"The power and value of placebo and nocebo in painful osteoarthritis"

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ABSTRACT:

This paper reviews some recent advances in our understanding of the effects of sham or dummy interventions on pain and other symptoms in osteoarthritis, and outlines two new approaches to the investigation of placebo and nocebo effects.

We argue that the placebo effect provides us with a valuable way of investigating the nature of conditions like osteoarthritis (OA). For example, by examining which symptoms, biochemical markers or imaging features do or do not respond to placebo, we might learn more about the relationships between pathology and symptoms in OA.

Placebo and nocebo effects are positive or negative outcomes resulting from the human interactions and contexts in which healthcare consultations take place. Subtle changes in behaviours and the environments in which consultations take place can have major effects on pain and other symptoms being experienced by people with OA. Nocebo effects are particularly powerful, leading to many health-care professionals causing unintended harm to their clients.

Based on our own research, we conclude that beneficial outcomes are most likely to occur when both the health-care professional and the client feel safe and relaxed, and when the experiences of the client are validated by the health-care professional. These findings have important implications for clinical practice.

We believe that research in this field needs to be 'trans-disciplinary', escaping from the constraints of the purely biomedical, deterministic, positivist paradigm of most medical research. We provide the example of our own work which combines performance studies and scholarship, with psychology and medicine.

The power and value of placebo and nocebo in painful osteoarthritis

Introduction:

The placebo response is generally described as the improvement in health status that occurs with the administration of a sham intervention [1,2]. Following the uptake of the randomised controlled trial (RCT) as the central method for assessing the efficacy of interventions, it became commonplace to contrast the effect of a therapy that was targeting a particular problem (such as pain) with a sham therapy, as identical as possible to the 'real' one. This resulted in the trials-based definition of the placebo response. But, as pointed out recently, the idea that placebo is about a sham treatment is misleading and unhelpful [2].

Some authors have questioned whether the placebo effect exists, as improvement with no active intervention could occur for other reasons, such as regression to the mean [3, 4]. Yet we believe that phenomena termed 'placebo' offer a rich source of data, and suggest that better understanding, and clearer delineation of terms, could enable their beneficial use. As suggested by Kirsch [5], we separate placebo *responses* from placebo *effects*. As shown in Figure 1, the placebo response is the change seen in response to a sham intervention, whereas the placebo effect is the difference in response between *doing* nothing (a no-treatment control group), and *giving* 'nothing' (giving a sham treatment that should do nothing).

In this article, we concentrate on the placebo effect rather than response. We focus on changes in health status occurring after a health-care consultation involving no administration of a specific drug or other medical intervention. We are not concerned with trials, rather our interest is in the contextual factors [6, 7] that can allow people to improve as a result of an encounter with a health-care professional (HCP) even if no specific therapy is used.

This article is based on extensive primary and secondary research by a multi-disciplinary team that includes a doctor with an interest in OA (PD) a humanities scholar (SG) and a psychologist (M G-H), who have been working together on this topic for the last 5 years. It is split into two parts; first we review some of what is known about the importance of placebo and nocebo effects and their mode of action, with an emphasis on pain in OA, secondly we describe the different research approaches that we are using to investigate the topic further, which emphasise client-practitioner interactions.

PART 1: Placebo and Nocebo Effects

The placebo effect appears to be particularly important in the relief of symptoms such as pain and depression [1, 2, 8, 9]. But sham interventions and encounters with HCPs can do harm as well as good, a phenomenon called the nocebo effect [10]. Nocebo reactions have been noted to worsen both pain and anxiety [11, 12]. Pain, anxiety and depression are amongst the most important symptoms occurring in people with osteoarthritis (OA) [13]; this article will concentrate on pain, the dominant symptom for most people, but almost everything we say about pain and placebo/nocebo could also apply to anxiety and/or depression, and to other common symptoms and chronic disorders.

The efficacy and effectiveness of placebo on pain in OA

The efficacy of an intervention describes the changes that occur when the treatment is used in the artificial test conditions of a RCT. Effectiveness refers to the changes that occur when that treatment is used in routine clinical care [14]. Efficacy demonstrated in a trial may not translate into effectiveness because of the influence of numerous context-related effects. Efficacy is often calculated and presented as the effect size of an intervention, which is the difference between the standardised mean effects of the intervention compared to that of no intervention.

