The powerful placebo effect in osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis. Pain and its related function and stiffness are currently the major symptoms and primary outcomes for treatment. However, the treatment in the past has been primarily targeting on the peripheral changes in the joint that has led to suboptimal outcomes. Recently, we find that people with OA respond better to treatment which targets on both peripheral and central pain abnormalities. We also find that placebo per se is very effective for OA. On average 75% pain reduction, 71% functional improvement and 83% stiffness improvement in the treatment of OA are attributable to the placebo/contextual effect. The effect varies between treatments, for example for pain, from 47% with intra-articular corticosteroid injection to 91% with joint lavage. This begs a question on how to improve the overall treatment effect of an OA therapy in clinical practice by enhancing the contextual effect, rather than to separate a specific treatment effect from the contextual effect as we normally do in clinical trials. The enhancement may be achieved by improving contextual factors such as patient-physician interaction or quality of care. Further research on the development of a simple contextual enhancement package that may be delivered by all physicians according to individual needs would be very helpful.

Osteoarthritis

About one in four people aged 55 years have knee pain related to osteoarthritis (OA) of whom one in ten have disability (1). Half of us would develop knee OA if we all could live for 85 years (2). Both the incidence and prevalence of OA increase with age and are greater in women than men (3). Important risk factors for OA, in addition to age and female gender, include obesity (4), knee injury (5) and occupation (*e.g.* heavy lifting and professional sporting) (6). New risk factors identified more recently such as shape of hips (7), malalignment of knees (8), finger length ratio (2d4d ratio) (9) and genes (10, 11) may add to understanding of pathogenesis. OA may be diagnosed clinically or radiographically (12). It is suggested that a confident clinical diagnosis of knee OA can be made based on 3 symptoms (pain on usage, short-lived morning stiffness and functional limitation) and 3 signs (crepitus, restricted movement and bony enlargement) without radiographic examination (12).

Treatments of OA

More than 50 treatments have been developed for OA, the majority of which are symptomatic therapies (13). The beneficial effects of these treatments are marginal, with an average effect size (ES) of 0.31 (95% confidence interval (CI) 0.23, 0.39) (13). The benefits often are outweighed by the adverse effects (13). For example, paracetamol (acetaminophen) is currently recommended the first line analgesic for OA. However, its ES for pain is only 0.14 (95%CI 0.05, 0.23), which does not reach the threshold of the minimum clinical importance difference (MCID) of ES of 0.5 recommended by the National Institution of Health and Care for Excellence (NICE) (14). In contrast its side effects could be substantial (15). A population-based study in Canada demonstrated that paracetamol at 3g/day or more was associated with 20% increased risk (relative risk=1.20, 95%CI 1.03, 1.40) of the hospitalisation due to gastrointestinal (GI) complications (16). A further population-based study in the UK General Practice Research Database (GPRD) showed that paracetamol was associated with an increased risk of upper gastrointestinal (GI) bleeding, myocardial infarction (MI), stroke, heart failure, renal failure and all cause death. The risk profile was similar to ibuprofen it was and dose-dependent (17).

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It is well known that non-steroidal anti-inflammatory drugs (NSAIDs) are associated with GI and cardiovascular (CV) adverse events. In the US, for example, more than 16,500 deaths from GI bleeding are associated with the use of NSAIDs (18). In the UK, over 2,000 people die annually from NSAID-induced GI bleeding, which is the third leading cause of death (ovarian cancer, road accidents and NSAIDs…) (19). More than 2 billion dollars are spent annually to treat NSAID complications in the US (18), that means for every dollar spent on NSAIDs, approximately one more dollar is spent on treating NSAID-induced complications (18). Furthermore, NSAIDs are associated with increased CV adverse events. Current evidence confirm that the CV adverse events are not only associated with COX-2 inhibitors (coxibs) but also with conventional NSAIDs (15).

