



Placebo effects in osteopathy and other manual therapies – What they are and why they matter to clinical practice, education, and research

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ABSTRACT

Placebo effects are measurable changes in health outcomes arising from treatment context, driven by learning and expectancy mechanisms. While increasingly well documented and understood, their role in osteopathic and other manual therapies remains underexplored. Given the inherently complex and interpersonal nature of these interventions, understanding placebo and nocebo effects is essential for refining clinical practice, education, and research.

This narrative review synthesises current research on placebo mechanisms and their implications for osteopathic practice, education, and research. A non-systematic literature search was conducted using Google Scholar, structured by pre-defined learning outcomes, and prioritising high-quality studies and systematic reviews where available. Contradictory findings were sought and critically appraised to provide a balanced perspective.

Beginning with a historical overview and up-to-date summary of placebo-related concepts and mechanisms, the review highlights how expectancy, contextual factors, and psychobiological processes contribute to treatment effects in manual therapy. On this basis, the article advocates for a person-centred, biopsychosocial approach that leverages positive expectations while minimising nocebo effects. It also underscores the need for education models that incorporate placebo science to enhance clinical practice. Future research should prioritise well-designed efficacy trials, while also advancing knowledge of how expectancy and learning mechanisms influence treatment outcomes in manual therapies.

Implications for practice

- Placebo effects are always part of the delivery of an intervention, likely more so in contextually rich complex interventions such as osteopathy and other manual therapies.
- Knowledge of placebo and nocebo effects and their underlying mechanisms may enable practitioners to harness placebo effects and avoid nocebo and other undesirable effects.
- A better understanding of context-dependent effects may contribute to evidence-based mechanistic models and foster the development of education and practice models towards a person-centred biopsychosocial approach.

1. Introduction

Placebo effects are measurable improvements in clinical symptoms due to positive expectations and learning mechanisms [1–3]. Just as expectations can lead to beneficial effects, they can also contribute to new or worsening symptoms, called nocebo effects. For example, pain perception may be changed through suggestions: When people are told a gel will have a pain-numbing effect, they perceive less pain during medical procedures. When they are warned that something might hurt or that a drug might have side effects, they are more likely to have an unpleasant experience [4,5]. Importantly, these changes in symptoms are not imagined, they are the result of measurable neurophysiological changes. Apart from pain, placebo effects have been demonstrated in immune disorders, anxiety and depression, Parkinson's, sports performance, and others [2,6].

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When patients receive treatments for these conditions, placebo effects will always contribute: Expectancies and learning cannot be switched off. Instead, these mechanisms are triggered by inherent features of a treatment as well as contextual factors, i.e., perceived cues that arise from previous experiences or current dynamics of all therapeutic encounters such as the treatment setting, practitioner and patient characteristics, and interpersonal dynamics [7]. For clinicians and researchers in fields susceptible to placebo effects, this means that expectancies cannot be ignored. Placebo effects are part and parcel of clinical practice, whether a given treatment has documented specific effects or not. This recognition is particularly important in chronic, functional, and possibly subjective conditions such as pain [1]. Also, considering the impact of contextual factors and expectations on the individual is aligned with modern concepts of manual therapy [8,9] and person-centred care [10,11].

As an example of manual therapists, osteopathic practitioners use a wide range and combination of manual therapeutic approaches, often also providing education and advice to patients [12]. A fictitious treatment is presented in [Box 1](#), inspired by common osteopathic practice. Osteopaths have different trainings, skills, and experience and they may also focus on treating patients with a variety of demographic and clinical profiles [12–14]. Despite these differences, all practitioners can truthfully relate countless success stories. In a large UK (United Kingdom) patient survey, six weeks after having seen an osteopath, an astounding 74 % of patients report their symptoms to be ‘much improved’ or ‘completely recovered’ [15]. This article examines some of the possible mechanisms through which osteopathic and other manual treatments (and the clinical example in [Box 1](#)) can have clinical effects, contributing to so many patients getting better.

Firstly, a manual therapy approach can of course have specific biomechanical and neurophysiological effects, such as changing muscle function, autonomic parameters, or pain sensitivity [16]. In particular, spinal manipulation [17,18], massage [19,20], and joint mobilisation techniques [21–23] have some evidence to support specific effects. In

the example in [Box 1](#), such effects may be part of a possible explanation for any perceived patient benefits. At the same time, conflicting evidence or uncertainty about particular mechanisms exist when reviewed systematically [22–27]. In general, study methods remain heterogeneous [23,28,29], and many commonly proposed manual therapy mechanisms can be challenged [30–35]. In any case, the main mechanisms proposed by traditional theories of manual osteopathic treatment may not be the only mechanisms influencing clinical outcomes.

The second possible explanation for clinical improvements is that many musculoskeletal symptoms improve by themselves, or they fluctuate. People tend to seek care when their suffering is at its worst [36, 37], making natural symptom fluctuations and regression phenomena possible sources of what can be perceived as an effect of the treatment [1]. Importantly, such natural improvements are well-documented in clinical trials of any type of back pain intervention [38,39]. Regression refers to the statistical effect of symptom improvements from the point at which an observation is initiated to a point further down the line. In clinical practice, without something to compare a patient to, regression and natural history effects cannot be ruled out as the reasons for improvement. This is why research designs with a control condition are required to establish causation [40].

Apart from specific treatment effects and natural improvements, placebo effects may explain benefits from the clinical scenario in [Box 1](#). Especially elaborate and intricate treatments may instil positive expectations in patients [41] - the main drivers of placebo effects [3].