It has been possible to calculate the effect size of placebos in OA trials, because an examination of the literature uncovered enough RCTs that included a no-treatment control group to allow a valid statistical comparison of the effects of dummy treatments to no treatments. Zhang et al [15] found that the effect size of placebo for pain in OA was 0.51 (95% confidence intervals 0.46-0.55) in comparison with 0.03 (+/- -0.13 - 0.18) for untreated control groups. An effect size of 0.5, or thereabouts, is of considerable clinical value, and comparable to that of many of our commonly used interventions [16]. The same group published a further analysis, in which they used random-effects modelling to calculate the amount of pain relief that could be attributed to placebo (contextual) effects, and how much to the treatment being tested for its effects on pain in OA [17]. They report that on average 75% of the overall treatment effect is due to the contextual factors rather than the specific intervention. Another recent review used a network meta-analysis technique to synthesise data from 149 RCTs of adults with knee OA in which placebos were used [18]. The findings confirmed the power of placebo in OA, and also showed clearly, as reported in the aforementioned papers, that 'all placebos are not equal': intra-articular and topical sham therapies were superior to oral treatments in pain control. Sham surgical interventions can also result in a great deal of pain relief [19]. This work suggests that we need to take more account of contextual factors when trying to interpret clinical trials in OA.

The effectiveness of placebo in OA is unknown, as no large-scale pragmatic trials of sham treatment, or of a purely context-based intervention, compared with no treatment control groups have been undertaken. However, it seems likely that the effectiveness of placebo for pain relief in OA can be considerably larger than its efficacy. The artificial conditions of a

trial constrain the extent to which context effects and the behaviours of clinicians, thought to be crucial to the placebo effect [2,6,7], can be used to enhance the value of an intervention. Conversely, an appropriate consultation, within a safe environment, as explained below, could greatly enhance the effects of an intervention.

Recent trials indicate that consultation style can enhance the size of a placebo response in OA and other chronic disorders. In one study comparing Traditional Chinese Acupuncture (TCA) to sham acupuncture in patients with OA of the knee, no difference between the TCA and sham acupuncture was found, but the consultation style used by the acupuncturists made a big difference to outcomes [20]. A secondary analysis of the data suggested that the communication of optimism about likely outcomes led to a greater degree of pain relief [21]. A similar study has been undertaken in irritable bowel syndrome [22], and secondary analysis of the data from that study indicates not only that communication styles matter, but suggests that some practitioners obtain good outcomes, whether they are trying to communicate in a positive way or not, whilst others consistently achieve less placebo-related relief of symptoms [23]. This is in keeping with a large body of research in psychotherapy that indicates that different practitioners have widely varying abilities to help people improve their mental health [24,25].

Nocebo effects and pain

Nocebo effects, or 'negative non-specific effects', have been observed in many different contexts [26]. For example: health-care interventions can sometimes result in idiosyncratic, unexpected adverse effects in individual patients [27]; sham pills used as 'controls' in RCTs often cause adverse side-effects [28]; and population-based interventions, such as the introduction of mobile phones or wind farms, can result in widespread, unexplained illness [29,30]. These are examples of what have been called 'adverse outcomes resulting from negative expectations' [31] because most investigators have assumed that expectations are responsible for the effects observed. However, Greville-Harris and Dieppe have recently argued for the need to look more widely for explanations of negative outcomes, which can arise from several different contextual, environmental and interactional factors [10].

It is difficult to undertake nocebo experiments, because, by definition, one is trying to make people feel worse, not better. However, some elegant pain experiments have been carried out in the laboratory of Fabrizio Benedetti and colleagues [11,12,32]. They demonstrate that negative expectations can make pain more severe, and that anxiety makes a nocebo pain response more likely [12]. Although the majority of data available about pain and nocebo effects refers to acute rather than chronic pain, we have no reason to believe that nocebo effects cannot make OA pain worse; indeed, as outlined below, we believe it highly likely that this is a common, important phenomenon in routine health-care.

