Message from the Chair

Dear Members:

It is with pleasure that I write to you late in 2011. In this edition of the newsletter, Dr. Luana Colloca from the National Institutes of Health has written a very interesting paper for the group on research in placebo and nocebo, and how this may be translated to clinical care. Importantly, this paper addresses the importance of not only considering enhancement of placebo mechanisms, but looking at how to approach factors which may mediate nocebo effects. Further understanding and translation of mechanism research to clinical care remains an interesting and important component of pain management and broader health care.

It is on this basis that I can inform you that the IASP SIG on Placebo will host a satellite meeting of the 14th World Congress on Pain in Milan, August 26, 2012. The focus of the day will be on translation of placebo mechanism research to clinical care. I look forward to confirming the academic program early in 2012, with several international leaders already committed to being involved in what will be an interesting and engaging day.

On behalf of the SIG Board, I would like to thank all members for their involvement in the SIG this year and hope that you enjoy a pleasant festive season.

Damien Finniss, Chair

Guest Editorial

Can placebo and nocebo research improve pain management?

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Studies show that the mind has the remarkable ability to adapt to pain, thus providing the potential capacity for improving pain management through placebo mechanisms [1]. Placebos given after effective treatments may work to extend the effects of active painkillers with the advantage to maintain the therapeutic outcomes. Sophisticated pain models and brain imaging techniques applied to placebo and nocebo research, seem to prompt interesting avenues for a better understanding of pain and its management.

The basic mechanisms underlying the formation of placebo and nocebo responses are verbal anticipation of benefit, prior experience of positive or negative therapeutic outcomes, and observation of beneficial outcomes in others [2]. Placebos given along with verbal suggestions of improvement and after a pharmacological or non-pharmacological conditioning acquire the ability to mimic the properties of active treatments. Whereas the magnitude of placebo analgesic responses is relatively small when only verbal suggestions are used, the exposure to an effective treatment can elicit long-lasting and robust analgesic responses [3,4]. Verbal and conditioned analgesic cues strongly influence brain areas of the pain descending system [5,6] with a release of endogenous substances such as opioids and dopamine [7].

The negative twin of the placebo effect, the nocebo effect that refers to any worsening of symptoms related to negative expectations, is another promising field of research to better understand the relation between prior
unsuccessful therapies, cognition and pain. Previous experience of negative outcomes impact subsequent responses [8] with an effect at level of the brain pathways [9]. More interestingly, negative information given verbally can convert painless stimulations into pain and induce nocebo responses as strong as those which are induced by direct experience of negative outcomes [8]. Moreover, information about the occurrence of pain increase even if given only once, interferes with the natural course of pain perception by inducing a hyperalgesic effect associated with hyperactivity of the insular cortex. These effects can be observed over a time period as long as 8 and even 90 days [10]. Further investigations of the central and peripheral mechanisms underlying these effects are necessary to better understand their formation in patients suffering from acute and chronic pain.

Expectations, painkillers and analgesic interventional procedures

Expectations can modify the response to active analgesic treatments and interventional procedures either positively or negatively. Expectations are active and dynamic mental processes in which anticipation of a specific outcome, memories of past experiences; bodily sensory information and probabilistic evaluation for future events are combined, triggering a behavioral change.

Some studies in the literature illuminate the role of expectations in shaping responses to drugs and other interventions. For example, thoracotomized patients who received morphine for management of post-operative pain showed a significant better pain relief when the therapeutic dose was administered openly –patients were told that they would receive morphine, thus their pain will get better soon. Delivering similar therapeutic dosages in a hidden way – patients were not alerted about the beginning of the treatment and the delivery of medication was performed by a computer-controlled pump of infusion - results in a significant reduction of drug effects [11].