It takes considerable training to master the complex assessment and treatment sequence described in [Box 1](#). Often, complex interventions (defined as per Skivington et al. [42]) such as osteopathy have strong ritualistic elements, meaning repetitive special actions that convey purpose [43,44]. The above example also illustrates how practitioner beliefs and training can promote trust and certainty in patients. Ritualistic actions and the conveyance of positive treatment expectations form part of every medical intervention, both mainstream and complementary [44,45].

In clinical practice, the total benefit to patients will always

Box 1

A fictitious clinical scenario. This vignette uses a fictitious osteopathic consultation to illustrate a hypothetical patient experience, illustrating the richness of osteopathic practice and the complexity of most patients' experience. The vignette was inspired by techniques commonly taught to and used by osteopathic manual therapists.

35-year-old Nicky has experienced widespread pain for most of their adult life and sometimes sensory disturbances in the right thigh. Recently a good friend told Nicky about his ‘fantastic experience’ with an osteopath. Nicky wants to find out more and reads brief explanations of osteopathic treatments on the osteopath's website: So-called ‘mobilisations’ are used to treat joints and the spine, ‘soft tissue techniques’ aim at changing muscle tension and affecting ‘fascia’, and there are also ‘gentle techniques targeting organ function’. Nicky reads how treatment is supposed to change ‘peripheral and central sensitisation and interactions between nerve, skin, muscle, bone, organ, vascular structures and fascia, which form the basis for diagnosis and treatment and thus the restoration of allostatic processes’. Nicky finds this interesting and books an appointment with the osteopath, paying £85 in advance.

When Nicky visits the practice, the osteopath takes time to listen to Nicky's story, even going back to early childhood, and Nicky feels listened to. The osteopath then spends more time on a physical examination. First, Nicky is asked to perform certain movements or to stand still for a few moments, with eyes open and then closed and both feet touching, and then also on one leg only. With Nicky now lying down, the osteopath remains very focussed while their hands seem to follow an examination routine in which various parts of Nicky's body are touched. The osteopath also asks about touch qualities in certain areas and how parts of Nicky's body feel.

For treatment, the osteopath uses massage-like touch to treat areas in the lower lumbar spine, followed by rhythmically moving vertebral segments and joints, and then a crunching manipulation. In addition, the osteopath says that the so-called femoral nerve is mobilised, as Nicky's symptoms and the osteopathic tests indicate a strain on this nerve. With their hands, the osteopath also treats what they call the ‘right lower intestinal region and the psoas muscle’, as these may be connected to the nerve. Finally, the osteopath places their hands on Nicky's chest and lower back, before holding on tightly to the thigh, saying they are now ‘treating the femur with very small movements’ to ‘decrease tensions in the bone and increase mapping in the sensorimotor cortex’. The osteopath also recommends a homework exercise consisting of gently stretching the thigh.

After the appointment, Nicky is surprised about this therapeutic experience but briefly wonders whether such a treatment can improve the complaints that have developed over years and decades. Nicky is reassured by the osteopath's empathetic manner and clear explanations. Nicky is told that a few more treatments may be required to determine how many treatments are needed and at what intervals. Nicky is already feeling a little better and books another appointment for in three weeks' time.

encompass natural history and expectancy (placebo) effects. While these influences may interact with multiple other allostatic and intervention-driven mechanisms, understanding placebo effects, as well as their ‘evil twin’ the nocebo effect, is thus paramount for every manual therapist. Such understanding enables providers to harness positive treatment expectations and learning in an ethical manner while reflecting critically on any actions that may lead to negative expectations or other undesirable effects [1,46].

This article provides a description of the placebo phenomenon and discusses current evidence regarding neurophysiological and psychological mechanisms. Finally, several implications of placebo and nocebo effects for osteopathic and other manual therapy practice are proposed. The aims of this article are to sharpen practitioners’ awareness of these expectancy mechanisms and to contribute to current debates about manual therapy mechanisms.

2. Methods

This narrative review was prepared based on a non-systematic but structured review of current literature. The authors are an expert in research methodology and the topic, as well as a clinical and education expert. A subjective narrative review was deemed appropriate to summarise research across various methodologies, concepts, and research questions, and for its educational potential [47,48]. Although the review was structured by an overarching goal, four prospectively developed intended learning outcomes (Appendix), and a didactically informed lesson plan for an associated lecture, no review protocol was developed or pre-registered. Methodological standards for narrative reviews are limited [49,50], and there is currently no applicable reporting guideline.

To find relevant literature, dedicated non-systematic searches for individual manuscript sections were conducted, mainly using Google Scholar. For example, to understand the evidence regarding patients’ attitudes towards placebo use in clinical practice, the following search string was used: (survey OR beliefs OR attitudes) AND patients AND (placebo OR contextual). Articles were then selected based on their relevance to respective discussion points, their topicality, and their methodological quality. Contradictory evidence was deliberately sought and critically evaluated. When discussing clinical implications, we favoured high-quality systematic reviews and meta-analyses wherever possible. Articles of other methodologies and conjectures were identified as such and assigned adequate notes of caution in the review text where required. The manuscript was drafted and refined in several rounds of co-author review and topic-specific discussions.

This narrative review is limited by its non-systematic approach and reliance on a single search engine. While efforts were made to include diverse perspectives and contradictory evidence, the lack of a systematic database searches and formal eligibility criteria means some relevant studies may have been overlooked. Readers should view this review as a largely subjective synthesis of existing literature rather than a comprehensive systematic analysis and consider consulting additional sources for specific clinical or research decisions.

