Review

Patients' direct experiences as central elements of placebo analgesia

**Lene Vase^{1,2,*}, Kathrine Næsted Nørskov^{1,2}, Gitte Laue Petersen^{1,2}
and Donald D. Price³**

¹*Department of Psychology, Aarhus University, Jens Christian Skous Vej 4, 8000 Aarhus C, Denmark*

²*Danish Pain Research Center, Aarhus University Hospital, Noerrebrogade 44, Building 1, 8000 Aarhus C, Denmark*

³*Division of Neuroscience, Department of Oral and Maxillofacial Surgery, University of Florida, 1600 SW Archer Road, Gainesville, FL 32610-0416, USA*

Placebo analgesic effects appear to be related to patients' perception of the therapeutic intervention. In this paper, we review quantitative findings of how the relationship with the physician and the verbal suggestions given for relief may influence patients' perception of a treatment and how patients' expectations and emotional feelings may affect treatment outcome. We also present qualitative data from interviews with patients who have experienced pain relief following a placebo or an active treatment. A special focus is given to the temporal development of placebo analgesia at psychological and neurophysiological levels. Finally, we discuss the extent to which the quantitative and qualitative findings supplement or contrast with each other, and we touch upon possible implications of patients' direct experience as central for placebo analgesia.

Keywords: placebo analgesia; patient–physician relationship; verbal suggestions; expectations; emotional feelings; temporal development

1. PERCEPTION IS CENTRAL TO AT LEAST SOME TYPES OF PLACEBO ANALGESIC EFFECTS

Placebo effects have traditionally been associated with administration of inert treatments, such as sugar pills or saline injections [1]. However, as the inert treatment in itself is unlikely to contribute to the symptom reduction, such as pain relief following placebo treatment, it has become evident that patients' *perception* of the treatment [2] and its *meaning* [3] is central to placebo effects. Recently, the placebo response has been defined as 'a reduction in a symptom in an individual that results from one's *perception* of the therapeutic intervention. This response may be considered both a biological and psychological event' [2,4]. Therefore, placebo responses in individual patients and placebo effects across groups of patients offer an opportunity to investigate how patients' perceptions of a treatment may influence the treatment outcome as well as the psychological and neurophysiological interactions involved in the symptom reduction.

So far placebo effects have primarily been investigated through psychophysical techniques and brain imaging methods that have led to significant advances in understanding of some factors that contribute to placebo effects. However, in order to gain more insight into how patients' direct experiences contribute to treatment

outcome, it may also be helpful to directly interview patients about their experience during a placebo or active treatment. A qualitative approach allows for an investigation and understanding of patients' experiences as they receive active and placebo treatments and as they experience the possible effects of these treatments. In this way, a qualitative approach may provide a different type of finding that may corroborate or contradict quantitative findings and thereby help advance understanding of factors involved in treatment efficacy.

In the present context, the 'perception of the therapeutic intervention' is seen as an integration of visual cues and auditory inputs that gives rise to the meaning of being given a pain-reducing treatment. This means that our definition of placebo responses applies to a category of responses that require conscious recognition of an external agent, such as seeing a type of medication, and in some instances understanding suggestions for relief. This type of placebo response and its definition takes into account those therapeutic responses that do not depend on conscious perception (e.g. responses to classical conditioning). In this paper, we primarily look at patients' conscious experiences and discuss some of their possible neurophysiological correlates.

We will review quantitative findings on how the relationship with the healthcare provider and the verbal suggestions given for relief may influence patients' perception of a treatment and how patients' expectations and emotional feelings at least partly mediate placebo analgesia. Furthermore, we will present qualitative interview data from patients undergoing active and placebo

* Author for correspondence (lenevase@psy.au.dk).

One contribution of 17 to a Theme Issue 'Placebo effects in medicine: mechanisms and clinical implications'.

treatment in order to investigate factors that are central to patients' experience of the treatment and treatment efficacy. Finally, we discuss the extent to which qualitative and quantitative data supplement each other and we touch upon the implications of the importance of understanding patients' experiences of treatments in generating placebo responses.

2. FACTORS THAT MAY INFLUENCE THE PERCEPTION OF A (PLACEBO) TREATMENT

(a) *The relationship between the patient and the healthcare provider*

One of the factors that influence the patient's perception of the treatment is the relationship between the patient and the physician. In fact, the very presence of a physician may increase the magnitude of the placebo effect [5]. Frank [6] was one of the first to point out that the treatment 'ritual' that takes place between the physician and the patient may in itself contribute to a treatment effect. It is generally believed that a good relationship between the physician and the patient is characterized by an empathic, optimistic and competent physician as well as a motivated and cooperative patient [7]. Patients may especially focus on the physician's *likeability, credibility or competency* which, in turn, may strengthen expectations of efficacious treatments [6,7].

