

Placebo effect of an inert gel on experimentally induced leg muscle pain

James G Hopker¹
Abigail J Foad²
Christopher J Beedie²
Damian A Coleman²
Geoffrey Leach¹

¹Centre for Sports Studies, University of Kent, Chatham, Kent, UK; ²Department of Sports Science, Tourism and Leisure, Canterbury Christ Church University, Canterbury, Kent, UK

Purpose: This study examined the therapeutic effects of an inert placebo gel on experimentally induced muscle pain in a sports therapy setting. It aimed to investigate the degree to which conditioned analgesia, coupled with an expectation of intervention, was a factor in subsequent analgesia.

Methods: Participants were sixteen male and eight female sports therapy students at a UK University. With institutional ethics board approval and following informed consent procedures, each was exposed to pain stimulus in the lower leg in five conditions, ie, conditioning, prebaseline, experimental (two placebo gel applications), and postbaseline. In conditioning trials, participants identified a level of pain stimulus equivalent to a perceived pain rating of 6/10. An inert placebo gel was then applied to the site with the explicit instruction that it was an analgesic. Participants were re-exposed to the pain stimulus, the level of which, without their knowledge, had been decreased, creating the impression of an analgesic effect resulting from the gel. In experimental conditions, the placebo gel was applied and the level of pain stimulus required to elicit a pain rating of 6/10 recorded.

Results: Following application of the placebo gel, the level of pain stimulus required to elicit a pain rating of 6/10 increased by 8.2%. Application of the placebo gel significantly decreased participant's perceptions of muscle pain ($P = 0.001$).

Conclusion: Subjects' experience and expectation of pain reduction may be major factors in the therapeutic process. These factors should be considered in the sports therapeutic environment.

Keywords: conditioning, expectation, perception, positive belief, sports therapy

Introduction

It is incumbent upon sports medicine practitioners to acknowledge developments in their field. Whilst some developments, eg, new imaging technologies or manipulation techniques, are relatively simple to incorporate into the therapeutic process, others, such as new insights into human cognition and behavior, are sometimes less so. In fact, such developments are often deemed the realm of the sports or clinical psychologist. A phenomenon that arguably falls into this latter category is the relationship between a person's beliefs and health outcomes, a phenomenon termed "the placebo effect". In summary, evidence from medicine,¹ psychology,² and anthropology,³ suggests that an individual's beliefs in therapeutic outcomes are often significant factors in the treatment process. Positive beliefs and perceptions can lead to positive outcomes and vice versa (the nocebo effect).

Correspondence: James Hopker
Centre for Sports Studies, University
of Kent, Chatham, UK
Tel +44 016 3488 8814
Fax +44 016 3488 8809
Email j.g.hopker@kent.ac.uk

The placebo effect has been researched in sport, and significant effects of belief on sports performance have been reported (see Beedie and Foad⁴ for review). In a study of placebo analgesia related to sports performance, Benedetti et al⁵ investigated the placebo analgesic effects of morphine on a pain endurance test. Subjects had a tourniquet wrapped around their forearm and were required to squeeze a hand spring exerciser repeatedly until they could no longer continue. During precompetition training, two “teams”, A and B, received no pharmacologic substance, whilst teams C and D were trained with morphine. During competition, team A received no treatment while teams B and C were given placebo. Team D also received what they believed was morphine, but they actually received naloxone, a drug expected to antagonize the opioid pathways and offset any analgesic effect. As hypothesized, naloxone negated the morphine preconditioning effects in Team D. The largest placebo effect on pain tolerance was observed in team C, who received the morphine preconditioning in the “training” trials, believed that they had ingested morphine in the competition trials, and had been told to expect an increase in pain tolerance as a result of the morphine. The combination of a conditioning procedure and a verbal expectancy manipulation designed to enhance subject’s beliefs in the efficacy of the treatment maximized subsequent perceptions of pain relief.