3. Results

3.1. Historical perspective on placebos

Before placebo effects were scientifically studied, the term ‘placebo’ referred to treatments given to satisfy patients’ desires for remedies,

even when their medicinal effects were unknown or believed to be false. This practice was acknowledged by figures like Thomas Jefferson, who noted the prevalence of prescribing inert substances like bread pills [51, 52]. Throughout history, medical treatments have often relied on the placebo effect (Box 2), which was recognised as a significant factor in patient outcomes and became a subject of scientific study as early as the late 18th century [53]. Blinded and placebo-controlled studies became a cornerstone of scientific methodology after an influential conference at Cornell University in 1946, emphasising their necessity in avoiding subconscious bias. Since 1980, the practice has been mandated by the US Food and Drug Agency (FDA) for drug approval [2,52].

Today, placebos serve dual roles: as inactive agents used in clinical settings to please patients and as controls in comparative experiments to study the effects of real treatments. Over time, the understanding of placebos has transitioned from denial to recognition, spurred by Henry Beecher’s seminal paper in 1955 [55], with further acceleration in the 1990s [2,52]. The history of placebo consideration follows three stages: denial, acknowledgment of its disruptive effects, and ultimately, full recognition of its significance. Currently, the field finds itself at the outset of the third phase.

3.2. Placebo effects

3.2.1. Concepts

The understanding of placebo effects has long been inconsistent and fraught with conceptual challenges [56], with criticisms aimed at the contradiction of defining a placebo as inert while acknowledging its measurable effects on symptoms [57]. The term ‘placebo’ has acquired negative connotations due to its complicating role in clinical research and perceptions of its effects as somehow less real [52,58]. While still commonly utilised in medical practice [59,60], the undisclosed use of placebos conflicts with modern ethical principles of patient autonomy and consent [1,61]. Instead of placebo, it appears more helpful to speak of contextual factors to describe aspects of a therapeutic interaction that are not regarded as particular to a given treatment (with the terms ‘non-specific’ or ‘common’ factors also used), and of expectancy- and learning-related effects following exposure to such contextual factors [1]. Others advocate for the term ‘meaning response’ [45] to emphasise the subjective patient experience driving clinical changes [62].

3.2.2. Definitions

Expectation and learning are key mechanisms underlying the health effects from contextual factors, such as treatment environment, therapeutic relationship, and verbal/non-verbal suggestions, forming the basis of the widely accepted definition of placebo and nocebo effects; According to Evers et al. (2018), “the placebo and nocebo effect [are changes in health outcomes that are] specifically attributable to placebo and nocebo mechanisms, [such as] the neurobiological and psychological mechanisms of expectancies [and learning]. These mechanisms are shaped, for example, by verbal instruction, or nonverbal or situational cues that affect treatment expectancies.”. These authors also make the important distinction between these mechanistically specified placebo effects and the changes in health outcomes in the control group of an efficacy trial. These are termed the placebo response but will include regression phenomena and natural fluctuations in symptoms [58,63] (see Fig. 1).

Box 2

Historical perspective on placebos.

“From Asclepius through Hippocrates to Galen, and until very recently, the history of medical treatment was largely the history of the placebo effect, because all medical treatments, with rare exceptions, were at best placebos, at worst unknowingly deadly.” [54].

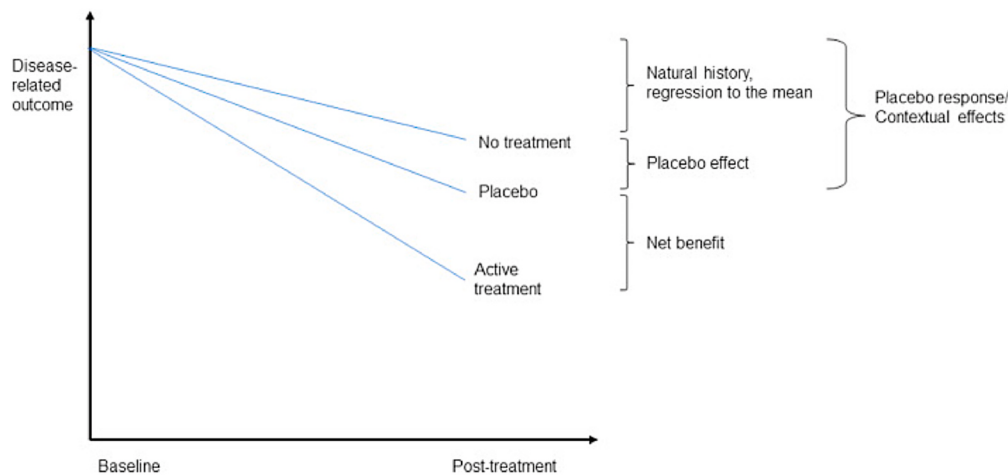


Fig. 1. Graphical representation of the various contributors to symptom change over time, as observed after the administration of no treatment, a placebo, or an active treatment. Proportions are not necessarily indicative of effect sizes. Image source: Hafliðadóttir et al. (2021) [114], reproduced in accordance with the applicable Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>) and with agreement of the authors.