One of the first empirical investigations of the patient–physician relationship in relation to placebo treatment was conducted by the general practitioner Thomas [8]. Patients with symptoms where no definitive diagnosis could be given were randomly assigned to a 'positive' or a 'negative' consultation with or without a placebo treatment. In the positive consultation, patients were given a firm diagnosis and told confidently that they would be better in a few days. In the negative consultation, patients were told 'I cannot be certain what is the matter with you'. Two weeks after the consultation a significantly larger number of patients in the positive consultation group improved compared with patients in the negative consultation group, thereby indicating that the physician's attitude towards the patients may influence the treatment outcome.

More recently, Kaptchuk *et al.* [9] have investigated the elements of the patient–practitioner relationship in relation to placebo acupuncture treatment. Patients suffering from irritable bowel syndrome (IBS) were randomized to receive 'waiting list condition', 'limited interaction' or 'augmented interaction'. In the waiting list condition, the patients had no interaction with the practitioner. In the 'limited interaction' the acupuncturist introduced himself and said that 'he knew what to do', after which the conversation ceased and the treatment began. In the 'augmented interaction' the patient and the practitioner had a 45 min conversation before the treatment began where the practitioner expressed empathy, asked the patient about the symptoms, and told the patient that he had very positive experiences with treating these symptoms. The patients in the 'augmented interaction' group had a significantly larger global improvement and more relief when compared with the group exposed to 'limited interaction'. The latter, in turn, had significantly more improvement than the waiting list group. These

results indicate that the more contact, empathy and positive information that patients receive from the practitioner, the greater the placebo effect. In this study, however, the outcome measure was not a change in pain rating but, for example, a more global measure of changes in 'adequate relief' from baseline to three weeks after the intervention. Previous studies have indicated that patients may report high levels of relief for small actual changes in pain intensity [10] and that retrospective ratings may give rise to larger placebo effects than concurrent ratings [11]. Thus, the placebo acupuncture study by Kaptchuk *et al.* does not determine whether actual pain intensity is directly reduced by the extent of patient–physician interaction.

(b) *Verbal suggestions for pain relief*

The types of verbal suggestions given for pain relief are also likely to influence the treatment outcome. Pollo *et al.* [12] randomized post-operative patients to receive saline infusions along with three different types of suggestions: 'no information', 'double blind' (placebo or active agent) or 'deceptive' (powerful painkiller). Patients who were told that the agent was a powerful painkiller requested less medication than patients who were told that there was a 50–50 chance for pain relief. The latter group requested less medication than patients in the no information condition. Hence, progressively stronger verbal suggestions for pain relief result in progressively higher magnitudes of placebo analgesia.

Similar findings have been found in two experimental studies of IBS patients who were exposed to rectal balloon distension and treated under no treatment, rectal placebo or rectal lidocaine conditions. The first study was conducted as a standard clinical trial where patients were told that they 'may receive an active pain-reducing medication or an inert placebo agent' [13]. This study found a significant pain-relieving effect of rectal lidocaine when compared with rectal placebo and a significant pain-relieving effect of rectal placebo as compared to the untreated natural history condition. The second study was conducted in a similar manner, the main difference being that in this study patients were told that 'the agent you have just been given is known to significantly reduce pain in some patients' [14]. A much larger placebo effect was found in this second study (an effect size 2.0, Cohen's *d*) and the magnitude of the placebo analgesia effect was so high that there was no longer a significant difference between the magnitude of rectal lidocaine and rectal placebo (figure 1). Hence, these two studies suggest that by adding an overt suggestion for pain relief, it is possible to increase the magnitude of placebo analgesia to a level that matches that of an active agent.

3. FACTORS RELATED TO THE EXPERIENCE OF ANALGESIC TREATMENTS AND PLACEBO RESPONSES

Patients are likely to experience different relationships with the healthcare provider and with the suggestions given for pain relief. Therefore, it is important to examine how these relationships influence experiential

Figure 1. An illustration of how verbal suggestions for pain relief may increase the magnitude of placebo analgesia. Adapted from Vase *et al.* [14], with kind permission from the publisher. Solid lines with plus symbols, natural history; grey dashed line with open circles, rectal placebo; black dashed line with filled triangles, rectal lidocaine.

dimensions, such as expectations and emotional feelings about treatments, because these latter factors contribute to pain relief during placebo analgesia [4,15].

(a) Expectancy and desire

Verbal suggestions given for pain relief are likely to exert their influence through patients' expectations, desires and emotional feelings. Although neither expectation nor desire is necessarily emotional, they co-constitute many ordinary emotions, such as anxiety, relief, disappointment and excitement [16], that may be central to the experience of a treatment outcome [4].