Perhaps the most fruitful area of placebo effect research over the last 10 years has been in pain and analgesia. As Benedetti¹ suggests, this is largely because pain is highly susceptible to social and psychologic modulation. Beedie⁶ has also noted that reduction in pain might partially or fully explain the placebo effects observed in sports performance. Evidence demonstrates that expectation of pain relief can modify the effectiveness of administered substances, be they active analgesics or inactive placebos. These effects can be both hypoalgesic and hyperalgesic. Several complex designs have been used to elucidate this phenomenon, ranging from covert manipulation of experimental pain stimuli to direct comparison of the effects of the hidden/deceptive administration of biologically active treatments with the overt administration of biologically inactive substances. For example, Voudouris et al⁷ introduced an experimental manipulation in order to examine the role of conditioning in the placebo analgesic response. Baseline pain tolerance was assessed via the application of a pain generator to the forearm, following which a topical cream (a placebo described as a fast-acting local painkiller) was applied. During the conditioning trials, the pain stimulus was deceptively (ie, without subjects’ awareness) increased for half of the subjects (control

group), and decreased for the others (the placebo group). As hypothesized, in a subsequent trial with pain stimulus intensity equivalent to baseline levels, subjects in the placebo group exhibited significantly increased pain tolerance whilst subjects in the control group exhibited significantly decreased pain tolerance. Montgomery and Kirsch⁸ expanded on the original design of Voudouris et al⁷ by verbally manipulating the subject’s expectancy of pain relief. Like Voudouris et al,⁷ subjects were exposed to a pain stimulus at baseline, the level of which was surreptitiously reduced in subsequent trials following the application of a placebo analgesic cream. However, subjects were then split into two groups whereby the first group was correctly informed about the deception, and the second was not informed. On re-exposure to the pain at baseline level, subjects who had been correctly informed of the deception experienced no pain relief when the placebo analgesic cream was applied, while those in the second group reported substantially lower pain. Levine et al^{9–11} administered active painkillers covertly, and placebo painkillers openly, to two groups of subjects following dental surgery. They reported that the overt injection of a saline placebo described as morphine was as effective as a covert injection of morphine. Similarly, Benedetti et al^{12–14} compared the open administration of five different painkillers with hidden and automated administration of the same drugs. The authors reported that in hidden administration conditions the time taken for postoperative pain to diminish by 50% was greatly increased for all drugs compared with open administration. These findings suggest that expectation of analgesia is a major factor in subsequent perceived analgesia.

Although the placebo effect has yet to be systematically examined in sports therapy, research in related fields has demonstrated placebo effects on therapeutic outcomes. For example, Hashish et al¹⁵ tested the value of therapeutic ultrasound for reducing inflammation following dental surgery. The subjects were divided into three groups, ie, control, placebo ultrasound, and actual ultrasound. Postoperative symptoms of swelling and pain were significantly reduced in patients in both the actual and placebo ultrasound groups compared with controls.

Inadvertent evidence for what might legitimately be described as placebo effects in sports therapy derive not from placebo effect research per se, but from investigation of an “active” treatment. For example, in a study by Reeser et al¹⁶ of magnetic therapy, the experimental treatment was found to perform no better than the placebo. That is, the placebo was as “active” as the active treatment itself in reducing perceptions of delayed onset muscle soreness. In a study by

Hornery et al¹⁷ of cooling protocols, the authors reported a “dramatic” placebo effect from the cooling application on anaerobic performance and ratings of perceived exertion. However, it is noted that the study by Reeser et al¹⁶ did not include a no-treatment group to identify whether the magnitude of the placebo effect was greater than would have been experienced following no treatment at all, and in the study by Hornery et al¹⁷ there was no placebo control with which to differentiate placebo from active effects. Thus, while the findings of both studies are suggestive of placebo effects in sports therapy, limitations in design preclude valid and reliable estimation of such effects.

The aforementioned data support the idea that an individual’s belief in, or perceptions of, the efficacy of a received therapeutic sports treatment may impact on the outcome of that treatment. However, the empiric evidence required to move beyond such speculation is lacking. Deliberate placebo effect research in sports therapy is necessary in order to gain a better understanding of the mechanisms underlying observed treatment effects, of the role of placebo effects in the rehabilitation process, and of the potential to utilize such effects to the benefit of the patient in practice. The present study sought preliminary data on the relationship between expectation and outcomes in the sports therapy environment. Using a similar conditioning protocol to those of Voudouris et al⁷ and Montgomery and Kirsch⁸ described earlier, the current study aimed to investigate the effects of a placebo muscle gel in the treatment of experimentally induced muscle pain. It was hypothesized that, if expectation of pain reduction were linked with the application of an inert placebo gel, a higher level of pain stimulus would be required to elicit a given pain response than in controls.