Thus, elements of the clinical setting such as patients’ information, presence of therapist providing support, and being aware that medication is being given may become meaningful cues impacting pain experience. Indeed, these findings have been recently confirmed and extended by applying a type of open-hidden paradigm in a brain imaging study [12]. When healthy subjects were told that a drug infusion of µ-opioid agonist remifentanil was going to be started the analgesic effect was doubled as compared to the baseline – no information about the medication. Moreover, informing subjects that the remifentanil was stopped when actually they continued to receive the drug induced hyperalgesia and brain related-changes. This suggests that expectations can strongly interfere with the response to painkillers, reversing their potential analgesic properties. Verbal information conveyed during standard medical procedures can produce worsening of clinical symptoms. This observation is true, not only in the context of clinical trials, but also in daily clinical practice. For example, a small difference in framing the information provided along with labor anesthetic injection produced pain relief outcomes. Women at term of gestation requesting labor epidural analgesia were randomized to either a common description of the pain experience from local anesthesia injection (“You are going to feel a big bee sting; this is the worst part of the procedure”) or a more reassuring description (“We are going to give you a local anesthetic that will numb the area and you will be comfortable during the procedure”). A blinded observer assessed the level of pain experienced during the procedure. Those women informed to expect pain like a ‘bee sting’ during the local anesthetic injection (nocebo group) rated pain significantly higher than those receiving the procedure along with positive words and encouragement [13].

These findings in the field of pain potentially have relevance for clinical trials and clinical practice with patients suffering from acute and chronic pain, and likewise for other clinical situations where mental processes act as a major factor affecting pain outcomes.

The clinical relevance of placebo and nocebo research

Translating placebo research findings into improved clinical trial designs and practice opens promising avenues for improvement within most areas of pain medicine [14]. At least two aspects seem relevant in translating placebo research – on the one hand, the possibility to deliberately create learned placebo responses to benefit patients and, on the other hand, intentionally avoiding negative learned effects.

Placebos given after effective treatments can extend the effects of active treatments, while side effects and costs are reduced. By using a conditioning paradigm, placebo responses can be elicited on the basis of a planned sequence of active drug and placebo administrations. Such learned therapeutic effects have been demonstrated in patients suffering from chronic conditions. For example, patients with severe psoriasis gained similar benefit when randomized to either full-dose of corticosteroids or a conditioned schedule of treatment consisting of full dose of corticosteroids 25-50 % of the time and placebos other times [15]. The fact that symptoms can be managed appropriately under a full-dose and a reinforced schedule of drug and placebo encourages new research aimed at integrating placebos in pharmacotherapeutic protocols to extend the durability of pharmacotherapeutic effects while reducing the overall amount of medication required.

While learned placebo effects can be useful in clinical practice, they may bias crossover trials where patients are exposed first to a treatment A - experienced as either effective or ineffective- and then switched to treatment B. When treatment A is experienced as effective, the effectiveness of subsequent treatment B is magnified. The opposite holds for treatments given after ineffective treatments: their effectiveness tends to be reduced if administered after an ineffective treatment. In a recent randomized controlled study including 45 patients with neuropathic pain, the analgesic effect of sham repetitive transcranial magnetic stimulation (rTMS) was studied either before or after an active rTMS, which could be either successful or unsuccessful. Placebo analgesia differed significantly when the sham rTMS session followed a successful or an unsuccessful active rTMS. Placebo sessions induced significant analgesia when they followed a successful rTMS, whereas they tended to worsen pain when following an unsuccessful rTMS [16].
These aspects are only an example of the need for translating knowledge regarding placebo and nocebo research in clinical practice and methodology of clinical trials. It is also worthwhile to mention briefly that on the basis of nocebo research, careful attention must be paid to the ways in which information about pain experience (and adverse events) is disclosed to patients with ethical implications on how physicians must communicate adverse events (and prognoses) to minimize nocebo effects and maximize placebo effects [17].

The impact of placebo and nocebo research is becoming increasingly expanded and refined. In the field of pain, placebo and nocebo research suggests promising ways to harness these responses consistently with therapeutic goals.

References


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www.iasp-pain.org/SIGs/Placebo