Several studies have shown that expectations of pain relief contribute to placebo analgesia [11,17–19]. IBS patients in the study described earlier §2b were exposed to rectal balloon distension under no treatment, rectal placebo and rectal lidocaine conditions [14]. They were asked to rate expected pain levels and desire for pain relief on well-validated visual analogue scales right after each of the three conditions were started and just before any analgesic effects took place [14]. The combination of ratings of expected pain level and desire for pain relief accounted for 77 and 81 per cent of the variance in the pain ratings during the placebo and lidocaine conditions, respectively. These strong correlations show that expected pain level and desire for relief are central to the experience of pain relief during placebo treatment as well as during active treatment.

In a subsequent and similarly designed study of IBS patients, the temporal development of the placebo analgesia effect as well as the temporal changes in expected pain levels, desire for pain relief and anxiety levels were investigated [20]. Similar to the study just described, IBS patients were asked to rate expected pain levels, desire for pain relief and anxiety levels at the beginning of the study and then again half way through the study. The study showed an increasing placebo analgesia effect during the 40 min of investigation. Interestingly, expected pain levels, desire for pain relief and anxiety *decreased* from the early part (first 20 min)

to the late part (last 20 min) of the session, and the three psychological variables came to account for considerably more of the variance in the placebo response and in the response to lidocaine treatment over time. These findings may be interpreted as follows. In the beginning of the experiment, IBS patients had a mild to moderate desire for pain relief and expected a reduction in pain as a result of suggestion for pain relief and administration of an agent. This psychological mindset is likely to have contributed to the actual experience of some pain relief during the first part of the session. The actual experience of pain relief could then have led to the further reductions in anxiety and expected pain levels in the second part of the session, and these changes may have contributed to further self-reinforcing pain reduction in the late part of the study. Thus, combinations of expectations and overall reduction in negative emotions are likely to have contributed to an increase in the placebo effect over time (figure 2). These findings have been supported by more recent studies showing that expectations of pain relief may lead to a reduction of anxiety and this may be a central component of the placebo effect [21]. On the basis of these studies, it appears that expectations and emotional feelings are embedded in active and placebo treatments, and that the dynamic interactions between these parameters contribute to a self-reinforcing analgesic effect over time.

(b) Neurophysiological changes

The changes at the psychological level have been shown to be associated with neurophysiological changes. Functional magnetic resonance imaging (fMRI) studies have shown that during the period where patients *anticipate* pain (relief) during a placebo treatment there is an increased activity in brain areas such as the orbitofrontal cortex and the dorsolateral prefrontal cortex, regions known to be involved in expectation and emotional factors [22]. During the actual *experience* of pain and pain reduction, however, there is decreased activity in pain-processing areas of the brain, such as the thalamus, somatosensory cortices, the anterior insular cortex

Figure 2. An illustration of how expectations and emotional feelings may contribute to a self-reinforcing placebo analgesia effect. Following the verbal suggestions given for pain relief patients have moderate expectations of pain relief and moderate levels of negative emotional feelings. These psychological factors are likely to contribute to the actual experience of pain relief during the first 20 min of the study. The actual experience of pain relief appears to contribute to lower expectation of pain and lower levels of anxiety and desire in the late part of the study which are likely to contribute to the even further experience of pain relief in the last 20 min of the experiment. In this manner, the placebo analgesia effect may be self-reinforcing (see [20] and appendix).

and the anterior cingulate cortex [22,23]. Thus, patients' expectations of pain relief and their emotional feelings in relation to a treatment seem to be related to both reduction in afferent processing of pain and the generation of analgesia.

Interestingly, one of these fMRI studies involved IBS patients who were exposed to rectal distention and received rectal placebo [23]. A subsequent fMRI analysis of these data revealed areas of the brain that showed *increased* neural activity during placebo analgesia [24]. During the early phase of the study (first three inflations), there was an increased activity in areas of the temporal lobe (involved in memory), the precuneus (involved in associative thinking) and the amygdala (involved in descending modulation of pain). Similar to the magnitude of the placebo effect itself, neural activity in these three areas was much greater during the early part of the session wherein the placebo effect increased over time and reached peak levels. These findings may be interpreted in terms of several possibilities. During the early part of the placebo condition (first 3–4 min), patients were likely to make associations between prior suggestions about the placebo agent, internal cues that suggest whether or not the agent is working and their expectations about future experiences. These associations require memory, somatic focus and comparison of present experience to expectation of pain following placebo suggestion. Once the placebo effect was established, there was much less activity in these brain areas during the remainder of the experimental session. Thus, the placebo effect may persist beyond the time of activation of brain structures that induce it. These findings and conceptualizations are consistent with associative learning as well as with a self-enhancing feed-back mechanism [20,25].

4. DO ACCOUNTS OF PATIENTS' DIRECT EXPERIENCES SUPPORT THIS EXPLANATION?

(a) *Interview setting and approach*

The experiential factors that may help explain placebo analgesia effects were examined by interviewing participants of the study described above (see §3a) wherein 26 IBS patients rated desire, expectation, and anxiety at early and late phases of both the placebo

and lidocaine conditions [20]. They were interviewed about their direct experiences of receiving a treatment and of possible pain relief following a placebo treatment and a standard active treatment (i.e. lidocaine; see appendix A and [20]).