Methods

Ethical considerations

The placebo effect is problematic to study and represents something of a paradox to researchers. That is, if a participant is aware that they are taking a placebo they are unlikely to experience a beneficial outcome (ie, a placebo effect). Thus, the placebo effect can only operate when a deliberate or inadvertent deception has taken place. Given that some form of deception is therefore necessary to make valid assessments of placebo phenomena, consideration of the ethical guidelines of the American Psychological Association¹⁸ concerning the use of deceptive protocols is a prerequisite to all placebo effect studies. In this instance, the recommendations of guideline 8.07 “Deception in research” were observed throughout the research process. Experimental

procedures and possible risks were explained verbally and in writing prior to informed consent being obtained. Each participant was fully informed of the study deceptions after completion of data collection. Participants also completed a medical history screening questionnaire to identify potential interferential electrotherapy contraindications, as outlined by Watson,¹⁹ and undertook a sharp/blunt skin sensory test prior to each electrotherapy treatment.

Participants

Twenty-four (16 male and 8 female) untrained university students volunteered to take part in this study (mean age \pm standard deviation [SD] 20.7 \pm 3.9 years).

Equipment

The Ultracom 2 Model M4220 was used to elicit pain responses. It was set to two poles with a carrier frequency of 5.0 kHz, and lower and upper treatment frequencies were 125 to 130 pulses per second, respectively. The sweep was set at 1:1. These interferential settings are within the range typically used during conventional electrotherapy treatment sessions.²⁰ Two electrotherapy poles were used for maximum location consistency. One pole was placed on the superior aspect of the gastrocnemius between the two heads and distal to the knee, the second on the inferior aspect of the gastrocnemius proximal to the Achilles tendon. The frequencies were set at high levels to avoid involuntary muscle contraction and so eliminate movement as a variable. The frequencies and sweep were selected to limit the effect of surges from base to top frequency, and so allowed a more gradual increase in intensity. This enabled the participant to make a more precise assessment of the level of stimulation.

Procedure

Data were collected in the sports therapy suite of a UK university. The participants undertook an experimental pain induction on five separate occasions over a five-week period. In each condition, one leg was under the experimental manipulation whilst the other acted as the control. This was reversed in the subsequent condition.

The dependent variable was the level of interferential electrotherapeutic stimulation required to elicit a pain response equivalent to a rating of 6 on a 10-point visual analog pain scale, with 0 = no pain felt and 10 = unbearable pain.²¹

Participants were informed that an initial test was required to identify any adverse responses to the procedure. However, the true purpose of this trial was to link the unconditioned

stimulus (the inert gel) to a conditioned response (pain reduction). This involved first determining an initial level of interferential stimulation by which the participant, supine on a physiotherapy table, was told to plantar flex and dorsiflex their ankle. The interferential stimulation was introduced by rapidly increasing the electrotherapy current until the participant felt the treatment start, which was usually a slight tingling sensation. The current was subsequently increased every two seconds and the participant asked to tell the tester when the level of stimulation reached the equivalent of 6 on the pain scale. Once participants perceived the stimulus to have reached a level of 6, this level of interferential stimulation was recorded. The level of stimulation was also held at this point for 30 seconds to enable the participant to commit the sensation to memory, before being returned to zero. After a further 30 seconds, the current was again increased until the participant assessed the level of stimulation to be the same as before, at which time the current was recorded and the test finished. The purpose of this repeated test was to check the reliability of the participant's perception of a pain rating of 6/10. The same protocol was then followed for the other leg. The participant was not informed of the result of either test.

Immediately following the reliable determination of the participant's perceived pain rating of 6/10, a placebo gel was applied (ultrasound transmission gel, Parker Laboratories Inc. Aquasonic 100, supplemented by two drops of camphor essential oil to provide an olfactory stimulus). The gel was described to participants as an analgesic used by professional sportsmen in American football and English rugby. Participants were further informed that there was considerable anecdotal evidence among sports therapy practitioners that

the product reduced muscle pain. To enhance participants' expectations of a therapeutic effect further, the gel was placed in an authentic muscle gel dispenser.

Following application of the placebo gel, the process described above was repeated. However, although participants were informed that the level of stimulation was equal to the initial stimulation, the level of stimulation was in fact deceptively decreased by 20% to create the impression of an analgesic effect resulting from the gel application.

In baseline trials, the level of stimulation required to elicit a pain rating of 6 was measured for each leg.

