al.*[37] studied the magnitude of placebo hypoalgesia in participants presenting with chronic low back pain. Participants receive saline injections over two sessions. During one session, the saline injection was provided with an instructional set suggesting a powerful hypoalgesic agent. During the other session, the saline injection was provided with an instructional set suggesting an inert agent. Pain ratings were obtained for participant rating of low back pain before and immediately following the injection. Significant placebo-related hypoalgesia was observed in response to the enhanced expectation instructional set (Cohen's d=2.23–3.28) and not in response to the instructional set suggesting an inert agent. Collectively, these studies suggest expectation as causative of placebo-related hypoalgesia in both experimentally induced pain and clinical pain.

Conditioning as a mechanism of placebo-related hypoalgesia

Placebo-related hypoalgesia is enhanced through a learning/conditioning effect. For example, a person conditioned to experience relief from a headache each time he takes an aspirin may obtain similar relief if, unbeknownst to him, he is given a sugar pill of the same size and shape as the aspirin. Experimental studies support this mechanism of conditioning for placebo-related hypoalgesia. For instance, placebo-related hypoalgesia is greater when a painful stimulus is surreptitiously lowered immediately following the application of a placebo.[38–40] Specifically studies may obtain a baseline measure of experimental pain sensitivity to a standardized noxious stimulus such as heat. Following the application of a placebo, the noxious stimulus (such as the temperature of a thermal stimulus) is surreptitiously lowered and the participant experiences less pain. The hypoalgesia is then associated with the placebo. Following this type of conditioning program, the magnitude of placebo-related hypoalgesia is increased when the placebo is used with the original level of the noxious stimulus. For example, Watson *et al.*[41] induced experimental pain in healthy participants through a serious of laser stimuli. Following baseline assessment of pain sensitivity, participants received a placebo cream with the instruction they were receiving either an analgesic agent or an inactive cream. A conditioning trial was then performed where the participants received the same series of laser stimuli surreptitiously lowered in intensity. A third trial was then performed of the series of laser stimuli at the baseline noxious level. A significant hypoalgesic response was observed with pain ratings for the third trial significantly lower than those observed on the first (Cohen's d=0.99). Additionally, a social learning response is associated with placebo. Colloca and Benedetti performed a study in which healthy participants observed a research assistant acting as a 'simulator' demonstrate a significant placebo hypoalgesic response.[42] The investigators observed significant placebo-related hypoalgesia in participants after observing the reaction of the research assistant to the placebo corresponding to a 39% reduction in pain.[42] Subsequently, placebo-related hypoalgesia appears to have a conditioning mechanism and the conditioning may be affected by different forms of learning related to prior experience and observation.[43,44]

Physiological Mechanisms of Placebo Responses

A placebo response is a physiological occurrence accompanied by specific neurophysiological responses. Placebo hypoalgesia appears related to descending inhibition of pain from the supraspinal structures and functional MRI is beginning to clarify specific brain regions likely involved in placebo hypoalgesia. Current studies suggest that placebo-related hypoalgesia is associated with responses in regions of the brain related to pain modulation,[45–47] emotion,[47–49] and cognitive appraisal.[41,48] Both the opioid system[50,51] and the reward system[52,53] are involved in placebo-related hypoalgesia and brain imaging further supports these relationships.[54,55] Additionally, the placebo effect is significantly lessened in patients with Alzheimer's disease with pre-frontal cortex involvement[56] and can be abolished with experimental disruption of the prefrontal cortex through transcranial magnetic stimulation.[57]

Beyond a specific supraspinal mechanism, more recent imaging studies demonstrate spinal cord-related

responses to placebo[58,59] and suggest that placebo may modulate pain throughout the continuum of the nervous system.

Placebo-related hypoalgesia may be quite specific and localized to the expected site while not present in regions separate from the area of application.[40,60,61] For example, a placebo provided to the left hand is associated with hypoalgesia at the site of application but not in the right hand or either leg[60] and placebo hypoalgesia has even been localized to a single finger.[61]

Collectively, the current literature suggests a specific response to 'non-specific' treatment effects such as placebo. Additionally, studies are providing a better understanding of characteristic neurophysiological responses and potential mechanisms corresponding to placebo-related hypoalgesia.