Twenty-five of the 26 patients participated in the interview as one patient declined the interview (patient no. 14). The interviews were performed immediately after the third session, which was either the placebo or lidocaine condition. The patients, the investigators conducting the study, and the interviewer were all blind with respect to whether the patients had received rectal placebo or rectal lidocaine in the third session. The interviews consisted of an open and a structured part. In the open part, patients were asked to relive the session and describe their experience throughout the treatment session. In the structured part, they were asked about their experience of the doctor conducting the study and their perception of the description of the agent. They were also asked about their focus of attention, ongoing thoughts and feelings during the first as well as during the last 20 min of the session. Finally, they were asked about their expectations and desires towards their pain and pain reduction during the session as a whole.

The data were transcribed and the following data analysis was conducted using a template approach [26]. Categories were partly determined on prior theoretical knowledge and partly on the information in the interviews. These categories served as a template where segments from the interviews were put into text. Finally, the results were summed in table 1. The categories were as follows: (i) Do the patients think that they are getting an effective treatment? (ii) Which factors influence their perception of the treatment? The subcategories here were (ii(a)), the perception of the healthcare provider and (ii(b)), the perception of the description of the agent. (iii) Which factors are related to the temporal development in the experience of placebo analgesia effects? Factor (iii(a)) was the focus of attention during early and late phases of the experimental session and factor (iii(b)) was emotional feelings during early and late phases of the experimental session. The interviews were analysed according to

Table 1. Categorization of patients' perceptions of the treatment. Numbers indicate positive answers in the category.

prior to the interview the patients received the following treatment			
	lidocaine		12
	placebo		13
	total		25
(i) perception of getting an active treatment			
	perception of getting an active treatment		25
	perception of getting an inactive treatment		0
	total		25
(ii) factors that influence the patient's perceptions of the treatment			
(a) <i>perception of healthcare provider</i>			
	likeability		10
	credibility		0
	likeability and credibility		15
	total		25
<i>best descriptor</i>			
	likeability		10
	credibility		5
	total		25
(b) <i>perception of description of agent</i>			
	it's likely to be an active agent		20
	I will just see if it works		4
	it's likely to be an inactive agent		0
	out of category		1
	total		25
(iii) factors that may be related to the temporal development in the experience of placebo analgesic effects			
(a) <i>focus of attention</i>			
	<i>first 20 min</i>	<i>last 20 min</i>	
	inner	inner	6
	outer	inner	5
	outer	outer	4
	inner	outer	3
	mixed outer/inner		4
	out of category		3
	total		25
(b) <i>emotional feelings</i>			
	<i>first 20 min</i>	<i>last 20 min</i>	
	calm	calm	17
	anxiety	calm	4
	anxiety	anxiety	2
	calm	anxiety	1

these categories by all authors. Each interview was carefully read and scored according to the three categories indicating whether each of the categories applied. In cases where more than one subgroup of categories was applicable, the best descriptor was also indicated.

Following this procedure, the code was broken and the patients were divided according to whether they were interviewed after the placebo session (13 patients) or the lidocaine session (12 patients) to see if there was a difference in how patients perceived a placebo treatment and an active treatment. Among the 13 patients receiving placebo only three had small analgesic (placebo) responses, whereas the remaining 10 patients had large analgesic (placebo) responses. Large analgesic responses occurred in all 12 patients receiving lidocaine. Thus, it was not meaningful to analyse the data according to whether patients experienced small or large analgesia. First, patients receiving lidocaine and patients receiving placebo were analysed separately. However, the results for the two groups were very similar, which corroborate that part of the analgesic effect in patients receiving lidocaine may be due to a placebo effect [2,13,23].

Therefore, in the following analyses, the data from the placebo group and lidocaine group were combined. The analgesic response developed within the first 20 min and plateaued during the second 20 min for all patients. This difference allowed an assessment of how experiential factors changed over time in relation to placebo analgesia.

(b) *Perception of placebo versus active treatment*

Based on an overall reading of patients' experiences during the treatment session as well as on the specific categorization of their reports, there were no apparent or systematic differences in patients' experience of the treatment depending on whether they were interviewed in relation to the placebo treatment or the lidocaine treatment. Hence, the experiences of a placebo treatment and an active lidocaine treatment were similar. To our knowledge, this is the first study to directly compare patients' experience of a placebo treatment versus an active treatment. The lack of differences between the two types of treatment is probably related to similar magnitudes of analgesia and the

absence of side effects in both conditions. Thus, since patients' perception of the two treatments appear to be very similar, we combined the interviews from patients who had received placebo and lidocaine treatments in order to better understand the factors that influence whether patients perceive a treatment as being effective or not.