Placebo research and the mechanisms responsible for placebo and nocebo effects

Research has been dominated by two disciplines – psychology and neurophysiology – both have concentrated on the brain of the patient, and worked more on placebo than nocebo.

Psychologists pursue two main theories – conditioning and expectation [1,32] – and there is good evidence to support them both. For example, experiments with cyclosporine A show that immunosuppression can be conditioned in both animals and humans [33, 34]. There are also numerous examples of experimental or observational work which indicates that positive and negative expectations can have a large influence on outcomes after the use of an intervention [1,32]. Psychologists have also investigated the influence of the patient's personality on their response to placebo [35].

Neurophysiology and functional neuro-imaging show what happens in the brain when a placebo response is activated [36,37,38]. For example, work on Parkinson's disease has proved instructive, as placebos can result in huge improvements in patient function, associated with demonstrable changes in brain images, mediated by changes in dopamine release [40]. In the field of pain, it has been shown that placebo pain relief is blocked by naloxone, suggesting that it is mediated by endorphin release, and that reduced cholecystokinin release is important, in addition to activation of reward centres through dopamine release [11,32,39,40,41]. The activation of descending inhibitory pain pathways appears to occur, and it has been suggested that the functional network architecture of the brain [42], as well as genetics [43] can predict placebo responsiveness.

Moerman has tried to rename the placebo response the 'meaning response' as his work suggests that the key mediator of the effects is the meaning of the whole intervention to the individual [44,45]. Recently, LeBlanc has tried to marry together the different psychological and physiological theories (expectation, conditioning and meaning) through his 'full correspondence theory' which points out that our memories result in certain environmental cues activating emotional responses that translate into physiological changes in the body [46]. Another interesting strand of research concerns the alignment of beliefs and rituals between the HCP and their client; this work indicates that a shared belief and involvement in a given ritual or mechanistic belief will enhance a placebo response [47].

Neurobiological mechanisms within patients' brains, thought to be important in placebo, were reviewed in this journal recently [48] and have been extensively reviewed by other authors [1,32]. But we believe that these avenues of research – which concentrate on the patient alone – do not address the most important mediators of placebo and nocebo effects. The practitioner-patient interaction is the focal point of all medical transactions. In our view, the behaviours of the practitioner, and the nature and quality of the transactions that occur between HCP and client, as well as the environment in which these transactions take place, are the keys to placebo/nocebo induction.

Transactions between health-care professionals and their clients

Health-care revolves around the interaction between a health-care professional (HCP) and client. This is a particular form of human interaction played out within certain unwritten rules: the person in the role of HCP usually has the dominant power; they are seen as the person with superior knowledge and the ability to deal with health problems, while the 'patient' is expected to play the role of a supplicant, sick person. Certain rituals are expected to take place, such as taking the history, and the physical examination. Numerous symbols of medical power, such as the stethoscope, are generally on display, and the HCP may be

wearing a distinctive uniform. It is usual for the patient to be anxious when ushered into the room in which these rituals take place, and little attention is paid to the ways in which the environment (the colours, decorations, smell, and 'feel' of the consulting room, for example) might affect the transaction.

Some placebo research has concentrated on the HCP rather than the patient alone (the work on consultation style quoted above, for example), and on concepts surrounding their interaction. Carl Rogers' theory about the importance of clinical behaviours has been particularly influential in psychiatry [49,50]. Rogers suggested that if a clinician was to be an effective 'healer' (which we interpret as meaning someone who induces a good placebo effect) they must be genuine (expressing their true feelings), display positive regard (caring for and valuing the client), be empathic (communicate understanding) and show unconditional regard (a positive attitude should be maintained whatever the client says or does). Another HCP-related factor that has been stressed in the healing literature is that of 'presence' (being there for another person). A framework of four levels of therapeutic presence has been described (presence, partial presence, full presence, and transcendental presence) [51,52]. Empathy - has been introduced into training in some medical schools, however, in this context the human interaction of the consultation is often reduced to a script. As a result, the words spoken are no longer 'genuine' because they are not the clinician's own and do not arise from the current consultation. We argue this process of de-contextualisation reduces effectiveness [53].

