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Nocebo vs. Placebo: The Challenges of Trial Design in Analgesia Research

L Vase¹, M Amanzio² and DD Price³

The placebo effect in randomized clinical trials appears to have increased thereby contributing to problems of demonstrating statistically reliable effects of treatments that directly target biological mechanisms. The shortcomings of randomized clinical trials are currently discussed along with potential improvements of trial designs. In this review we explain how utilizing knowledge from the placebo and nocebo mechanisms literature could improve the information that can be obtained from randomized clinical trials. We present three major challenges in randomized clinical trials: (i) increasing placebo effects, (ii) variability of the placebo effect, and (iii) risk of un-blinding. We then explain how recent placebo and nocebo studies of effects of verbal suggestion, expectancy, and emotions may improve understanding and discussion of increasing placebo effects, account/control for large parts of the variability of placebo effects, and suggest ways to improve blinding in future trials.

CHALLENGES OF CLINICAL TRIALS

The randomized clinical trial (RCT) is currently facing several challenges as recently reviewed.^{1,2} Three of the major challenges relate to the following topics. First, the placebo effect in clinical trials appears to be increasing.³⁻⁷ In relation to anti-depression trials this has been documented via meta-analyses,⁸ but in relation to analgesic trials this is so far primarily based on unsystematic observations and indications from meta-analyses.^{3,7} Still, it has been proposed that the apparently increasing placebo effect may make it difficult to determine the effects of presumably active and previously approved active pharmacological treatments.³ Although the underlying reason for the increase in the placebo effect is unknown, several attempts are currently made to overcome this by improving RCTs or suggesting alternative test designs.^{1-3,9} One way of addressing the problem has been to develop designs that minimize the placebo effect, for example, by having placebo run-in phases, enriched enrollment, or randomized withdrawal in order to identify and eliminate participants who respond well to placebo. The underlying assumption in many of these trials appears to be that if placebo responders are removed from the trials, it may be easier to assess the effect of the active drug.¹ The ecological validity of this approach may be questioned, as placebo responders are not eliminated from treatment in clinical practice. Also, although in theory the study design is intended to reduce the placebo effect, it does not always

succeed in doing so in empirical tests.^{1,10} Hence, a more detailed examination of this assumption seems warranted.

Second, placebo and nocebo effects and responses are highly variable.¹¹⁻¹ Attempts have been made to identify stable factors, such as demographic variables,^{5,15} personality traits,¹⁶ genetic profiles,^{17,18} and illness characteristics¹⁹ that may predict high placebo responders, but consistent findings across studies have been rare.^{1,20} This may in part be due to the lack of a sufficiently large body of well-controlled studies, but it may also in part be due to the circumstance that placebo and nocebo effects are influenced by participants' perceptions of receiving the treatment that are variable across treatment settings. Thus, stable factors may not in themselves be good predictors of the placebo response and, therefore, new ways of accounting for the variability is needed that take into account the variability in placebo and nocebo responses that result from interactions with the treatment setting.

Third, un-blinding is a major risk for the validity of clinical trials. Although almost all clinical trials are set-up to be doubleblind, only a small percentage of studies actually test whether the trial is in fact double-blind. Often group allocation is revealed by the experience of adverse events during active treatments or by the experience of different adverse events during active treatment and placebo treatment (e.g., in cross-over trials).²⁴ Thus, if it were possible to find simple ways to account

¹Department of Psychology and Behavioural Sciences, School of Business and Social Sciences, Aarhus University, Aarhus, Denmark; ²Department of Psychology, University of Turin, National Institute of Neuroscience, Turin, Italy; ³Division of Neuroscience, Department of Oral and Maxillofacial Surgery, University of Florida, Gainesville, Florida, USA. Correspondence: L Vase (lenevase@psy.au.dk)