The protocol for the two placebo trials in weeks 3 and 4 was the same as for the conditioning trial, except that the level of interferential stimulation was set by the participant. After attaching the electrodes, participants identified a level of stimulation that elicited a perceived pain rating of 6/10. This enabled the determination of a day baseline level of stimulation that allowed for comparisons when under the placebo condition. The placebo gel was then applied to the experimental leg, and the procedure repeated on both experimental and control legs. The experimental leg was randomly selected for each participant at the first treatment trial, then the experimental and control legs were reversed for the second treatment trial.

Postintervention baseline trials were conducted, which essentially were repeats of the preintervention baseline trial. The procedure for the placebo and control conditions is shown in Figure 1.

Data analysis

Data were found to be non normally distributed. A non-parametric Friedman test was conducted to identify

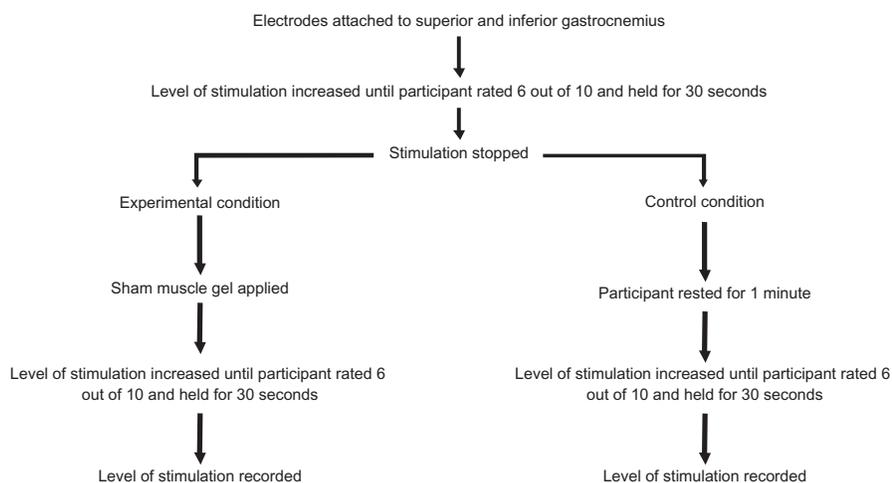


Figure 1 Schematic of procedure in experimental and control conditions.

differences between placebo and control conditions. Subsequent analysis via the use of Wilcoxon signed ranks identified differences between individual tests. Change scores were calculated comparing test administration 1 to 2 across the same test session. Analysis was conducted on these change scores across baseline, placebo, and control conditions. Significance was accepted at $P < 0.05$ and data expressed as means \pm SD unless otherwise stated. Data from the conditioning trials are excluded from the analysis.

Results

Statistical analysis of the results demonstrated a significant effect of the application of the placebo gel ($P = 0.001$). The mean values presented in the Table 1 represent the differences in level of interferential stimulation to generate a perceived pain rating of 6/10 above the initial stimulation.

Subsequent analysis revealed that significant differences existed for all placebo gel application treatments compared with control conditions. The amplitude of interferential stimulation required to elicit a pain rating of 6/10 was 8.2% higher following the application of the placebo gel (prebaseline to placebo condition + 1.6 versus + 16.6 mA, $P = 0.003$). A significant difference was also observed in the change in amplitude of stimulation above an initial level between the same trial control and placebo legs (+ 3.7 versus + 16.6 mA; $P = 0.002$). Finally, a significant difference was evident between the change in amplitude of stimulation above the initial level at postbaseline compared with the placebo condition (+ 4.5 versus + 16.6 mA; $P = 0.002$). There were no significant differences between either of the baseline or control conditions (prebaseline to control + 1.6 versus + 3.7 mA; $P = 0.4$; prebaseline to postbaseline + 1.6 versus + 4.5 mA; $P = 0.2$; postbaseline to control + 4.5 versus + 3.7 mA; $P = 0.7$). Figure 2 illustrates the magnitude of changes from initial same session stimulation to baseline, control, and placebo conditions.