3.3. Placebo mechanisms

3.3.1. Neurophysiology

Placebo effects have primarily been explored in regard to pain relief (placebo analgesia), but also exist for allergies and other immune responses, itch, nausea, blood pressure, Parkinson's disease, and anxiety and depression [2,3]. In pain research, laboratory experiments have illuminated the underlying neurophysiological processes, including the release of endogenous opioids and endocannabinoids in the brainstem, suppressing nociceptive signals and engaging higher brain centres [64]. In humans, the involvement of endogenous opioids was first demonstrated by Grevert et al., in 1983 [65], showing suppressed placebo pain relief when simultaneously administering naloxone, an opioid-antagonist. In the early 2000's functional brain imaging studies by Eippert and team [66] elucidated the role of prefrontal cortex-brainstem interaction. More recently, however, the analysis of a large brain imaging dataset suggested that the descending modulation of nociception and activity in pain-related brain regions is less important than previously thought [67]. Instead, other mechanisms may be involved: Positive expectations can reduce anxiety and stress, demonstrated by reduced back pain from placebo injections being partly mediated by anxiety levels [68], and conditioning may involve reward mechanisms in the dopamine system [69]. Further, even when pain-related brain activity occurs, a person's experience of pain may differ according to its cognitive evaluation or the person's affective response, possibly leading to lower pain reports [67]. Conversely, the harmful effects of negative expectations and learning, the nocebo effect, involve the pro-nociceptive Cholecystikinin (CCK) system and the hypothalamus-pituitary-adrenal 'stress' axis [2,3].

The neurobiological study of placebo effects has shown that there "is not a single placebo [effect] but many, with different mechanisms across different conditions and different systems" [64]. Further, placebo effects are arguably difficult to differentiate from other therapeutic processes, such as the therapeutic relationship [70], touch [63], cognitive and emotional reassurance [71], expectation management [1], relaxation [72], changes in mindsets and beliefs [73], and even marketing and interior design [74]. Despite their complexity, scientific exploration confirms the measurable and neurobiologically grounded nature of placebo effects.

3.3.2. Expectations and learning

The neurophysiological mechanisms of placebo effects primarily stem from the psychological processes of expectations and learning, influenced by various factors such as previous experience, verbal and

nonverbal suggestion, and social observation [3,4]. Conditioning effects also play a role, where repetition pairs a physiological response with a stimulus, as illustrated by Pavlov's dogs salivating at the sound of a bell. Conversely, negative expectations and conditioning can lead to undesirable outcomes, such as increased pain during vaccination procedures [75,76]. This underscores the vulnerability of expectations and learning to factors such as the clinical context, method of intervention delivery, purpose, and provider, rather than solely the content of interventions. Furthermore, even inherently effective therapies may be enhanced or diminished based on their framing and the expectations they elicit, not to mention the behavioural effects of expectations [46]. Consequently, disregarding placebo and nocebo effects in osteopathic clinical practice appears unwise.

3.4. Contextual factors

Numerous features of the therapeutic ritual and context have been demonstrated to influence clinical outcomes via expectancies and learning, resulting in placebo or nocebo effects. The research community's understanding of such interactions is derived from 1) laboratory experiments, where context factors and expectations are deliberately manipulated and their effect on outcomes assessed; and 2) clinical trials, where placebo control interventions are used to balance placebo effects across study groups, enabling assessment of the efficacy of the designated treatment components or pharmacological ingredients under investigation. These trials also yield data allowing for the study of the placebo effect itself, including comparisons of different control interventions, the influence of patient characteristics on changes in placebo arms, and the examination of participants' expectations and their differential effects on trial outcomes. Through such research, a list of contextual factors presumed to influence placebo effects has been compiled – first by Di Blasi and colleagues in 2001 [77] (Table 1).

3.5. Placebo effects in clinical trials

Observing benefits in patients in clinical practice, clinicians can never be certain that it was their treatment that produced such benefit, despite a natural inclination to assume such a relationship. Clinical trials, on the other hand, can establish causal relationships between interventions and outcomes, made possible by randomising participants to a treatment and a control group (thus the term randomised *controlled* trial, RCT) [40,82]. A range of further trial design features and methods are employed to increase trust in the validity of any findings [83]. Efficacy trials are RCTs that exert tight control on what happens during a

Table 1
Contextual factors known or with some evidence to suggest that they might lead to placebo or nocebo effects, and therefore potentially influencing clinical outcomes in manual therapy practice. Informed by relevant systematic reviews [77–81].

Contextual factor	Description
Provider factors	<i>Characteristics of the treatment provider that are communicated to patients in various ways.</i>
• Reputation • Professionalism and appearance • Beliefs and behaviours	
Patient factors	<i>Patient characteristics that make patients differentially susceptible to placebo effects, either through biological or psychological factors.</i>
• Preferences and previous experience • Demographics and clinical presentation • Beliefs and expectations	
Relational factors	<i>Factors related to the therapeutic relationship and the interaction between patients and providers.</i>
• Trust • Communication (e.g., verbal and non-verbal suggestion, positive communication such as empathy to enhance the therapeutic alliance, communication of diagnosis and prognosis)	
Treatment factors	<i>Features inherent in the treatment and its application.</i>
• Credibility • Type (e.g., gentle vs. strong; calming vs. stimulating; passive vs. active) • Personalisation • Repetition (to harness conditioning mechanisms) • Touch and sensation • Immediate pain relief • Presence of side effects • Amount of treatment • Addressing maladaptive illness beliefs • Price • Visual or physical cues to suggest pain-relieving treatment properties (e.g., invasiveness)	
Circumstantial factors	<i>The physical and social context in which an intervention is delivered and received.</i>
• Setting and environment • Sociocultural context	

trial to minimise bias, for example by concealing from patients which treatment they receive (called blinding) [42,58]. Other RCT types can compare two treatments with one another or to no treatment, and employ methods that more closely resemble real clinical practice (such as flexible treatment regimens and heterogeneous patient populations) [84,85]. Only efficacy trials, however, can study whether an intervention works as it is hypothesised to work (addressing mechanistic research questions) or whether it provides benefits beyond placebo effects. In other words, efficacy trials are required to clarify whether interventions like osteopathy are more than placebos.