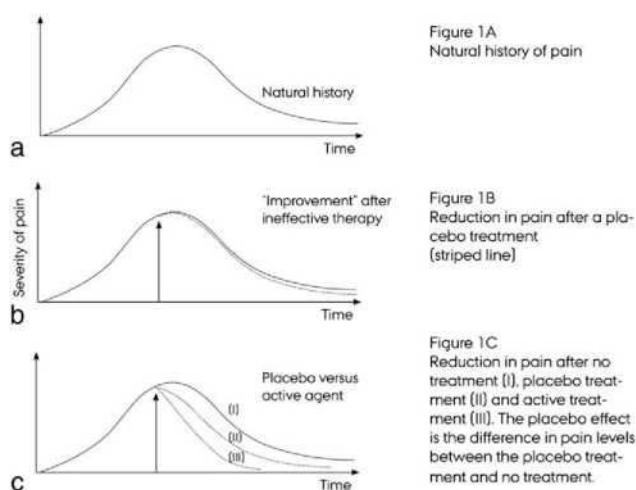


Figure 1 A placebo effect that is controlled for the natural history of pain (c) and a placebo effect that is not (b).

for this, the information that could be drawn from the clinical trial would be greatly improved.

We review here placebo and nocebo mechanisms studies to see if knowledge from these studies could facilitate discussion of these three challenges and suggest ways to account for and/or control for these factors in future trials. A special focus will be given to recent placebo mechanisms studies that investigate how verbal suggestion for pain relief may influence the placebo effect, the drug effect, and the interaction between the two (i.e., the additivity assumption). We also discuss the influence of expectations and emotions on placebo and nocebo effects.

DEFINITIONS

The terminology in relation to placebo effects is complex as several different definitions exist and as no general taxonomy has been agreed upon.^{20,25,26} A further complication is that the term *placebo effect* often refers to two different phenomena in clinical trials and in placebo mechanism studies, respectively.

In clinical trials, where the aim is to use placebo as a control condition for the active medication under study, the placebo effect typically refers to the change in a symptom following administration of an inert placebo agent (Figure 1b). However, it is important to be aware that in this use of the term, the effect is *not* compared with the effect of no treatment (Figure 1a) and, therefore, the effect of the placebo treatment cannot be separated from confounding factors such as changes in the natural history

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of pain.

In placebo mechanism studies, on the other hand, there seems to be consensus that the placebo analgesic effect is “the measured difference in pain across an untreated and a placebo-treated group or across an untreated and placebo treated condition within the same group (as in cross over studies)” (Figure 1c). Thus, this placebo effect is controlled for by the natural history of the pain and other confounding factors (Figure 1a) and it, therefore, conveys changes in pain due to the placebo intervention.

The term *placebo response* has by some been used to denote the effect in the individual – as indicated in the following defini-

tion: “reduction in pain in an individual that results from his or her perception of the therapeutic intervention.”^{28,29} The experience of receiving a treatment is assumed to be different *within an individual* across natural history and placebo conditions, and like the “placebo effect,” is measured by difference in symptom intensity across natural history and placebo administration conditions. This conceptualization of “placebo response” is used in the current article.

Conceptually, the placebo effect has been related to the social

context,^{1,25} meaning,^{26,30} and more specifically to participants’ *perception* and *experience* of receiving a pain-reducing treatment,

i. e., seeing, smelling, and hearing verbal information about the treatment as well as actively integrating this sensory information

with memories of previous experiences and current

11,29

expectations.

The *nocebo effect* was originally coined to describe the negative side effects of a placebo treatment and the term may still be used in this manner.^{33,34} Today however, the nocebo effect is primarily conceptualized as an independent phenomenon that mirrors the placebo effect. Accordingly, the nocebo effect is seen as the effect that follows the administration of an inert treatment along with behavioral procedures and/or verbal suggestions for symptom worsening. When patients expect to feel worse, they eventually tend to do so. Like placebo effects,

nocebo effects are differentiated from the natural history of pain.^{11,25}

Patients’ positive or negative perception of a treatment does not only contribute to placebo and nocebo effects, but also adds to the efficacy of pharmacologically active drugs.^{29,35-42} This fact has important implications for the understanding and investigation of the relationship between placebo effects and drug effects. Verbal suggestion appears to be one profound way in which patients’ perception of the treatment is influenced.