(c) Factors that influence the perception of the treatment

Based on transcribed interviews, patients had several experiences that pertained to the possible effectiveness of the administered agent, likeability and/or credibility of the doctor administering the agent, and focus of attention and feelings towards 'inner' (e.g. body sensations, feelings) and 'outer' events (e.g. words of experimenter, outer aspects of procedures, clock).

(i) Experience of relationship to doctor

Most of the patients mentioned the relationship with the doctor as central to their perception of the treatment. Generally the perception of the doctor can be analysed according to *likeability and/or credibility* (see table 1 for incidence of endorsements). Fifteen of 25 patients stressed both likeability and credibility as central to their perception of the doctor with likeability being the best descriptor for 10 patients and credibility best descriptor for five patients. Ten of 25 patients stressed likeability alone whereas no patients attributed importance to the doctor's credibility alone. An example of the patients' description of likeability is illustrated by this statement 'He's very friendly and he's very personal and I don't feel like I have a problem opening up to him' (patient nos. 15, 16). The credibility is illustrated by this statement 'He's intelligent...he seems to know what he is doing [...] I feel like there is research behind it. He is a specialist...I feel he has more experience than others...he is an expert so he can help me' (patient no. 16). These results are in line with previous studies showing that the perception of the physician and the relationship with him is essential to the treatment [9,27,28]. These interviews further specify these findings by indicating that, at least in this study, the likeability of the doctor seemed to be the most important aspect. This could be due to the circumstance that many of the patients in this study knew the doctor from the clinical setting at the hospital, and therefore had a personal relationship with him. These findings may especially apply to family practice or other types of practice involving a relationship over time.

(ii) Experience of treatment

The doctor gave the same verbal suggestion to all patients, 'The agent you have just been given is known to powerfully reduce pain in some patients' but the patients perceived this description of the agent differently (see table 1 for incidence of endorsements). The patients' perceptions were analysed according to how likely they thought it was that they were getting an effective treatment. Twenty of the 25 patients found it likely that they were receiving an active agent. This is illustrated by a patient saying 'I believe it and also I am waiting to experience it' (patient no. 23). These patients

went along with the suggestion and generated positive expectations of treatment efficacy. Four of the patients did not use the verbal suggestion to guide their expectations of treatment efficacy but were waiting to see if the agent worked. This is illustrated by patients saying 'I'm just waiting to see' (patient nos. 8, 4) and 'I'm not convinced...I just go with the session...and that's how I evaluate how it's working' (patient nos. 11, 4). None of the 25 patients thought that the agent was or was likely to be an inactive agent. One patient, however, could not be categorized according to these divisions as she just thought 'that it is something that he is supposed to say to me...as part of...the project...' (patient no. 4). These findings are in agreement with the general finding of strong verbal suggestions for pain relief leading to high expectations of pain relief and large placebo (or active treatment) effects [2,12,14,20].

(d) Factors that may be related to the temporal development in the experience of placebo analgesia effects: focus of attention and emotions

The magnitude of the placebo analgesia effect and the efficacy of the active (lidocaine) treatment have been shown to increase over time [14,20,23,24] (figure 1). In the psychophysiological data from the study, we found that expectations of lower pain levels and reduction in negative emotions appeared to contribute to this increase in the placebo effect ([20]; see above, figure 2). Therefore, we sought to determine whether the patients' experience of focus of attention and emotional feelings throughout the study were related to the temporal development of the treatment.

Eighteen of the 25 patients could be divided as having either an *inner* or an *outer* focus of attention (e.g. bodily sensations versus looking at the wall). Four patients had a mix of inner and outer focus and three patients were difficult to place in these categories. For example, one patient reported that 'My mind is free...I'm not really paying attention to anything' (patient no. 11). There seemed to be a fairly equal distribution of patients having either the same focus of attention in both the early and the late phase of the study (e.g. inner-inner or outer-outer) or shifting focus from the early to the late phase of the study (e.g. outer-inner and inner-outer focus of attention; table 1).

Approximately, half the patients had an outer focus at the beginning of the study, which can be illustrated by the patient saying 'I paid attention to...I guess...just his description of it...more so than anything' (patient no. 10) and some patients had both an inner and outer focus such as 'I'm paying attention to what he says and...um...trying to get in touch with how I feel...physically...' (patient no. 21). For some of these patients, the focus of attention went more inward in the late phase of the study 'I'm just paying attention to my [gut]...making sure that I give accurate readings...so I guess that's what I'm focused on...making sure that...I'm staying in tune to what I feel...and being able to transport those ratings...' (patient no. 10), whereas other kept an outer focus of attention though mainly on different aspects of the setting such as 'I'm mainly just listening...to you...the various beeps of the pump and everything' (patient no. 18)...or

'...The clock...' (patient no. 8). Thus, overall it looked as if many of the patients were focused on things relating to the initial procedures in the beginning of the study, such as the doctor's description of the agent, their bodily sensations or a comparison of the two. Later in the session, they seemed to engage in a more general monitoring of the body or in simply focusing on things in the room or about what they were doing afterwards.