To control for placebo effects is thus the paramount function of control interventions in efficacy trials (also called ‘placebo’ or ‘sham interventions’). This is achieved by, ideally, producing the same placebo effect in the control intervention arm as in the treatment group, allowing for the identification of clinical benefits beyond placebo effects by comparison and subtraction [58]. The design and implementation of control interventions in efficacy trials of physical and psychological interventions such as osteopathy, is regulated by the CoPPS Statement, a consensus guideline which recommends matching all treatment aspects, apart from those whose effect the trial aims to study [58] (CoPPS: ‘Recommendations for the development, implementation, and reporting of control interventions in efficacy and mechanistic trials of physical, psychological, and self-management therapies’). The CoPPS Statement also advocates for the measurement of participant expectations and blinding status to ensure balanced placebo effects. This novel guidance is an advancement from earlier practice, where ‘dummy’ interventions

were used that did not closely resemble the study treatment. Common examples in osteopathy are the use of switched-off ultrasound devices or simple touch without movement [29,86,87]. Especially when expectancies and participant beliefs are not assessed, such dissimilar control interventions cannot guarantee comparable placebo effects between groups [63], and have been shown to bias trial results [81]. Still, the design of an appropriate control intervention in the field of manual therapy research entails several difficulties.

In osteopathic and other manipulative therapy, all hands-on techniques include an element of therapeutic touch, which can itself have physical and mental therapeutic effects [88] through designated neurobiological pathways [89]. Designing a control intervention for an osteopathic hands-on treatment according to the CoPPS Statement requires specifying the treatment mechanisms of interest and the treatment components thought to act on these mechanisms [58]. For example, one may wish to study the effects of a manually applied force to the spine on pain intensity or spinal movement [90]. Unless touch is the designated component of interest (and thus removed from the control intervention), the therapeutic effects of touch will occur in the control group. Consequently, labelling most manual therapy control interventions as inactive or ineffective is inappropriate, not just because expectations can also have neurophysiological effects. Apart from considerations of scientific rigour as defined by CoPPS [58], several considerations relevant for manual therapy trials are discussed in Table 2.

3.6. Interactions of placebo and treatment effects

3.6.1. The magnitude of placebo effects as a proportion of overall treatment changes

One will often hear that placebo effects make up about a third of treatment effects. This number, however, is usually misappropriated from its original source, which was the famous Henry Beecher [55] who showed a supposed placebo response in about 30 % of his study subjects, and thus did not at all quantify the size of the placebo effects as a proportion of overall treatment effectiveness. This number does also not account for the considerable variability of placebo effects between studies, individuals, and time points. What is known is that the placebo effect is generally larger in dedicated experimental studies than in RCTs. Such experiments normally aim to maximise placebo effects, showing on average ‘moderately large’ effect sizes. In RCTs, researchers may (in)avertedly try to minimise the placebo effect because the aim of such trials is usually to show larger treatment effects compared to placebo. Also, trials, like clinical practice, are messier than lab experiments, with plenty of room for other factors and biases to influence clinical outcomes. For example, not all patients receiving a control treatment may believe in its authenticity or develop expectations of benefit. Therefore, the placebo effect derived from clinical trials is on average smaller (for a discussion, see reference [63]). A recent large meta-analysis of ‘sham’ procedures in musculoskeletal pain found low-to very low-certainty evidence for small placebo effects on pain, physical function, depression, and quality of life when measured in the short-term [99]. Although small, this effect likely represents a sizeable proportion of overall treatment effects (possibly in the realm of 1/3), as found in another recent review [63]. While trials are a good approximation of clinical practice, very little is known about how placebo effects play out in real clinical practice, simply because this is difficult to measure. Either way, the research suggests that placebo effects are not zero and that they may, at times, contribute a considerable proportion of the overall benefits after receiving a treatment.

3.6.2. The interaction between placebo effects and characteristic treatment effects

Placebo effects could simply add to any treatment effects (X% of pain relief from a drug, plus another Y% from the placebo effect). This is termed the additivity assumption [100]. For clinical practice, additivity would mean that clinicians can choose to exploit placebo effects (as

Table 2
Difficulties in the design of control interventions in osteopathic efficacy and mechanistic RCTs and potential solutions.