We tend to ignore the time element: for example, we are usually concerned with a single moment or mode of HCP/patient interaction but the effectiveness of a treatment is shaped by other contexts such as the patients' home or work. A typical prescription of a drug is not just about a pharmaceutical, but about a ritual that the patient enacts three times daily until the course of drugs is complete. The patient's interaction with the context for the treatment is characterised by a process of interpretation: a process by which they make their experiences meaningful. As both time and context shift, so does the patient's response.

What can change as a result of placebo or nocebo effects in OA, and how might we use placebo experiments to aid our understanding of the condition?

As outlined above, we know that placebo and nocebo effects in OA can change pain, stiffness, anxiety and depression. We also know that giving sham interventions can alter immune function and autonomic nervous system activity, but what about other changes that might occur, in health-related behaviours for example? Changes in activity or medication use resulting from a client-practitioner interaction could be of great long-term significance to symptoms, long term outcomes and general health. Table 1 summarises what we regard as the likely and unlikely changes that occur in people with OA.

TABLE: What might change in people with OA as a result of placebo/nocebo effects:

LIKELY

- Symptom perception, such as an increase or decrease in pain severity, or altered mood

- Physiology, such as alterations in autonomic nervous system activity
- Changes in health-related behaviours, such as improved self-management

LESS LIKELY

- Changes in pathophysiology, such as altered amounts of inflammation in the joints

UNLIKELY

- Changes in joint structure

We believe that this should be investigated, and that we can use sham interventions to help us understand diseases better – in other words *we recommend the use of placebo as an investigative tool in OA research*.

Recently 'open' placebo studies, in which the recipient is told that the tablets they are being given have no active ingredient that should make any difference, have been successfully carried out [54], and the participants' symptoms have improved, indicating that we could give people with OA a placebo without deception, and study their responses (both positive and negative) using a variety of clinical, biochemical and imaging outcome measures, in order to help us understand the disease, as well as the illness.

The relationship between pathological changes, biomarkers, and symptoms in OA is unclear [55]. For example: why is one damaged joint painful and another not, and why is the symptom experience so variable? By carefully examining which symptoms improve (or get worse) in response to placebo and which do not, which biomarkers change, and what structural change we might observe, we could answer such questions in a totally safe, ethical manner, and we could explore the extent to which other outcomes, such as health behaviours, are affected.

PART 2. A DIFFERENT APPROACHES TO THE 'PLACEBO PROBLEM'

Methodology:

Methodological problems abound. One is the paucity of theoretical frameworks applied. The main theories used have been patient conditioning and expectation, each of which centres on the response of the 'receiver' of the intervention. We believe that the 'giver' and the interactions between the giver (HCP) and receiver (patient or client) are more important. A number of theories of human interactions are available, and we have tested one of them (validation/invalidation), as outlined below.

The experimental approaches used are also problematic. Most data on placebo and nocebo effects comes from experiments (including trials) in which sham interventions are used, but fully informed consent is generally required, which alters expectations, and expectation is thought to be one of the main factors mediating these responses. It has been argued that consent can induce a nocebo effect in some people [56]. Trials and experiments take place in artificial contexts and involve patient-practitioner interactions that may affect outcomes, and

are predicated on a linear cause and effect, biomedical model, that does not take account of complexity [57].

Many of these problems are, of course, recognised, and there are many different designs available that get round some of them [57,58,59]. For example, the modified Zelen design may avoid the need for consent [60], and a wait-list design can reduce the need for patient-provider interactions in a control group [61]. Novel trial designs are one approach, but we believe that more radical solutions are needed, with the use of multi-disciplinary approaches, moving away for the reductionist scientific paradigm, and linear causal pathways, to a whole systems approach, concentrating on the contexts in which health care is delivered.

In the remainder of this article we summarise two approaches that we are taking, which put the emphasis on practitioner-client interactions.

The importance of validation and social safety

We have investigated the importance of one communication theory [62] and one neurophysiological theory concerned with social interaction and safety [63-66] in relation to placebo and nocebo [67].