Placebo Responders

Placebo has a likely role in all interventions for pain. For example, Amanzio *et al.*[62] studied buprenorphine, tramadol, ketorolac and metamizol in participants following thoracotomy. Participants received either an open injection of the studied medication (provided in view of the patient) or a hidden infusion (provided without the patient's knowledge). Significantly greater analgesia and variability of pain relief followed the open injection as compared to a hidden infusion. In fact, the authors conclude placebo to be the equivalent of 0.14 mg of buprenorphine, 31 mg of tramadol, 12 mg of ketorolac, or 521 mg of metamizol. The authors conclude that placebo mechanisms related to expectation and conditioning likely are responsible for the variability of individual response to analgesic agents and contribute to the effectiveness.[62] In a hallmark and frequently quoted study, Beecher reported an overall response rate to placebo of approximately 35%.[63] The methodology of this finding has more recently been questioned[64] and placebo response rates are likely quite variable. Currently, factors indicative of a placebo responder have not been identified.[65] A primary problem in identifying placebo responders is that prior studies are often not designed to define or evoke the placebo effect. Placebo is often studied as a comparative control and these studies frequently do not include a no-treatment control group. A no-treatment comparison group is necessary in order to account for factors such as regression to the mean and natural history and allow the calculation of the magnitude of the placebo effect. For example, without a comparative no-treatment control group, improvements in clinical outcomes associated with placebo cannot be differentiated from factors such as the natural history of the disorder. Subsequently, without a comparative no-treatment control group, conclusions cannot be made as to whether participants responded to the placebo intervention or simply demonstrated changes due to natural history or a regression to the mean. Despite the failure to identify consistent responders to placebo, the magnitude of placebo-related hypoalgesia may be enhanced. Both expectation and conditioning increase placebo-related hypoalgesia and experimental manipulation of either of these results in heightened placebo hypoalgesia.[31,36,38–40] Additionally, factors related to negative mood alter placebo-related hypoalgesia. Specifically, desire for pain relief,[31] fear of pain,[66] and anxiety[31,67] are all negatively correlated with placebo-related hypoalgesia. We would argue that everyone is a placebo responder; however, individual differences in expectation and prior experiences make the type of placebo to which individuals respond and the magnitude of the observed response variable.

Ethical Considerations

The use of placebo both in clinical practice and in research is controversial due to concerns regarding potential harm related to lack of appropriate medical care or distrust resulting from deception. Medical research requires that participants are educated regarding the goals, aims, and methods of a study and provide consent before participation.[68] Participants in placebo-controlled research studies provide consent with the knowledge of potentially receiving a placebo. Placebo provided in clinical practice is done deceptively without the knowledge of the patient. Subsequently, placebos are ethical with informed consent in studies to establish efficacy or safety of an intervention; however, their use in clinical care is questionable.[69] The *Declaration of Helsinki* mandates the use of placebo in clinical trials in only two specific situations: (1) when no proven intervention exists; and 2) when use of placebo is necessary to establish the efficacy or safety of a studied intervention and provides no risk to the participant.[68]

A primary concern for the use of placebo in clinical practice is for loss of trust between patient and provider;[70] however, adverse effects resulting from the disclosure of having received a placebo are speculative and have not been systematically studied. Deception is inherent to placebo-related hypoalgesia as the magnitude of placebo-related hypoalgesia is dependent upon expectation for the provided intervention. Specifically, greater placebo-related hypoalgesia is observed when participants believe that a placebo is an effective intervention and this deception has raised significant ethical issues regarding the use of placebo.[71] The concern for deception results from older studies of deception to cause harm.[72]

Placebo-related deception differs markedly in that deception is provided with the intention of a beneficial effect such as pain relief. Consequently, deception in and of itself is not necessarily negative[73] and particularly if provided with noble intentions.