INFLUENCE OF VERBAL SUGGESTIONS ON PLACEBO EFFECTS AND DRUG EFFECTS: ADDITIVITY ASSUMPTION

In the placebo mechanism literature, it is well-known that verbal suggestions for pain relief, e.g., “*You are receiving a powerful painkiller,*” either alone or in combination with previous experiences (i.e., conditioning) may influence patients’ perception of a treatment and the placebo effect^{10,25,29,43}. The very framing of the verbal suggestion may influence the magnitude of the placebo effects.^{36,44-46} Verbal suggestions for pain relief that indicate *certainty* such as “*this is a powerful pain killer*” are typically given in placebo mechanisms studies and usually produce larger magnitudes of placebo analgesia than do *uncertain* verbal suggestions “*this medication could be either a painkiller or a placebo.*”³⁷ The latter are typically given in clinical trials, when compared to a no treatment control condition. Recently, four placebo mechanism studies have directly investigated how verbal suggestions for pain relief influence not only the placebo effect but also the drug effect as well as the relationship between the placebo effect and the drug effect within comparable designs.^{40-42,47} The relationship between the placebo effect and the drug effect is a topic of current interest and is related to “assay sensitivity” (i.e., the ability of a clinical trial to distinguish

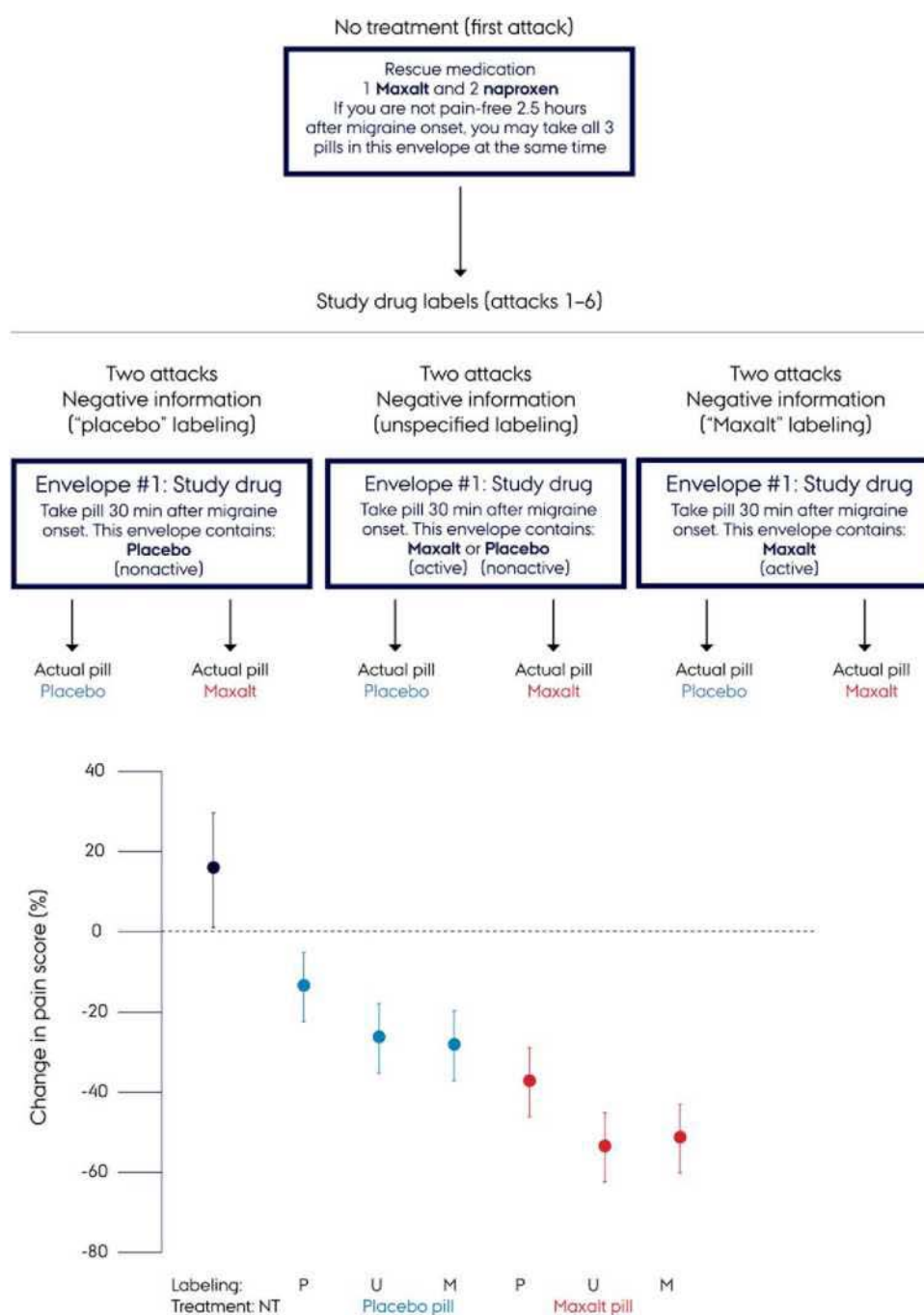


Figure 2 Research design and results. P = placebo, U = unspecified (Maxalt or placebo) and M = Maxalt. Reprinted with permission from AAAs, Kam-Hansen, S. et al. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci. Transl. Med.* 6, 218ra5 (2014).