We used Linehan's therapeutic construct of validation/invalidation to try to understand the role of 'feeling heard and understood' to placebo/nocebo effects [62]. Validation is a communication strategy used to convey acceptance and understanding to another person about their thoughts, feelings desires or behaviours [68]. Invalidation is the opposite, i.e. communicating non-acceptance or a lack of understanding to another. Fruzzetti [69] developed a comprehensive framework for delivering and measuring validating and invalidating behaviours during person-to-person interactions; validating feedback includes active listening, clarifying what the other person has said, or normalising their behaviours. Invalidating feedback includes actions such as ignoring or dismissing another person, pathologizing their behaviours or insisting on what they should think, feel or do.

Building on Shenk and Fruzzetti's experimental work [70], we randomly assigned healthy participants to receive validating (understanding), invalidating (non-understanding) or no feedback after they completed a series of stressful maths tasks. Invalidated participants reported significantly higher levels of negative mood, lower levels of perceived safety, were less likely to agree to take part in the study again, and showed higher levels of physiological arousal (indexed by increased heart rate and shorter pre-ejection period) than participants in the other two groups [26, 67]. This suggests the potentially detrimental and powerful effects of non-understanding (invalidating) communication.

We believe that an important mediator of these powerful negative effects is how safe we feel in our social environment. According to Porges' evolutionary-based polyvagal theory [63-66] when we perceive our environment as safe we engage the 'smart' vagus (the myelinated pathways of the vagal nerve). This 'smart' vagal pathway slows our heart rate and decreases autonomic arousal levels, by facilitating a calm visceral state. Because of the connection (via the vagus) between the heart and the striated muscles of the head and face, the 'smart' vagus also allows us to engage with our social world; to listen and express more effectively. In contrast, when we perceive the environment as threatening, the 'smart' vagus is down-

regulated and instead we engage our sympathetic nervous system. This increases our heart rate, down-regulates the striated muscles of the face and head, and results in a hampered ability to engage socially.

Our experimental and qualitative research [10,67,71] suggests that it is important that the patient feels listened to, understood and safe in their environment. If the client feels invalidated, and perceives the environment as threatening, this may have detrimental effects.

A 'trans-disciplinary, whole-systems approach to investigating practitioner-client interactions

We believe that we need to move from a reductionist to a systemic view in two ways; first, to recognise that context effects are interdependent and therefore to reduce the consultation to isolated elements removed from time and context, is unhelpful. Second, that practice-led research outside the fields of medicine and psychology (drama, performance and religious studies, for example) have methods of research and analysis which, although unfamiliar to medicine, offer rich potential to help us understand what is effective, and generalizable, and what can only be understood in an individual encounter.

We see the clinical encounter as a ritualistic performance. Our collaboration draws on the discipline of Performance Studies which is concerned with how material culture and the stories we tell ourselves about our lives, shape our embodied experiences, and determines how we each interpret encounters (that appear the same) very differently. For example, a play like *Hamlet* is repeatedly performed using the same script, but no two performances are ever the same, even if done by the same company on the same day. The performance blueprint – the script – remains the same, as do the settings and the costume, but its subtle interpretation is a matter of individual and collective interaction and experience. And while different consultations may appear very similar, conducted on the same day, in the same room, by the same HCP, the interaction of ritualised performance produces different experiences and outcomes.

Shakespeare said, 'All the world's a stage'. People who make theatre analyse the performance of everyday life in order to reproduce it and make it effective for its audience. If, as men and women, we are merely players (actors) then to create everyday life on stage is to understand complex systems of culturally situated processes of communication and interpretation. Performance specialists shape these systems in order to produce an effective outcome. The discipline draws on two thousand years of scholarship, and a rich tradition of theory, enabling engagement in deep-listening with audiences to shape responses with profound empathy. This deep-listening is not only aural but also spatial and embodied. Actors are trained to be reflexive about their work, to take their physical and emotional care seriously, to prepare before every encounter, and to learn through experience. We want to use such work to understand how the HCP in context creates a placebo response.

But how do we establish what the key processes are, come to understand what works, for whom and in what circumstances? And, perhaps more difficult, make that understanding useful to HCPS whose world-view is shaped by biomedical thinking? We can begin with three assumptions: first - humans are complex bio-cultural entities, second - our body's innate

healing (placebo) response can be shaped by contextualised human interactions, third - an understanding of 'culture' is important.