	Challenge in designing control intervention for manual therapy interventions	Potential solution
1	Designing a control intervention that does not have any neurophysiological effects other than those related to expectancies and learning [89]. For example, can a touch-based control intervention avoid affecting the autonomic nervous system [91] or pain sensitivity [92]?	Recognising that a touch-based control intervention may not be entirely inert. Instead, a control intervention in a specific RCT must ensure that its effects are not produced by the components and mechanisms of interest of the tested intervention. For example, Hawk et al. [90] carefully specified which supposed mechanism and thus treatment component were of interest in their trial and then removed it from their control intervention.
2	Being touched in a therapeutic context can arguably produce positive expectations and thus contribute directly to placebo effects [63].	Producing the same placebo effect as in the treatment arm is desirable. Therefore, touch-free control interventions of osteopathic manipulative therapy should be avoided. Touch in the control arm should mimic the real intervention regarding the characteristics <i>not</i> of interest in the study (e.g., duration of manual contact, anatomical areas touched, type of hands movement), to be able to delineate the effect of the intervention components of interest (e.g., specific force parameters, intention, etc.) [93].
3	Touch-based techniques include many elements that are not commonly described in the wider literature on control interventions and placebo effects, for example the quality of touch, biomechanical parameters of handholds and force application, and the intention and internal imagery of providers.	The same touch ‘choreography’ should be used in both groups (i.e., matching all characteristics of the touch, including the body areas touched and the type of treatment, e.g. passive/active role of the patient, light touch/pressure). D’Alessandro et al. [94] further propose to define: relevant manual therapy diagnostic procedures, each technique and its elements, the treatment protocol, the target of the partitioner’s attention focus, the tailoring of techniques to individual patients, and the barriers of the tested intervention to clearly delineate it from the control intervention.
4	There exist a multitude of osteopathic models, each with a range of possible interpretations and varying impact on practitioners’ clinical actions [95].	If specific osteopathic thought models are employed, and if the trial allows for flexibility in intervention delivery, the osteopathic models underlying a practitioner’s reasoning should be clarified and their influence on therapeutic decisions defined. This should be harmonised across all trial providers.
5	The mechanisms of action of manual therapies have not been conclusively elucidated, and mechanisms are multiple and interact in complex ways [16]. Thus, control interventions may inadvertently activate the same or overlapping neurophysiological mechanisms. For example, a control intervention may lead to muscle relaxation not through manual pressure but autonomic relaxation. This holds the risk of wrongly assuming that a treatment is inefficacious.	This mechanistic challenge is best unravelled in preliminary mechanistic studies or in trial designs that allow to address mechanistic questions, such as factorial designs. If an efficacy trial shows no superiority of the tested treatment over a control intervention that was designed without incorporating key parameters central to the intervention’s theoretical framework, it may suggest that the intervention theory needs to be reconsidered—specifically, that the assumed mechanism of action may not be accurate.
5	Osteopathy is a complex intervention [96] and osteopaths seek to employ bio-psycho-social frameworks [97]. Deconstructing such complex interventions for the	Testing the role of specific intervention components does not negate the importance of testing packages of care in real-life settings (for example in pragmatic or comparative effectiveness

	Challenge in designing control intervention for manual therapy interventions	Potential solution
	purpose of efficacy trials may destroy the essence of the intervention, thus rendering its study in efficacy trials futile. For example, can a course of spinal manipulation therapy have an effect in the absence of a therapeutic relationship?	trials [84]). An absence of any, albeit possibly small effect of a particular intervention component in several well-designed efficacy trials, however, should stimulate debate about the importance of that intervention component in any given package of care.
6	Multiple mechanisms and intervention components may be considered important enough to be studied at the same time in a trial.	A control intervention can avoid multiple components of interest if it is otherwise as similar as possible to the tested intervention. This will enable the study of their combined effects, but complicate conclusions about individual components’ contributions [58].
7	Effect sizes (the magnitude of differences between control and test interventions) may be small in efficacy trials with highly matched control interventions.	The interpretation of RCT findings should take into account the nature of the control condition, and smaller effects are to be expected in trials with highly matched control interventions. CoPPS therefore states that “ <i>Positive signs from an efficacy trial with a well designed control intervention should increase end users’ confidence in an intervention under real world conditions, even if effect sizes in the efficacy trial are small.</i> ” (p. 11) [58]. Conversely, negative trial results should lead us to question intervention theory and/or clinical practice.
8	Clinicians may hold strong beliefs about the effects of a particular manual therapy technique and may not feel able to deliver a control intervention which they believe has no effects [98].	Anecdotaly, engaging providers in the design of the control intervention can generate practitioners’ buy-in, alongside training to highlight equipoise and the ethical basis of a given study. Methods for fidelity monitoring during the study exist and are essential to success here [58]. Finally, practitioners may find the delivery of control interventions easier in patient populations, techniques, and interventions that do not impinge on their professional identity [98].

‘icing on the cake’) or choose to ignore them at no further cost. However, placebo and treatment effects could also interact in a non-linear manner, synergistically or antagonistically potentiating or reducing treatment effects or even reverse them. The implications for clinical practice would be stark, as nocebo effects could do away with any benefit or even render a clinical interaction harmful. Such has indeed been shown with the effects of beta-blockers [101] and anaesthetic creams [102] which can be reversed by inducing negative expectations. Less dramatically, nonlinearity may mean that a minimum of placebo or nocebo processes are required for any treatment benefit [103], or that treatment effects are blunted with a therapeutic approach that does not also create positive expectancies. While more high-quality trials with a specific design are required, there is enough evidence to not assume additivity in all instances. Being aware of interaction effects means being aware of psychological determinants of treatment outcomes and how they may interact with any given treatment and individual [104].

3.6.3. The (un)predictability of placebo effects

For drug development, predicting placebo responses is somewhat of a holy grail. It would enable the selective inclusion of only those study participants who show limited placebo responses, thus maximising the treatment effect to be demonstrated (which is the difference between changes in the placebo and the treatment groups). Thereby, one would be more likely to find ‘effective’ drugs, a problem that has plagued the pain field for a long time now [105]. Unfortunately, it appears that the only considerably powerful predictors of the placebo response are

(unsurprisingly) participants' expectations [106], shaped for example by the chances of getting the real treatment in a trial, the investigational treatments reputation (e.g., larger placebo effects in opioid trials), or the amount of interactions with clinical staff [107]. In addition, several studies suggest influences of psychological traits and constructs (such as optimism and self-efficacy), biological factors (sex, some genetic variants, and neurotransmitter availability), several situational and interpersonal factors (e.g., doctor-patient relationship, study setting, previous medical experiences), and aspects of a patient's symptoms or disease (such as higher baseline pain predicting larger placebo responses [6,106,107]). Studies from physical and psychological interventions support a dominant role of the subjective patient experience in shaping expectancies and thus placebo effects [81,108]. Next to being hard to predict, placebo effects are also highly variable [100,105].