Safer agents such as glucosamine and chondroitin products have been developed. However, like many other nutraceuticals, the efficacy remains controversial (15). Non-pharmacological therapies (*e.g.* exercise) are currently the core therapies for OA. However, many patients require more than only exercise in order to control pain and functional disability (14, 20). While the development of new treatments is important, less has been done on optimisation of the current treatments according to the context of therapy and individual responses.

Suokas and colleagues recently demonstrated that OA was not simply a peripheral joint disease, but a condition related to the central sensitisation (21). It is well known that OA pain often is discordant with the underlying structure damages (22, 23). People with severe radiographic OA may not have symptoms, whereas those with very minor radiographic OA may complain more. OA also is associated with an increased likelihood of other joint pain (*e.g.* chronic widespread pain syndrome) (24). Persistent knee pain remains in some patients after total knee replacement (TKR) (25).

I have therefore proposed that the treatment should be tailored to the disease stage according to contributions from central and peripheral pain mechanisms and patient characteristics (Fig. 1). For example, at the early stage of knee OA pain, strengthening exercise and/or topical NSAIDs may be more useful due to the main contribution from peripheral risk factors at this stage. At the middle stage of the disease, mind-body exercise and/or intra-articular corticosteroid injection (stronger analgesic with greater placebo effect) may be more useful because of contributions from both central and peripheral risk factors. At the later stage or even after TKR, mindfulness (or meditation) and/or central analgesics such as duloxetine or opioids may be more useful, as central pain mechanism may play a major role at this stage. This proposed approach is subject to individual patient characteristics and is supported by our current research in knee pain, in which peripheral risk factors contributed more to the incidence of knee pain whereas central risk factors contributed more to the progression of knee pain (26). It is also supported by the lesson we have learnt recently that biologic agents for OA were no better than placebo if they were used, irrespective of the disease stage and individual patient characteristics (27). The treatment for OA pain should consider both peripheral and central pain mechanisms.

Placebo

Treating both peripheral and central pain abnormalities is not easy with drugs. It often requires combinations of two or more drugs for different sites of the pain pathway. Such combinations often cause more side effects, hence have limitations. In contrast, exercise is a unique therapy which may be delivered in different forms for multiple benefits (Fig. 1). Placebo is another treatment with such multiple benefits, but has been largely ignored because of ethical issues and controversial results from a mega-meta-analysis in over 60 conditions (28).

Placebo is defined as a substance or procedure… that is objectively without specific activity for the condition being treated (29). It is unethical to use an inert pill to treat patients if we know it contains no active ingredient. However, is it truly ineffective? Irrespective of the inadequate amalgamation of the different conditions which respond to placebo differently, the meta-analysis reported by Hrobjartsson *et al.* in fact confirmed that placebo was more effective than no treatment for pain (28). This is in line with Beecher's previous findings in terms of the placebo response (change from baseline in the placebo group) in the late 1950s (30), but more specific for the difference between placebo and no treatment group. It is further supported by recent randomised controlled trials (RCTs) where placebo has been compared with no treatment or waiting list control in common cold, hypertension, irritable bowel syndrome and OA (31-34).

Whether placebo works or not is no longer a question. How it works or what are the key contextual elements that make placebo work becomes a research agenda at the moment. From its initial use to please patients in the 1700s (31-35) to the first placebo-controlled RCT published in 1948 (36) and now back to clinical practice as a contextual enhancement therapy, an oldest treatment in the medical history faces a new era (Fig. 2).

Placebo effect in OA

In 2008, we undertook a meta-analysis of RCTs to examine whether placebo was effective and analysed its possible determinants in OA (37). A systematic literature search was conducted to search randomised, placebo/untreated control trials in OA. Efficacy data in pain, function, stiffness and global assessment, as well as walking distance, muscle strength, range of movement, etc. were extracted from each relevant trial.

Effect size (ES) was calculated as the mean difference from baseline to endpoint for each treatment arm. ES was compared between placebo and untreated arm to establish the placebo effect. Publication bias was determined using the funnel plot and the Eggers test. Heterogeneity was examined using the forest plot and the I^2 statistics. Subgroup and mete-regression analyses were undertaken to examine the determinants of the placebo effect.