During the time of the experiment, patients reported different types of emotional feelings, such as comfort, ease, relief, excitement, relaxation, peace, calm, tiredness, drowsiness, discomfort, apprehension, anxiety and nervousness. These feelings were further simplified according to the dimensions of anxiety and calm. Seventeen of the 25 patients could be categorized as being calm both in the early and the late phase of the study, which can be illustrated with a patient saying '[I'm feeling]...pretty calm...I'm not worried about anything...' 'cause I'm given something to affect my pain [...] in the beginning of the experiment and in the later part of the study she is saying '[I'm] Pretty relaxed...I'm pretty calm...pretty assured that it's gonna keep working...' (patient no. 16). Four of the patients were first anxious '... a little bit of anxiousness...' and later calm 'I'm actually feeling fairly calm' (patient no. 21), whereas two patients were anxious throughout the study and one patient started out as being calm but got more anxious as illustrated by the sentence 'I think I am a little bit more apprehensive...' (patient no. 9). Hence, these findings support that low levels of anxiety may be related to placebo analgesia effects [14,21,29] and they illustrate that this may be related to their belief that the agent is likely to work and that this belief seems to be maintained and/or confirmed throughout the study. In other words, the qualitative data seem to support the quantitative findings of increasing calmness throughout the temporal development of the placebo analgesia effect.

(e) *To what extent do the patients' descriptions supplement existing knowledge?*

The interview data appear to supplement the rating scale data (pain, desire expectation, anxiety) data [20] and brain imaging findings [23,24] to a high extent. They illustrate that the relationship with the healthcare provider and the verbal suggestions given for pain relief are important for the perception of the treatment and they underscore that likeability and credibility of the doctor may be central for treatment efficacy. These factors seemed to help patients to be actively engaged in generating a placebo effect in the beginning of the placebo condition where several of the patients reported listening to the doctors' verbal suggestions and focusing on how this matched their bodily sensations. These factors also appear to contribute to the patients' feeling of calmness. Once this analgesic effect has been established, the patients appeared to go into a mode of either maintaining the effect or focusing on other things, possibly because their pain was no longer salient for them. Thus, the combination of the interviews, the brain imaging data and the psychophysiological data provide a

picture of patients actively engaging in generating a mindset for pain reduction and a corresponding active engagement of a descending pain control system. Both neural and experiential generation of analgesia occurs early in the placebo process and once analgesia is established it may persist beyond the duration of factors that generate it.

Although the interview data corroborate previous quantitative findings, they are to some extent at variance with the results of a recent qualitative study by Kaptchuk *et al.* [28]. In relation to Kaptchuk's placebo acupuncture study (see [9], mentioned in §2a) where IBS patients were randomized to receive placebo acupuncture under 'limited interaction' or 'augmented interaction', six patients in each condition were interviewed at the beginning, midpoint and end of the trial. In this study, the patients stressed the importance of the relationship with the healthcare provider, which is in agreement with the findings from our interview study. However, according to Kaptchuk *et al.* [28] the patients in the acupuncture study were concerned with whether they were receiving placebo or genuine treatment and they did not have expectations of relief but reported hope [28]. There are several factors which may explain the partially different findings in the two interview studies. First, the main study by Kaptchuk *et al.* [9] was conducted as a randomized clinical trial, which may draw patients' attention to the possibility of receiving an inactive agent. In contrast, the main study by Vase *et al.* [20] was conducted as a placebo mechanisms study where patients were given strong verbal suggestions for pain relief. These differences in design and verbal suggestions are known to give rise to different expectations of pain relief [2,4,12–14,16,20]. Also, the IBS placebo acupuncture study was conducted by an acupuncturist whom the patients did not know beforehand, whereas the IBS placebo pharmacological study was conducted by a doctor that many of the patients knew from the clinic. Expectations of efficacy were likely to have been lower in the acupuncture study. Finally, hope is known to be a combination of expectations and desires as it has been defined as a wish or desire accompanied by an expectation of its fulfilment (www.wordnik.com). Therefore, in future investigations it may be informative to directly ask patients about expectations, desires and a range of emotional feelings in order to specify how these elements of the human experience may contribute to placebo analgesia in different combinations under different circumstances.