an effective treatment from a less effective or ineffective treatment)²⁹ and the “additivity assumption” (i.e., the assumption that the drug effect and the placebo effect are additive in clinical trials, whereby the effect of the active drug can be deduced by subtracting the placebo effect from the total treatment effect). Meta-analyses of RCTs investigating the efficacy of pain and anti-depressant medication have questioned whether the additivity assumption is correct. Yet, two of the four placebo

mechanisms studies do, as the first studies, directly test this assumption.

In the first study of how verbal suggestions influence both placebo effects and drug effects, 66 patients suffering from episodic migraine were observed during one initial attack (control) and followed over six subsequent attacks where they received inactive placebo and the active drug Maxalt, respectively, in a double blind manner and were given three different verbal suggestions:

(1) told placebo (“negative,” 0% chance of receiving active medication), (2) told placebo or Maxalt (“uncertain,” 50% chance of receiving active medication), and (3) told Maxalt (“positive” or “certain,” 100% chance of receiving active medication) (Figure 2).⁴¹ Thus, each patient was tested in seven conditions: one control condition, placebo with each of the three suggestions, and the active drug with each of the three suggestions. At the onset of a migraine attack, patients opened an envelope with a treatment and a labeling of the treatment. Thirty minutes after the onset of the attack, patients rated their pain intensity on a numerical rating scale (0-10) and subsequently the treatment was initiated. Two hours later, the pain was measured again using the numerical rating scale and, in case of insufficient pain relief, rescue medication was allowed (Figure 2). This landmark study had a number of important findings and implications (Figure 2). First, the verbal suggestions given for pain relief significantly increased the placebo effect and added to the drug effect. In particular, the placebo effect and the drug effect were significantly larger after receiving the uncertain suggestions than after receiving the negative suggestion. However, in contrast to previous studies,^{36,44-46} the effects were not significantly larger after receiving certain suggestions compared with uncertain suggestions, which may be due to potential floor effects. Second, the inactive placebo treatment, presented as an active treatment, was as effective as the active treatment, presented as a placebo, thereby showing that verbal suggestions are pivotal to the total treatment efficacy. Third, more than 50% of the drug effect appeared to derive from the placebo effect. Interestingly, in this study, an exploratory goal was to investigate the drug efficacy minus the placebo effect (here termed the therapeutic gain) and they found that although the difference in pain-free outcome between the active drug and placebo was reduced by negative information compared with neutral or positive information, the reduced therapeutic gain appeared to reflect a decrease in the efficacy of the drug rather than an increase in the efficacy of the placebo treatment. Thus, a reduced placebo effect did not seem to favor the test of the active medication under study (Figure 2).

Another study further investigated the interaction between verbal suggestions given for pain relief and treatment effects using a two-by-two balanced placebo design, in which “certain” verbal suggestions (present and absent) and treatment conditions (active and placebo) were statistically compared in a fully crossed double-blind design (Figure 3).⁴² Thus, 32 healthy volunteers were exposed to capsaicin induced sensitization of the skin and treated under four conditions: (1) lidocaine cream with a verbal suggestion for pain relief “*lidocaine/prilocaine, a highly effective analgesic treatment*” (total treatment), (2) lidocaine cream without a verbal suggestion for pain relief (drug), (3) inert placebo cream with the verbal suggestion for pain relief (placebo), and (4) inert placebo cream without verbal suggestions for pain relief (control). Participants rated pain on a visual analogue scale (VAS). In line with the results from the study mentioned above,⁴¹ it was found that the medication had a significant pain-relieving effect and that verbal suggestions significantly enhanced the overall pain relief provided by drug administration. No effects were found in the control (4) or placebo condition (3). Analgesic