Only one study, to our knowledge, has assessed participant response to placebo-related deception. Chung *et al.*[74] report on two studies of response to placebo: one in a clinical sample of participants with irritable bowel syndrome and the second in a sample of healthy participants. First, Chung *et al.* interviewed participants with irritable bowel syndrome who had received a placebo during participation in a prior study. Disclosure of placebo resulted in no changes in attitudes, willingness to participate in future studies, trust in the physician, or willingness to be treated with medical or non-medical interventions.[74] Additionally, Chung *et al.* studied healthy participants. All participants underwent a baseline thermal pain assessment using standardized temperatures and then a follow-up with a sham cream provided with verbal expectancies and a conditioning program to enhance placebo-related hypoalgesia. Significant hypoalgesia was observed in response to the placebo cream (Cohen's d=0.99). Disclosure of placebo was made to one-half of the participants while the others were kept blinded. A final session of thermal testing was then performed with a placebo cream and both groups again received verbal suggesting that the cream was a potent hyopalgesic agent for some people. Chung *et al.*[74] observed significant hypoalgesia in both groups (placebo disclosure versus placebo blinded) at both testing sessions (before disclosure and following disclosure) in comparison to a group provided with the cream with no verbal expectancies or conditioning program for hypoalgesia. These findings suggest that knowledge of having received a placebo does not diminish future placebo effects. Additionally, the participants demonstrated no worsening of mood or willingness to participate in future research studies following the disclosure of placebo. Subsequently, the findings by Chung *et al.*[74] provide preliminary evidence to discount concerns for adverse results of placebo on mood or trust in the patient–clinician interaction. Further studies are necessary to systematically consider the currently speculative concerns regarding negative effects of deception on the patient/participant and/or the relationship between the researcher/clinical and the patient/participant.

Placebo in Clinical Practice

Placebo as an inert intervention (traditional view) and the placebo effect as a contributing mechanism through which rehabilitation interventions alter musculoskeletal pain are two distinctly different concepts. The magnitude of placebo is dependent upon factors related to negative mood,[31,66] expectation,[31,36] and conditioning.[38,39] Subsequently, manual therapists should take measures to maximize the placebo effect within their interventions. We are not condoning the use of sham interventions or those known to be ineffective or inert in clinical practice as the ethics of such a recommendation are arguably questionable.[69] We do suggest that placebo as a mechanism likely plays a role in the outcomes of manual therapy interventions and believe that clinicians should attempt to maximize the hypoalgesic effect of placebo within (1) ethically accepted parameters (for example, stating a 'guarantee' for pain relief would *not* be ethically appropriate) and (2) accepted interventions for musculoskeletal pain conditions. We offer the following suggestions to manual therapists to enhance corresponding placebo-related hypoalgesia.

The placebo effect is lessened with negative moods such as greater desire for pain relief,[31] fear of pain,[66] and anxiety[31,67] and placebo-related hypoalgesia corresponds to improvements in these measures.[67] Manual therapists wishing to maximize a placebo response may wish to account for factors related to negative affect such as fear of pain and anxiety. Consideration of psychosocial factors is not new to manual therapy for the treatment of musculoskeletal pain. For example, the Fear Avoidance Beliefs Questionnaire is helpful in identifying individuals likely to respond to spinal manipulation.[75,76] The mechanisms of the relationship between psychological factors and clinical outcomes related to manual therapy are not established and factors related to negative mood may serve as both a prognostic factor for a specific intervention and as a means to enhance a corresponding placebo response. Furthermore, manual therapists may wish to intervene to address factors related to negative mood. For example, educational pamphlets have been observed to lower fear avoidance beliefs in individuals experiencing low back pain[77] and specific treatment approaches are associated with better outcomes in individuals with low back pain and high fear avoidance beliefs.[78] Addressing negative mood may maximize both general treatment effects as suggested by the fear avoidance model of pain[79] and placebo-related hypoalgesia.