Discussion

The results demonstrate that a conditioning procedure followed by administration of a placebo gel and an

Table 1 Mean change in test scores from an initial same day stimulation for all trials at a perceived discomfort level of 6/10

Trial	Difference in level of interferential stimulation (mA)
Prebaseline	1.6 \pm 14.7
Placebo	16.6 \pm 12.8
Control	3.7 \pm 11.5
Postbaseline	4.5 \pm 10.4

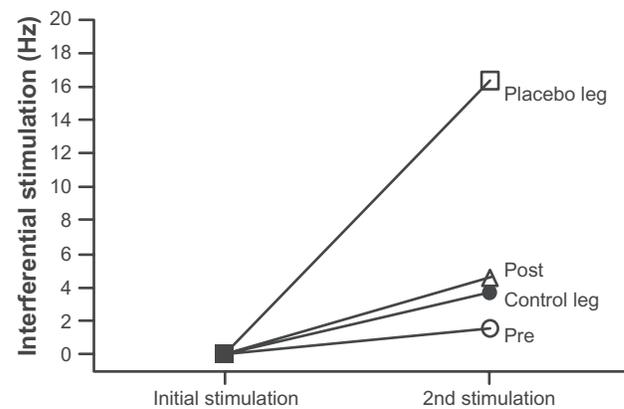


Figure 2 Stimulation changes from an initial same session stimulation across trials. Second stimulation followed no intervention in the baseline and control conditions and placebo gel application in the placebo condition.

expectancy of pain relief significantly decreased pain induced by electrotherapeutic stimulation. Participants tolerated significantly greater amplitudes of interferential stimulation than when in control conditions (placebo + 16.6 mA versus control + 3.7 mA; $P = 0.002$). Findings are consistent with those from biomedicine described above, particularly those of Benedetti et al,⁵ whose subjects demonstrated maximum levels of pain tolerance following a combined conditioning procedure and verbal expectancy manipulation.

Our findings are also congruent with those of Montgomery and Kirsch⁸ and Price et al²² who suggested that placebo effects do not always reflect a global, nonspecific response to treatment, as previously suggested,¹⁰ but rather a highly specific, localised response. The intervention resulted in a placebo effect in one leg that was not observed on immediate sequential stimulation of the control site that did not receive the topical gel application. This suggests a spatially restricted mechanism of placebo analgesia. That is, the effect observed was similar to that of a real analgesic gel applied locally, and distinct from an oral analgesic, which would have the more general action of alleviating pain in both legs. This finding is also consistent with recent findings suggesting that placebo effects mimic those of the drug they purport to represent.¹ In this case, had a true analgesic treatment been applied to one leg, analgesia would only be experienced in that leg, thus the placebo effect mimicked the real effect.

The data were derived from experimentally induced pain and thus have low ecological validity. However, they highlight once again the relationship between psychological variables and health outcomes. It is not possible to state whether the observed effects resulted from conditioning, expectancy, or both. However, recognition that multiple factors, such as experience and expectation, are more effective

than any one factor in isolation suggests that the individual perceives the placebo agent to be more powerful when these factors are combined and similarly directed. Thus, the individual's perception of the placebo agent, ie, their knowledge and expectation of the effects of the therapeutic intervention, appears to be central to the magnitude of the placebo effect.²³

Given that positive perceptions of treatment efficacy are based on an athlete's previous experience and received information, the obvious recommendation to applied sports medicine practitioners is that, as an important source of information, they should seek to encourage positive expectations of any given therapy. This may involve increasing the athlete's knowledge and understanding of the therapeutic intervention, or helping them to reinterpret any negative beliefs resulting from previous experience. The use of techniques/technology that the athlete has found to be effective in previous clinical settings might elicit a conditioned placebo response or positive expectations (eg, ultrasound, anti-inflammatory gel, manipulation) that strengthen the athlete's perception of the treatment efficacy, and perhaps the treatment efficacy itself. What must be made clear is that the placebo effect is not a "stand alone" phenomenon. Certainly it may stand alone in instances in which an inert substance is given, eg, to reduce a patient's pain. But in most instances, for reasons of ethical, biologic, or pragmatic imperative, this does not happen. A more likely scenario is that the biologic/pharmacologic qualities of an active painkiller may be enhanced by the beliefs and expectations of the patient (it should be noted that, by implication, such inherent biologic/pharmacologic qualities may be reduced by negative beliefs of the patient, ie, the "nocebo effect"). There is a definite synergistic action between the active treatment, the patient's beliefs, and the practitioner's beliefs.

However, these observations bring us once again to the issue of ethics. A discussion of the complex ethics of belief manipulation is beyond the scope of this paper. Knowingly providing false information to suffering patients is unethical, even if it might be helpful in the final analysis, but providing the athlete with sufficient belief of a potentially positive outcome of the treatment being administered may augment an existing therapy.