3.7. Implications for manual therapy clinical practice and education

How placebo effects can be harnessed in clinical practice is of practical relevance to clinicians (Figs. 2 and 3). In summary, placebo effects are largely based on the patient's perception and expectation, have a neurophysiological basis, and produce measurable effects. Manual therapy treatment engages multiple mechanisms, including those underlying placebo effects [10,16]. At the same time, clinical interactions hold the potential to create negative expectations or other

undesirable effects, which should be minimised [1,46]. Surveys suggest that patients are generally open to the idea of deliberately engaging contextual factors, fostering positive expectations, or even using placebos in clinical practice - however, patients value transparency and there's a small proportion finding placebo use unacceptable [109–113].

Learning about placebo and nocebo effects is clinically important and integrating this knowledge into everyday practice is possible by means of several simple steps [1]. For example, osteopathic authors such as Liem have provided guidance on how to harness contextual factors in practice as early as 2005 (unpublished lecture at *Kongress des Verbandes der Osteopathen Deutschland*. Schlangenbad. 02 - 04 Sept. 2005, and references [115,116]). In doing so, clinicians can target not just positive expectations [4] but also other positive outcomes, such as a trusting relationship [117], reassurance [71], patient agency [118], effective self-management strategies [119], and possibly patient satisfaction [120,121].

Bishop et al. [79] suggest an evidence-based list of clinical actions that can plausibly help to elicit placebo analgesic effects (also see Table 1). This includes patient-centred verbal and non-verbal communication to convey positive expectations and reduce negative ones. For example, practitioners can convey optimism, highlight known treatment effects and mechanism, or frame a prognosis in a positive way ("80 % recovery rate" vs. "20 % chance of developing persistent pain"). Communication with patients ought to also avoid terms that can be



Fig. 2. Caption: Overview of clinically relevant placebo mechanisms and factors influencing them.

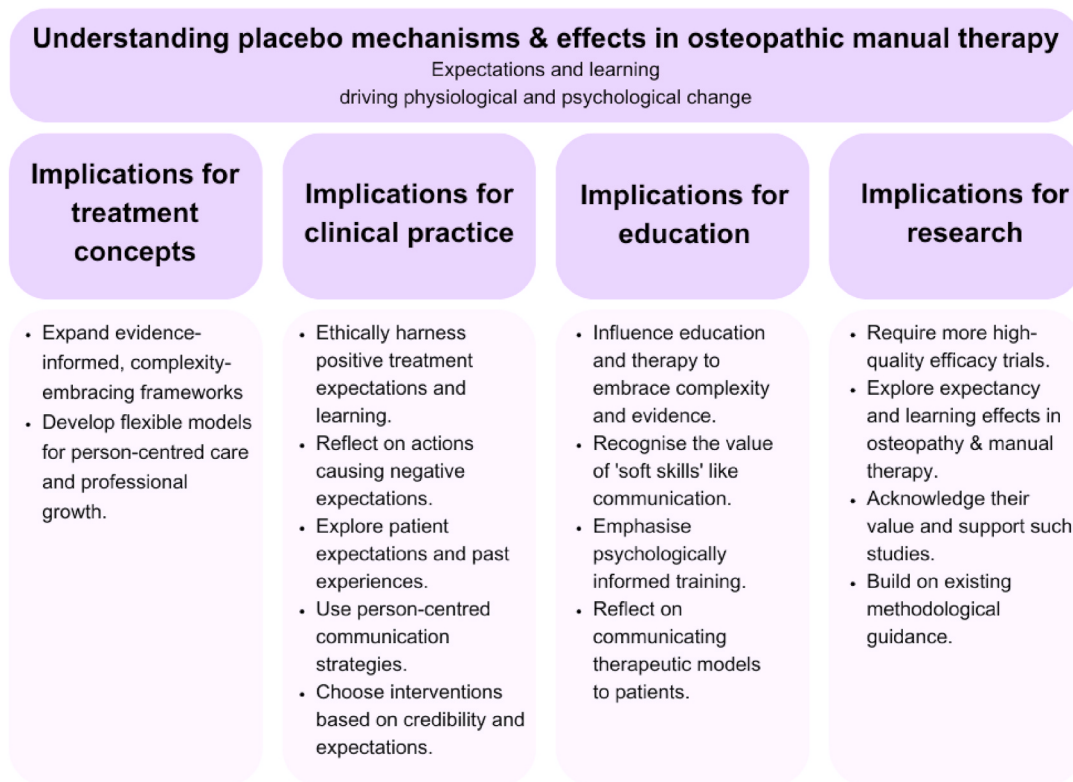


Fig. 3. Caption: Implications of understanding placebo effects and mechanisms for osteopathic and other manual therapy concepts, practice, education, and research.

misunderstood or that could imply harm (including, e.g., 'dysfunction', 'twisted', or 'stuck') [122]. Osteopaths and other professions ought to reflect carefully on their teaching and clinical habits to identify the potential for nocebo and other undesirable effects. Again an easy win, this rationale has been argued more thoroughly in another open-access article for clinicians [46]. Finally, patients' expectations and previous experiences can be explored during clinical conversations ("What do you expect to happen?", "What are your concerns?") [10], identifying harmful and promoting positive experiences (within realistic and ethical boundaries).

For manual therapists, delivering interventions into the effects of which they themselves believe, may also be relevant. Similarly, a practitioner's expertise and reputation can be highlighted to patients, the setting be enhanced to reflect professionalism and generate a 'healing' context, interventions can be chosen that are particularly credible to individual patients [123], and side effects can be used to underline the treatment's potency.