5. IMPLICATIONS OF PATIENTS' PERCEPTIONS OF TREATMENTS

The studies discussed in this paper provide the basis for concluding that factors within patients' experiences of an analgesic treatment contribute to the magnitude of placebo analgesia. The experiences of the treatment setting, relationship with the healthcare provider, and the suggestions given for pain relief may interact to influence the overall magnitude of pain reduction. These factors seem to influence placebo analgesia effects through expectations of pain relief and reductions in negative emotions. Over time, these

factors may contribute to self-reinforcing placebo responses. Interestingly, these factors contribute not only to the efficacy of placebo treatments but also to the efficacy of active standard treatments as illustrated in the studies and interviews of IBS patients receiving placebo and active treatment [14,20]. Hence, in the case of placebo and lidocaine treatments for IBS patients, the placebo treatment and the active treatment were equally effective, and effects of both treatments were strongly predicted by experiential factors of desire and expectation. Thus, if the clinician is able to optimize these experiential factors in ethically appropriate ways, this approach may serve as a potent way of helping patients derive optimum benefit from the placebo component of treatment, one that is potentially embedded in all treatments. This component can be further explained by neurobiological mechanisms.

Combining qualitative (i.e. experiential) and quantitative methods may be especially useful in clarifying patients' experiences as they receive active or placebo treatments. For example, the combination of qualitative and quantitative methods has been beneficial in the interpretation of the temporal changes that occur in placebo effects of some of the studies we have described. Thus, if future studies include both qualitative and quantitative approaches to analyse placebo responses, both the understanding of placebo mechanisms and predictions of placebo response magnitudes may be significant and have beneficial consequences.

This project was funded by the EU-EPIA joint Innovative Medicines Initiative as a part of the IMI European project, Grant Agreement No. 115007. It was also supported by the MINDLab UNIK initiative at Aarhus University which is funded by the Danish Ministry of Science, Technology and Innovation.

APPENDIX A. DESCRIPTION OF THE MAIN STUDY

The study included 26 women (age 29 ± 9) who had suffered from IBS for at least 5 years and who did not take any medication at the time of the study. The study took place at a hospital, and was performed by the doctor whom the patients normally consulted in the Hospital Clinic. Each patient was exposed to rectal stimulation (35 or 55 mm Hg for 30 s) and tested under natural history, rectal placebo (200 mg saline jelly) and rectal lidocaine (200 mg lidocaine jelly) conditions in a cross-over fashion (within subject design). Patients were always tested in the no-treatment condition first. The order of the rectal placebo and the rectal lidocaine condition was counter-balanced so that half the patients received lidocaine as their second session and placebo as their third session, whereas this order was reversed for the other half of patients. Prior to each treatment session (lidocaine or saline placebo), the patients were told that 'The agent you have just been given is known to powerfully reduce pain in some patients'. In the no-treatment condition, patients were told that they would receive no treatment. Patients rated expected pain level, desire for pain relief and anxiety at early (2 min after initiation of the condition) and late

stages (22 min after the initiation of the session). There was a large and significant placebo effect ($p < 0.001$) that increased over time. Ratings of expected pain levels, desire for pain relief and anxiety decreased over time and contributed to more variance in the placebo and lidocaine responses during the last half of the session (for further information, see [17]).

REFERENCES

- Andersen, L. A. 1997 Placebo-historisk og kulturelt. In *Placebo-historie, biologi og effekt* (eds L. A. Andersen, M. H. Claësson, A. Hrøbjartsson & A. N. Sørensen), pp. 69–119. Lyngby: Akademisk Forlag.
- Vase, L., Riley III, J. L. & Price, D. D. 2002 A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* **99**, 443–452. (doi:10.1016/S0304-3959(02)00205-1)
- Moerman, D. E. 2002 Explanatory mechanisms for placebo effects: cultural influences and the meaning response. In *The science of the placebo: toward an interdisciplinary research agenda* (eds H. A. Guess, A. Kleinman, J. W. Kusek & L. W. Engel), pp. 77–107. London, UK: BMJ Books.
- Vase, L., Price, D. D., Verne, G. N. & Robinson, M. E. 2004 The contribution of changes in expected pain levels and desire for pain relief to placebo analgesia. In *Psychological methods of pain control: basic science and clinical perspectives* (eds D. D. Price & M. C. Bushnell), pp. 207–234. Seattle, WA: IAPS Press.
- Amanzio, M., Pollo, A., Maggi, G. & Benedetti, F. 2001 Response variability to analgesics: a role for non-specific activation of endogenous opioids. *Pain* **90**, 205–215. (doi:10.1016/S0304-3959(00)00486-3)
- Frank, J. D. 1961 *Persuasion and healing: a comparative study of psychotherapy*. Baltimore, MD: John Hopkins University Press.
- Hougaard, E. 2004 *Psykotterapi: teori og forskning*. 2. udgave ed. (Kbh.). Copenhagen, Denmark: Dansk psykologisk Forlag.
- Thomas, K. B. 1987 General practice consultations: is there any point in being positive? *Br. Med. J. (Clin. Res. Ed)* **294**, 1200–1202. (doi:10.1136/bmj.294.6581.1200)
- Kaptchuk, T. J. et al. 2008 Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *Br. Med. J.* **336**, 999–1003. (doi:10.1136/bmj.39524.439618.25)
- Feine, J. S., Lavigne, G. J., Dao, T. T., Morin, C. & Lund, J. P. 1998 Memories of chronic pain and perceptions of relief. *Pain* **77**, 137–141. (doi:10.1016/S0304-3959(98)00089-X)
- Price, D. D., Milling, L. S., Kirsch, I., Duff, A., Montgomery, G. H. & Nicholls, S. S. 1999 An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* **83**, 147–156. (doi:10.1016/S0304-3959(99)00081-0)
- Pollo, A., Amanzio, M., Arslanian, A., Casadio, C., Maggi, G. & Benedetti, F. 2001 Response expectancies in placebo analgesia and their clinical relevance. *Pain* **93**, 77–84. (doi:10.1016/S0304-3959(01)00296-2)
- Verne, G. N., Robinson, M. E., Vase, L. & Price, D. D. 2003 Reversal of visceral and cutaneous hyperalgesia by local rectal anesthesia in irritable bowel syndrome (IBS) patients. *Pain* **105**, 223–230. (doi:10.1016/S0304-3959(03)00210-0)
- Vase, L., Robinson, M. E., Verne, G. N. & Price, D. D. 2003 The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome

- patients: an empirical investigation. *Pain* **105**, 17–25. (doi:10.1016/S0304-3959(03)00073-3)
- 15 Price, D. D., Finniss, D. G. & Benedetti, F. 2008 A comprehensive review of the placebo effect: recent advances and current thought. *Annu. Rev. Psychol.* **59**, 565–590. (doi:10.1146/annurev.psych.59.113006.095941)
 - 16 Price, D. D., Riley, J. & Barrell, J. J. 2001 Are lived choices based on emotional processes? *Cogn. Emotion* **15**, 365–379. (doi:10.1080/02699930126066)
 - 17 Montgomery, G. & Kirsch, I. 1996 Mechanisms of placebo pain reduction: an empirical investigation. *Psychol. Sci.* **7**, 174–176. (doi:10.1111/j.1467-9280.1996.tb00352.x)
 - 18 Montgomery, G. H. & Kirsch, I. 1997 Classical conditioning and the placebo effect. *Pain* **72**, 107–113. (doi:10.1016/S0304-3959(97)00016.X)
 - 19 De Pascalis, V., Chiaradia, C. & Carotenuto, E. 2002 The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. *Pain* **96**, 393–402. (doi:10.1016/S0304-3959(01)00485-7)
 - 20 Vase, L., Robinson, M. E., Verne, G. N. & Price, D. D. 2005 Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain* **115**, 338–347. (doi:10.1016/j.pain.2005.03.14)
 - 21 Morton, D. L., Watson, A., El-Dereby, W. & Jones, A. K. 2009 Reproducibility of placebo analgesia: effect of dispositional optimism. *Pain* **146**, 194–198. (doi:10.1016/j.pain.2009.07.026)
 - 22 Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M. & Cohen, J. D. 2004 Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* **303**, 1162–1167. (doi:10.1126/science.1093065)
 - 23 Price, D. D., Craggs, J., Verne, G. N., Perlstein, W. M. & Robinson, M. E. 2007 Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain* **127**, 63–72. (doi:10.1016/j.pain.2006.08.001)
 - 24 Craggs, J. G., Price, D. D., Perlstein, W. M., Nicholas Verne, G. & Robinson, M. E. 2008 The dynamic mechanisms of placebo induced analgesia: evidence of sustained and transient regional involvement. *Pain* **139**, 660. (doi:10.1016/j.pain.2008.07.025)
 - 25 Colloca, L., Tinazzi, M., Recchia, S., Le Pera, D., Fiaschi, A., Benedetti, F. & Valeriani, M. 2008 Learning potentiates neurophysiological and behavioral placebo analgesic responses. *Pain* **139**, 306–314. (doi:10.1016/j.pain.2008.04.021)
 - 26 Robson, C. 1993 *Real world research: a resource for social scientists and practitioner-researchers*. Oxford, UK: Blackwell.
 - 27 Rogers, C. R. 1951 *Client-centered therapy*. Oxford, UK: Houghton Mifflin.
 - 28 Kaptchuk, T. J., Shaw, J., Kerr, C. E., Conboy, L. A., Kelley, J. M., Csordas, T. J., Lembo, A. J. & Jacobson, E. E. 2009 'Maybe I made up the whole thing': placebos and patients' experiences in a randomized controlled trial. *Cult. Med. Psychiatry* **33**, 382–411. (doi:10.1007/s11013-009-9141-7)
 - 29 Benson, H. 1975 *The relaxation response*. New York, NY: William Morrow and Company.