There is commonality between medicine and performance: as practitioners (HCPs, actors, directors) we recognise that both performance and medicine depend on our practice. In some of the placebo literature the importance of rituals within the clinical encounter have been stressed [72,73], and the importance of social interaction is recognised in psychology [74], but such work and thinking is still embedded in a scientific, biomedical culture, rather than taking a wider perspective. HCPs are taught to listen, but they get little teaching about the importance of non-verbal communication, or about what they might *feel* in response to human distress. Medicine is dominated by facts, figures and machines rather than intuition, caring and empathy, and yet placebo research shows us that context, meaning-making and caring are central to our well-being and ability to self-heal [1,7,44,72,73].

So far, medical research has been unable to explain why interpersonal communication and caring is efficacious – how human interactions heal. An engagement with the placebo and nocebo effects using a Performance-led approach offers a new way into understanding how real-time culturally dependant complex interactions can be shaped to create a positive patient experience.

Implications for the management of people with painful OA

The principles of medical ethics teach us that we should act in the best interests of patients and 'first do no harm' [75]. This can be achieved by maximising placebo effects (with or without the use of an intervention), and avoiding nocebo effects. Most modern interventions are potentially harmful, so we would argue that the more that this can be achieved without their use, the better.

Our review of the placebo and nocebo literature, as well as our experimental work, suggest that some physicians are better than others, and that those who can convey a sense of optimism (and probably those that improve expectations) are most likely to induce a positive response. But we believe that there are two other key issues that clinicians need to be more aware of if they are to activate placebo (healing) effects, and avoid inadvertently doing harm (nocebo effects) when seeing patients:

1. Both the patient and the HCP need to feel 'safe' during any healthcare interaction, and as far as is possible, have any anxiety alleviated.
2. The patient's experiences need validating, and any words or behaviours that might be interpreted as invalidating must be avoided.

Feeling calm and safe:

Most people feel anxious when consulting a healthcare professional. Sadly, it is often the case that the HCP is also feeling anxious or unsafe during a consultation, as he or she may be scared of making a mistake, of missing an important diagnosis, or of not fulfilling the needs of the health-care funders, as well as those of the patient. But when we feel threatened we cannot communicate well [63-66]. Perhaps this is why so many patients say that 'the doctor did not understand me', or 'I was not listened to properly', or 'I did not understand what they

said'. And the nocebo literature indicates that anxiety can make a negative response to the non-specific effects surrounding any consultation or prescription more likely, by increasing pain perception for example [11,12].

Preparing yourself before consulting (actors always go through rigorous ritual of mental and physical preparation before going on stage), paying attention to the whole environment, finding out how to make any individual feel relatively at ease with you, and shutting out any fears of your own, should all be attended to.

Validating patients, and avoiding invalidation

Clinicians must try to validate the experiences reported by their patients, and strive to avoid invalidation. Much attention is paid to compassion and empathy in medicine, but you can be compassionate and empathic without your patient realising it. If your understanding and acceptance is not *perceived* by the patient, inadvertent invalidation can ensue, leading to potential negative outcomes [71]. Much of the language of OA (such as 'it is just part of getting older') may be invalidating for some clients.

How can healthcare professionals avoid invalidating their patients? We were struck by the wisdom of one of the clinicians whom we interviewed for the research outlined above, who said that he 'simply wanted to understand the person and their experiences as best he could'. It may be that simple, just being present with someone else and genuinely wanting to understand their plight and their point of view. Maybe that could help us all comply with our core ethical principles.

CONCLUSIONS

Humans are capable of restoring themselves to health, both physiologically and emotionally. We believe that what has been termed the placebo response is the ability of human interactions and contextual factors to activate what could be called the 'self-healing response'. In the context of health-care consultations it would appear that a positive response is most likely if both the professional and the client feel safe, calm, and lack anxiety, and if the experiences of the client are validated by the professional. The HCP needs to achieve *'focussed attention with good intention'*. This is about caring and love, and is, perhaps, the art of medicine [76]. We also believe that a transdisciplinary whole systems research approach has to be adopted, rather than a reductionist one, to explore these complex, socially constructed, contextual issues [76,77].

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