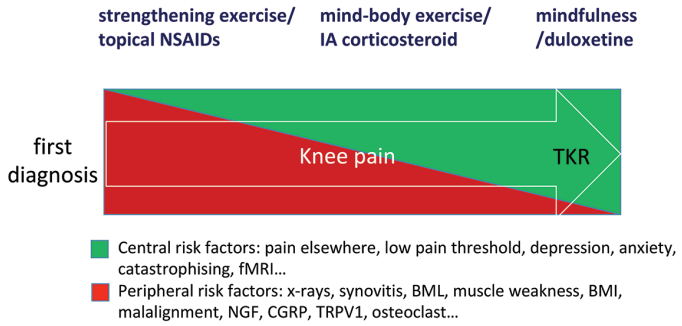

Fig. 1. Central and peripheral contributions to pain at different stages of knee osteoarthritis and optimal treatments.

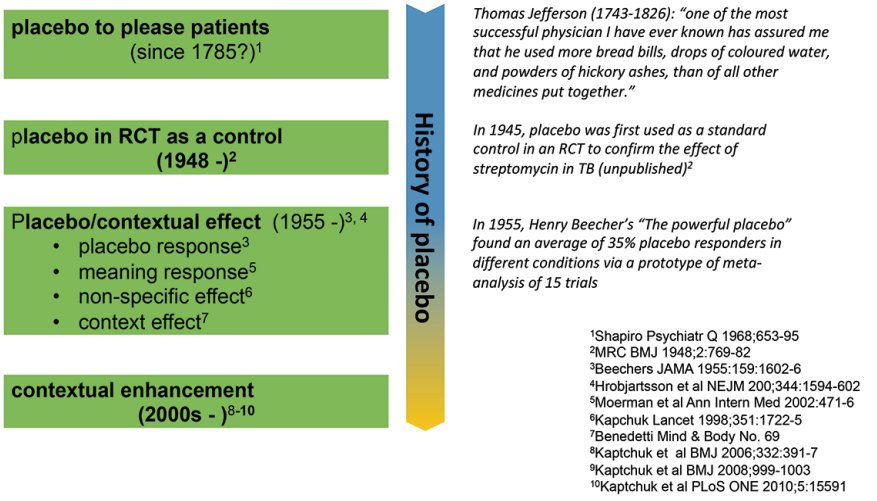

Fig. 2. Brief history and terminology of placebo.

Over 4000 studies were obtained from the search. After the scrutiny, 198 met the inclusion criteria, of which 184 with placebo, 3 with both placebo and untreated control and 11 with untreated control. The funnel plot demonstrated an asymmetric distribution, suggesting that the studies with smaller placebo effect are more likely to be published. This finding is in accordance with other evidence that the studies with a positive result for the new treatment (*i.e.* difference between active and placebo treatment) is more likely to be published.

The overall ES of placebo was 0.51 (95%CI 0.47, 0.56) for pain, which was significantly better than no treatment (ES 0.03, 95%CI -0.03, 0.18) (37), suggesting placebo is effective to relieve pain due to OA. The placebo effect increased with strength of active treatment, baseline pain score and sample size. Needle placebo was more effective than pill placebo. The study also found that placebo was effective for function, stiffness and physician global assessment, but not significantly for muscle strength, knee circumference, and range of movement (Table I).

Contextual effect of treatment

Placebo effect is in fact an integral part of treatment effect. It can never be or need not be separated from treatment effect in clinical practice. The separation is only needed when we do a RCT to develop a new treatment. In clinical practice, however, the separation becomes redundant. It has developed a gap between trial and clinical practice, *i.e.* what we get from RCTs is often different from what we observe in clinical practice, so called "efficacy paradox" (38). For example, intra-articular hyaluronic acid (IAHA) is no better than placebo in RCTs; therefore, we do not recommend IAHA for OA. In contrast, NSAIDs are better than placebo in RCTs; hence we recommend the use of NSAIDs for OA (with PPIs as appropriate to reduce NSAIDs-induced GI adverse effects) (14). However, in clinical practice, what we have observed is the total treatment effect that includes both specific treatment effect and the contextual (or placebo) effect, from which IAHA is better than NSAIDs (Fig. 3)!