Expectation is associated with both a greater magnitude of placebo-related hypoalgesia[20,31,36] and clinical outcomes in patients presenting with musculoskeletal pain conditions.[80–85] While generally predictive of outcomes related to musculoskeletal pain, the role of expectation as a moderator of specific interventions is not fully established. For example, the choice of intervention may supersede expectation

in predicting clinical outcomes related to musculoskeletal pain conditions.[86,87] In contrast, clinical outcomes in participants with low back pain receiving either massage or acupuncture were related not to the intervention, but rather individual expectation for the randomly assigned intervention.[88] Additionally, the experimental pain literature suggests a moderating effect of expectation on specific interventions.[35,36,89] In fact, both hypoalgesia and hyperalgesia are observed in response to the same placebo provided with expectations of lessening or worsening of pain respectively in healthy participants.[89] Subsequently, expectation is supported by the literature as a general prognostic factor in outcomes of musculoskeletal pain conditions and may act as a moderator of specific interventions in the treatment of pain. Manual therapists may wish assess or enhance (within ethical limits) patient expectation for manual therapy interventions in order to maximize clinical outcomes.

First, patients may be questioned as to their preference for competing evidence-based interventions. For example, one study observed similar outcomes in individuals with carpal tunnel syndrome treated with either a neurodynamic intervention or a carpal bone mobilization and both groups demonstrated improved outcomes in comparison to a no-intervention group.[90] Based upon these findings, a manual therapist could discuss neurodynamic interventions and carpal tunnel bone mobilization with a patient presenting with carpal tunnel syndrome and base the treatment decision upon the intervention for which the patient expressed higher expectation of effectiveness. Certainly, other factors must be taken into consideration such as contraindications to a specific technique and the strength of evidence for competing interventions; however, when presented with similar evidence for two opposing interventions, manual therapists may wish to consider patient expectation for individual rehabilitation interventions in their clinical decision-making process to maximize the contribution of placebo-related hypoalgesia.

Second, manual therapists may wish to enhance expectation for a given intervention by strongly suggesting the likelihood of a positive response when backed by appropriate evidence. For example, spinal thrust manipulation appears to be more effective than exercise alone[75] or joint mobilization[76] in some individuals with low back pain. A person who fits a pattern suggesting a high likelihood of a positive response to thrust manipulation may be questioned by the manual therapist regarding their expectation for this type of intervention. A patient fitting the pattern of a likely responder to thrust manipulation who expresses low expectations for thrust manipulation may benefit from additional education regarding the likely benefits before initiating treatment. An educational intervention successful in raising expectations for the evidence-based intervention may enhance the outcome by maximizing the contributing placebo response. Furthermore, the placebo literature suggests that the magnitude of placebo-related hypoalgesia is greater when a placebo is provided with an instructional set intended to enhance expectation.[20,31,36] Subsequently, manual therapists may strengthen the placebo response of their interventions; when supported by proper evidence, they promote the potential of treatment success to their patients.

The placebo response is enhanced by learning and conditioning. For example, placebo-related hypoalgesia is improved when a painful stimulus is surreptitiously lowered immediately following the application of a placebo.[38–40] Furthermore, placebo hypoalgesia is enhanced in participants who observe others report a hypoalgesic response to the same placebo.[42] Subsequently, past experience is significant in placebo-related hypoalgesia. Manual therapists may wish to question their patients as to prior experience with manual therapy with the potential for an enhanced placebo response in patients who report prior successes. Patients are commonly asked during the initial examination whether they have previously experienced a similar injury and how the prior injury was treated. Armed with appropriate evidence, manual therapists may wish to consider replicating prior interventions to which the patient responded as placebo-related hypoalgesia may be greater due to the positive association.

In summary, placebo-related hypoalgesia may be enhanced by factors related to negative mood, expectation, and conditioning. We believe that manual therapists should be aware of these influences and take steps to maximize their benefits during treatment. We are not suggesting that manual therapists provide inert or ineffective interventions. Additionally, we are not suggesting that manual therapists purposefully deceive their patients by knowingly promoting the benefits of inert or ineffective interventions. Rather, we recommend manual therapists view placebo responses as a beneficial piece of their interventions. Mechanisms other than placebo are likely pertinent to the way in which manual therapy inhibits musculoskeletal pain. We are simply suggesting that manual therapists may strengthen the treatment effects of evidence-based interventions when they embrace the placebo response.