A therapeutic alliance, based on trust and individualisation, is often considered integral to therapeutic success [11,124], including due to its impact on placebo effects [125]. Other types of communication, such as empathic communication may also have generic effects by creating trust, relaxation, and a positive relationship [126] (Fig. 2), but may also be associated with better treatment adherence and clinical outcomes [127,128]. Similarly, integrating cultural competency as part of an epistemologically flexible approach is also discussed [129]. Further, manual therapists are well-placed to supplement their clinical repertoire with approaches informed by psychology, including simple reassurance and active listening techniques which enable them to employ communication more deliberately [10,130,131].

In education and osteopathic and other manual therapy philosophy, incorporating the science of placebo effects may contribute towards a framework that embraces complexity and is evidence-informed (Fig. 3). This appears pertinent during a time when therapeutic models continue to evolve [132]. This is an opportunity, not a threat: With little

additional work, every practitioner could harness the rich potential inherent in many everyday clinical actions – translating them into direct patient benefit by fostering positive expectancies and creating a healing environment, as discussed above. Students of osteopathy and other manual therapies will be able to use the framework of placebo effects to understand the measurable value of 'soft skills', such as communication skills.

In education, biomechanical models and hands-on skills may need to be de-emphasised. Their current dominant representation in many osteopathic curricula and practices [13,133,134] no longer represents what is known about their relative importance in clinical practice. Instead, more training in psychologically informed skills is required in which manual techniques can be embedded [130,135]. Students should be made aware that traditional therapeutic models are potentially useful heuristics but that their terminology and concepts must not be communicated unfiltered to patients.

The potential for (largely unpredictable) interactions between treatment and placebo effects means that such considerations are not optional, they should form part of basic osteopathic and other manual therapy practice and education.

3.8. Implications for osteopathic research

In the view of the authors, two main research areas arise from recent developments in the placebo field (Fig. 3). First, there is a need for more high-quality efficacy trials in osteopathy, despite the challenges specific to the field discussed earlier. Second, much of the current understanding of placebo effects comes from other disciplines, presenting opportunities to explore expectancy and learning effects specifically within osteopathic and other manual therapy contexts. Key questions include how different therapy styles influence patient expectations, how prior experiences and expectations shape treatment outcomes, and how these factors interact with various elements of osteopathic consultations and the clinician-patient relationship. Additional research questions

potentially applicable to osteopathy have been identified in relevant expert consensus studies [1,136].

Efficacy trials should address unresolved questions identified in literature reviews, including whether interventions work beyond expectancy effects. As previously discussed, these trials must be grounded in explicitly defined mechanistic theories that specify the effects to be tested, and should be informed by both preclinical and clinical mechanistic studies where possible. Conducting such trials requires rigorous methodology, scientific integrity, and substantial financial and professional support from the entire professional community [137]. The manual therapy field needs more well-trained scientists, and clinicians may benefit from enhancing their understanding of scientific methods and literature, while being prepared to adapt based on emerging evidence [82]. The introduction of the CoPPS Statement provides, for the first time, an evidence-based methodological framework tailored to complex, interactive interventions like osteopathy [58]. With this standardisation disappears any justification for poorly conducted or absent efficacy trials.

However, the call for efficacy trials does not diminish the complementary value of pragmatic trials and other forms of research [84], which recognise the complexity of clinical practice and human experience while still underscoring the need for a robust scientific foundation in healthcare [84,138]. Such trials can be helpful to determine benefits of complex interventions beyond current usual practice irrespective of mechanism, compare multiple available intervention packages, or investigate person-centred treatment strategies [84,139].

4. Discussion

As demonstrated, the effects of manual therapy are likely intertwined with placebo effects, such as expectancy and learning mechanisms. These effects may be amplified by the inherently interpersonal, complex, repetitive, multisensory, site-specific, ritualistic, and touch-based nature of most manual therapies. Treatment is often guided by authority, recommended by others, costly, and sometimes based on simplistic but appealing rationales. One example is the assumption that subtle physical restrictions can contribute to symptoms and disease by disrupting bodily processes – an explanation that, while often lacking empirical validation, remains compelling to both practitioners and patients.

Osteopathy and other manual therapies are complex interventions [42], situated within a dynamic and multifaceted environmental context and various explanatory frameworks, providing multiple opportunities for expectancy and learning to influence treatment outcomes. Given this complexity, therapy should aim to find an individualised balance suited to each patient [11], rather than striving for average effects. Illness cannot be reduced to biological, social, or psychological dimensions; a comprehensive approach must consider all relevant aspects from the patient's perspective [10,139].

The science of placebo effects offers a valuable framework for integrating physiology, psychology, and context into treatment. Current evidence-based models of manual therapy rightly incorporate psychobiological processes, including expectancies, and embrace the inherent complexity of these interventions [8,11,16,140]. The science of placebo effects urges these professions to move beyond monocausal and linear explanations toward a more comprehensive biopsychosocial approach [104].

In the light of this complexity, some may argue that understanding precisely how an intervention works is less important than determining whether it is effective [141]. This article, along with related publications [58,84], explore the value of both efficacy-focused research and trials that study real-world effects in producing a comprehensive and practically relevant evidence base.

5. Conclusion

The universal role of positive expectations, and their capacity to enhance the effects of other therapeutic approaches and mechanisms, suggests that they should be integrated into osteopathic and other manual therapy models and practice. By viewing these models as fluid, practitioners can expand their skillsets, potentially adopting a more holistic, person-centred, and evidence-based approach to patient care.

CRediT authorship contribution statement

David Hohenschurz-Schmidt: Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **Torsten Liem:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of competing interest

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Torsten Liem declared the following potential conflicts of interest: Professional interests: Engaged in the practice and education of osteopathy, publishing books related to osteopathy, owning and managing an osteopathic teaching institution in Germany.

Appendix A. Supplementary data

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