These observations have made clinicians confused and many do not trust the guidelines. We have therefore proposed a measure to overcome this paradox – proportion of the contextual effect (PCE) (39). The PCE can be simply calculated from a trial with placebo response (*e.g.* change from baseline in placebo group) divided by overall

Table I. Placebo effect for different outcomes in osteoarthritis. Adapted from Zhang *et al.*: *Ann Rheum Dis* 2008; 67: 1716-23 with permission.

Outcomes	no. of studies	no. of patients	ES	95%CI	Chi-square (heterogeneity)	*p*-value (heterogeneity)
Pain	180	14686	0.51	0.46, 0.55	555.31	<0.001
Function	80	8289	0.49	0.44, 0.54	180.81	<0.001
Stiffness	72	7529	0.43	0.38, 0.49	150.22	<0.001
Physician global assessment	21	3459	0.66	0.53, 0.78	113.29	<0.001
Walking time/distance	11	526	0.22	0.08, 0.35	11.87	0.29
Quadriceps strength	2	35	-0.24	-0.72, 0.23	0.58	0.45
Joint space width	5	458	0.32	0.17, 0.46	4.58	0.33
Knee circumference	2	65	0.45	-0.21, 1.10	6.23	0.04
Range of motion	3	134	0.04	-0.36, 0.43	0.83	0.66

ES: effect size, CI: confidence interval.

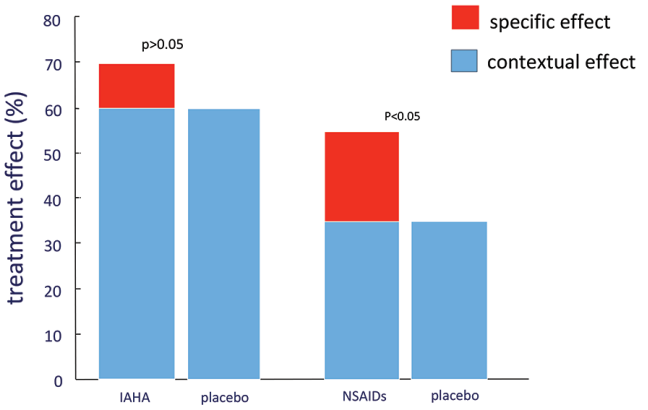

Fig. 3. Efficacy paradox.

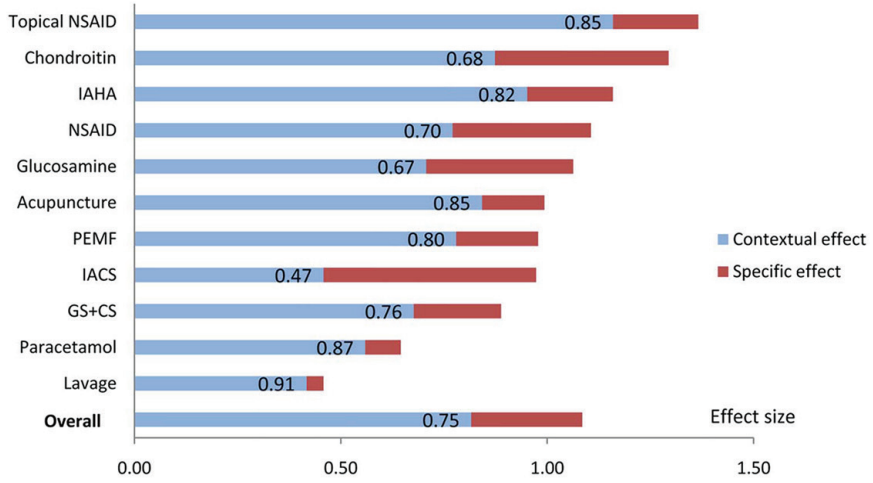

Fig. 4. Proportion of the contextual effect in the treatment of osteoarthritis pain. Adapted from Zou *et al*.: *Ann Rheum Dis* 2016; 75: 1964-70 with permission.