Placebo Considerations When Interpreting the Manual Therapy Literature

Several methodological shortcomings exist in the current manual therapy literature specific to placebo.

Manual therapists should be aware of these shortcomings when interpreting placebo-controlled studies of the efficacy of manual therapy and studies of the mechanisms of manual therapy.

Lack of a validated placebo for comparison to manual therapy

Manual therapy differs from interventions such as medication in that the primary active agent of many drugs is known and well characterized, while the primary active agent of a manual therapy intervention may be the experience itself. Subsequently, a sugar pill of the same size and shape as the studied drug may serve as an appropriate placebo-control; however, a proper placebo for manual therapy is not established. A valid placebo for manual therapy should blind participants to the fact they are receiving a placebo.[18,19] Prior studies have compared manual therapy to placebo interventions such as sham laser,[91] sham ultrasound,[92] and light touch[93] without regard to whether participants were adequately blinded. Furthermore, placebo-controlled studies of manual therapy have not considered how expectation for the effectiveness of the placebo differed from the studied intervention. For example, participants may find a sham ultrasound believable as a rehabilitation intervention; however, they have low expectations for the effectiveness in comparison to the studied manual therapy.[86] Expectation is both a primary factor in placebo-related hypoalgesia[30,35,40] and influential in the outcomes associated with manual therapy.[88,94] Subsequently, baseline differences in the believability of a placebo or expectations for treatment effectiveness have potential to confound study results.

Failure to directly measure the placebo response

The majority of efficacy studies for manual therapy fail to include a no-treatment control group and such a design is necessary to account for factors such as the natural history of the disorder and to calculate the magnitude of the placebo effect. No conclusions may be drawn regarding the impact of a placebo response upon the studied outcomes without a no-treatment comparison. A two-group design allows only the comparison between manual therapy and placebo. Manual therapy performing no better than placebo may not indicate a failed intervention if both outperform natural history. Furthermore, in studies where the manual therapy outperforms the placebo, a comparison is still possible between the placebo and the no-treatment control group to ascertain the magnitude of the placebo effect as a partial mechanism of manual therapy.

Placebo as a mechanism rather than placebo as a control

Finally, greater placebo effects are observed when placebo is specifically studied rather than included as a comparison intervention.[20,30] Participants in placebo-controlled studies receive the instruction, 'you will receive either the studied intervention or a placebo.' Conversely, studies of placebo may instruct participants, 'the intervention you have received is known to significantly reduce pain in some people.'[35] Subsequently, expectation may be higher for the effectiveness of the placebo in these studies and expectation is associated with greater placebo-related hypoalgesia.[35,40] Similar methodology has not been studied in manual therapy and may provide a more clinically relevant measure of the magnitude of placebo in the mechanisms of manual therapy.

Conclusions

Placebo is often considered an inert agent devoid of treatment effect. The more recent literature suggests, similar to manual therapy, that placebo has physiological and psychological effects on pain. We suggest that placebo is not 'nothing', but one of likely many potentially relevant mechanisms through which manual therapy improves clinical outcomes related to musculoskeletal pain conditions. We recommend that manual therapists take steps to maximize placebo responses within ethical limitations. We are not suggesting that manual therapists include ineffective or inert interventions in the care of their patients with the suggestion of likely positive responses. Rather, we recommend that manual therapists take steps to maximize placebo mechanisms through minimizing negative mood, maximizing realistic expectations, and drawing on patient preferences and past experience for evidence-based interventions. Future research should consider proper comparative placebos for manual therapy efficacy studies and include designs to allow the calculation of the placebo response within manual therapy outcomes. Placebo is likely one of many mechanisms through which manual therapy inhibits musculoskeletal pain. Knowledge of the magnitude of placebo responses in outcomes related to manual therapy will allow manual therapists to maximize this effect in clinical practice.

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