Conclusion

The present study demonstrated that a participant's experience of analgesia resulting from a reduction in pain might result in similar experience of analgesia when the

participant is subsequently exposed to what they believe to be the same analgesic agent, but which is in fact a placebo. By implication, patients in sports therapy could benefit from therapists maximizing the possibility of achieving positive outcomes via eliciting positive expectations of the treatment modality. Future research should aim to identify whether placebo effects seen in the management and treatment of pain and discomfort are also realized in real rehabilitation settings and with clinical, as opposed to experimentally induced, pain.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Benedetti F. *Placebo Effects: Understanding the Mechanisms in Health and Disease*. Oxford: Oxford University Press; 2009.
2. Kirsch I. *The Emperor's New Drugs: Exploding the Antidepressant Myth*. London: Bodley Head; 2009.
3. Moerman DE. *Meaning, Medicine and the 'Placebo Effect'*. Cambridge: Cambridge University Press; 2002.
4. Beedie CJ, Foad AJ. The placebo effect in sport. A brief review. *Sports Med*. 2009;39(4):313–329.
5. Benedetti F, Pollo A, Colloca L. Opioid-mediated placebo responses boost pain endurance and physical performance: Is it doping in sport competitions? *J Neurosci*. 2007;27(44):11934–11939.
6. Beedie CJ. All in the mind? Pain, the placebo effect, and the ergogenic effect of caffeine in sports performance. *Open Access Journal of Sports Medicine*. 2010;1:87–94.
7. Voudouris NJ, Peck CL, Coleman G. Conditioned response models of placebo phenomena. Further support. *Pain*. 1989;38(1):109–116.
8. Montgomery GH, Kirsch I. Mechanisms of placebo pain reduction: An empirical investigation. *Psych Sci*. 1996;7:174–176.
9. Levine JD, Gordon NC. Influence of the method of drug administration on analgesic response. *Nature*. 1984;312(5996):755–756.
10. Levine JD, Gordon NC, Fields HL. The mechanism of placebo analgesia. *Lancet*. 1978;2(8091):654–657.
11. Levine JD, Gordon NC, Smith R, Fields HL. Analgesic responses to morphine and placebo in individuals with post-operative pain. *Pain*. 1981;10(3):379–389.
12. Amanzio M, Pollo A, Maggi G, Benedetti F. Response variability to analgesics: A role for non-specific activation of endogenous opioids. *Pain*. 2001;90(3):205–215.
13. Benedetti F, Maggi G, Lopiano L, et al. Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. *Prevent Treat*. 2003;6(1). Available from: <http://journals.apa.org/prevention/volume6/toc-jun-03.html>. Accessed 2004 Apr 3.
14. Colloca L, Lopiano L, Lanotte M, Benedetti F. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol*. 2004;3(11):679–684.
15. Hashish I, Harvey W, Harris M. Anti-inflammatory effects of ultrasound therapy: Evidence for a major placebo effect. *Br J Rheumatol*. 1986;25(1):77–81.
16. Reeser JC, Smith DT, Fischer V, et al. Static magnetic fields neither prevent nor diminish symptoms and signs of delayed onset muscle soreness. *Phys Med Rehabil*. 2005;86(3):565–570.
17. Hornery DJ, Papalia S, Mujika I, Hahn A. Physiological and performance benefits of halftime cooling. *J Sci Med Sport*. 2005;8(1):15–25.
18. American Psychological Association. Ethical principles of psychologists and code of conduct. *Am Psychol*. 2002;57(12):1060–1073.

19. Watson T. *Electrotherapy: Evidence-Based Practice*. 12th ed. Edinburgh, UK: Churchill Livingstone; 2008.
20. Prentice W. *Therapeutic Modalities for Physical Therapists*. 2nd ed. New York, NY: McGraw-Hill; 2002.
21. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*. 1983;17(1):45–56.
22. Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain*. 1999;83(2):147–156.
23. Vase L, Riley JL, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain*. 2002;99(3):443–452.

Open Access Journal of Sports Medicine

Publish your work in this journal

Open Access Journal of Sports Medicine is an international, peer-reviewed, open access journal publishing original research, reports, reviews and commentaries on all areas of sports medicine. The manuscript management system is completely online and includes a very quick and fair peer-review system.

Submit your manuscript here: <http://www.dovepress.com/open-access-journal-of-sports-medicine-journal>

Dovepress

Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.