Table II. Proportion of the contextual effect in the treatment of osteoarthritis.

Treatment	PCE (95%CI)		
	Pain	Function	Stiffness
Glucosamine	0.67 (0.53, 0.84)	0.64 (0.49, 0.82)	0.82 (0.63, 1.05)
Chondroitin	0.68 (0.55, 0.84)	0.63 (0.47, 0.85)	1.00 (0.77, 1.30)
Glucosamine+chondroitin	0.76 (0.62, 0.93)	0.85 (0.71, 1.02)	0.91 (0.72, 1.15)
Paracetamol	0.87 (0.73, 1.03)	0.92 (0.78, 1.09)	0.95 (0.72, 1.24)
NSAIDs	0.70 (0.65, 0.75)	0.64 (0.59, 0.70)	0.73 (0.67, 0.80)
Topical NSAIDs	0.85 (0.77, 0.93)	0.71 (0.58, 0.87)	0.93 (0.84, 1.03)
PEME	0.80 (0.64, 0.99)	0.63 (0.47, 0.84)	0.71 (0.43, 1.17)
Acupuncture	0.85 (0.74, 0.97)	0.85 (0.72, 1.00)	0.79 (0.66, 0.94)
IACS	0.47 (0.32, 0.70)	0.68 (0.40, 1.18)	0.83 (0.34, 2.04)
IAHA	0.82 (0.75, 0.90)	0.84 (0.74, 0.96)	0.88 (0.77, 1.00)
Lavage	0.91 (0.60, 1.37)	0.93 (0.62, 1.40)	1.00 (0.46, 2.16)
Overall	**0.75 (0.72, 0.79)**	**0.71 (0.67, 0.75)**	**0.83 (0.79, 0.87)**

IACS: intra-articular corticosteroid; IAHA: intra-articular hyaluronic acid; NSAIDs: non-steroidal anti-inflammatory drugs; PEMF: pulsed-electromagnetic field therapy.

treatment response (*e.g.* change from baseline in treatment group). In OA, for example, on average, the PCE is 0.75 for pain, which means 75% pain relief effects are explained by the contextual effects. The PCE varies between treatments from 47% for intra-articular corticosteroid (IACS) injection to 91% for lavage on pain outcome (Fig. 4) (39). The PCE varies between outcomes, which is 0.71 for function, suggesting that 71% improvement in function are in fact obtained from the contextual effects. In contrast, it is 0.83 for stiffness, suggesting that 83% improvement in stiffness is obtained from the contextual effects. For chondroitin and lavage, 100 % treatment effects in stiffness are contextual (Table II).

The PCE also varies between diseases. It is slightly lower for pain in rheumatoid arthritis (PCE=0.63) (38) and fibromyalgia (PCE=0.60) (40). In addition, contextual effects are not only observed in subjective outcomes such as pain, but also objective outcomes such as ESR (63%) and CRP (42%) (38).

The PCE is useful to guide clinical practice, as it informs the clinician concerning an overall strength of each treatment, proportion gained from the treatment and the context of the treatment. It helps to fill the gap between RCTs and clinical practice; interpret evidence from trials more accurately, and encourage physicians to improve the quality of care (*i.e.* enhance/optimise the context of therapy) when they deliver a treatment.

Contextual enhancement

A number of contextual factors may be used to enhance contextual effects. Di Blasi *et al*. have classified them into five categories: patient characteristics, physician characteristics, patient-physician interactions, treatment characteristics and environment (41). Some are easy to modify, whereas others are not. Suarez-Almazor *et al*. recently undertook a two stage randomisation for communication style (high expectation *vs*. neutral expectation communication style) and acupuncture in knee OA (34). At the stage one, 560 patients with knee OA were randomly allocated to 3 groups: high expectation communication, neutral expectation communication or waiting list. At the stage two, patients in the high or neutral expectation communication groups were randomly allocated to either acupuncture or sham acupuncture. The treatments were given twice a week over 6 weeks. The outcomes were observed at week 0, 4, 6 and 3 months and repeated measure analysis of variance was used to assess the changes over time. The results showed that (a) all treatment groups

experienced superior results compared to the waiting list group; (b) differences were seen between high and neutral expectation groups for pain reduction and satisfaction; (c) there was no difference between acupuncture and sham acupuncture. The study suggests that the analgesic effect of either treatment may be enhanced by positive/confident communication of physicians.

What are the key elements in the high and neutral expectation communication groups? The authors defined high expectation communication as confident treatment, using positive utterances such as "I think this will work for you", "I've had a lot of success with treating knee pain", and "Most of my patients get better". A high expectation brochure was given to patients. The research co-ordinator assisting with these patients was also trained to interact with a high expectation style. In contrast, neutral expectation was defined as presenting uncertainty about the treatment, using utterances such as "it may or may not work for you", "It really depends on the patient", and "We're uncertain, and that's why we are doing the study. A neutral expectation brochure was given to patients. The research co-ordinator for this group was trained to interact with a neutral style.

These findings suggest that the contextual effect may be enhanced by simply adding the non-specific treatment elements such as positive communication about the treatment. More research is needed to identify the key contextual elements that may be used in every clinical encounter to maximise the treatment effect.

Other issues

Terminology

Placebo effect is defined as a difference between placebo and no treatment (28, 33), whereas placebo response is defined as change from baseline in the placebo group (30). The former measures the specific treatment effect due to placebo, whereas the latter measures all changes related to the use of placebo including the effect due to placebo (therapeutic ritual), effect due to being observed (Hawthorn effect), regression to the mean, and outcome fluctuation due to the natural history of disease. Several alternative terms have been used for placebo effect, including non-specific treatment effect (42), meaning response (29) and context/contextual effect (43) (Fig. 2). Despite the caveats, placebo and placebo effect (or response) are still the most commonly used terms. I would like to suggest using "context of therapy" instead of placebo, and "contextual effect" instead of placebo effect in clinical practice, as these terms emphasise the importance of the context of treatment and encourage physicians to improve their care for patient. Placebo and placebo effect/response are useful and meaningful primarily in RCTs.

Obecalp

This is a word that reads reversely for placebo. It is one of many forms of placebo treatment accessible on the market. Irrespective of the ethical challenge and debate for its benefits, placebo has been widely used by physicians and other health professionals all over the world. A systematic review of 22 surveys across 12 countries shows that 17 to 80% physicians and 51 to 100% nurses have ever prescribed placebo (44). The figure varies from country to country from 17% in Switzerland to 99% in Sweden. It has been prescribed in the form of either pure placebos (such as obecalp), or impure placebos (such as antibiotics for viral infection). With conversion of the terminology from placebo/placebo effect to context/contextal effect, physicians no longer need to prescribe the obecalp unethically, but to improve the patient-physician relationship.

Nocebo effect

Placebo is not free from side effects. Adverse effects of placebo or context of therapy are defined as nocebo effects (45). In RCTs, nocebo effects depend substantially upon active treatment (46), *e.g.* placebo to opioids causes more constipation, and placebo to colchicine causes more diarrhoea. In clinical practice, nocebo effects depend largely on patient – physician interactions (47). For example, while "doctor's touch" generally is beneficial, it could be harmful in some patients, simply because not everyone likes to be touched. It depends on individuals, culture and religion. Whom to touch, when to touch and where to touch remain questions to be answered through further clinical research and observations.

Conclusion

OA is a common chronic painful joint condition with a long list of treatment options. On average about 75% of pain relief, 71% function improvement and 83% stiffness improvement are gained from placebo or context of therapy. The contextual effect varies greatly between treatments, for example, from 47% with intra-articular steroid injection to 91% with joint lavage for pain relief. The contextual effect may be enhanced through improvement of contextual elements such as patient-physician interaction. Further research is required to identify the key contextual elements that can be delivered by physicians to enhance treatment effects in OA.

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