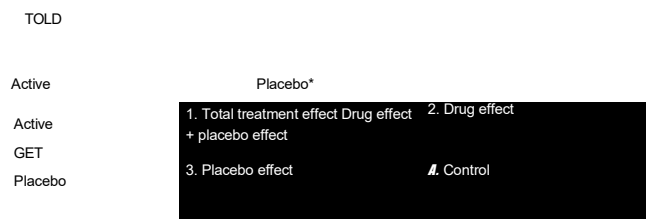


Figure 3 An illustration of the balanced placebo design. *Participants are primarily given suggestions to the effect that no treatment is given.

effects were only found when lidocaine was given (2) and the analgesic effect was significantly larger when lidocaine was combined with verbal suggestions (1>2). Based on comparisons between lidocaine (with and without verbal suggestions (1-2)) and inactive placebo (with and without verbal suggestions (3-4)) the authors proposed that the verbal suggestions interacted with the treatment effect and that verbal suggestions only had an effect when pain relief was experienced through treatment. Thus, based on these findings, the drug effect and the placebo effect did not appear to be additive. However, as their verbal suggestion for pain relief did not lead to a placebo effect, which is in contrast to previous studies,^{35-37,40,44,47,49} and also in contrast to studies using a highly similar design,⁴⁰ further studies are needed to clarify this issue.

Possible interactions between placebo effects and drug effects (i.e., additivity assumption)

Two recent studies have directly tested the additivity assumption. The first study investigated whether placebo effects and drug effects are *additive* in a two-by-two balanced placebo design (Figure 3).⁴⁷ Fourteen healthy volunteers were exposed to experimental heat pain stimuli and tested under two double blind treatment conditions (remifentanyl and saline) and given two verbal suggestions (“*you will receive remifentanyl!*” and “*you will not receive any drug!*”). Pain ratings were obtained on a VAS (0-10). They found a significant drug effect indicated by participants experiencing lower pain levels when they received remifentanyl (1 and 2) independently of the verbal suggestion. They also found a significant effect of the verbal suggestions in so far as participants reported lower pain levels when they received verbal suggestions for pain relief (1-3) as compared to when they did not (2-4). Importantly, they did not find an interaction between the treatment and verbal suggestions for pain relief, thereby suggesting that the placebo effect and the drug effect are additive. Yet, as only 14 healthy volunteers were involved in this study and as heat pain stimuli were employed, which in contrast to clinical pain can easily be terminated, further studies of the topic are needed.

The additivity assumption has also recently been tested in 48 healthy volunteers who were exposed to hypertonic saline injections into the masseter muscle, which may resemble clinical pain to a higher extent than heat pain.⁴⁰ This study also used a balanced placebo design (Figure 3) and the treatments were

active lidocaine and placebo saline and the verbal suggestions were “a potent pain killer” or “saline that produces experimental muscle pain” (i.e., no treatment just pain induction). Pain ratings were obtained on VAS (0-100 mm). There was a significant drug effect in this study (2-4) and a significant placebo effect (34), the latter both for participants who underwent conditioning and for participants who only received verbal suggestions for pain relief. Interestingly, the total treatment effect was smaller than the sum of the drug effect and the placebo effect ($1 < 2 + 3$). In fact, the difference between the total treatment effect vs. the sum of the drug effect and the placebo effect increased with the increasing magnitude of the placebo effect. Hence, for participants with a low placebo effect, the total treatment effect was not different from the sum of the drug effect and the placebo effect, but for participants with a high placebo effect, there was a significant difference. Based on these findings, the authors proposed that in clinical trials, the drug effect size may be underestimated in studies with large placebo responses, thereby contributing to problems with low assay sensitivity. On the other hand, the study also showed that there was a non-significant trend ($P = 0.089$) for the effect of the active drug to be higher for participants with a high placebo effect than for participants with a low placebo effect, and there was a positive correlation between placebo effects and drug effects thereby suggesting that attempts to decrease placebo effects and responses may also decrease overall effects during drug administration.

Thus, although the majority of the studies show that verbal suggestions for pain relief may increase the placebo effect and the drug effect, the exact nature of this interaction warrants further investigations. The two studies that directly tested the additivity assumption found opposing results. In the first study the drug effect and the placebo effect was found to be additive⁴⁷ but in the second study the total drug effect was less than the drug effect plus the placebo effect, thereby indicating that the drug effect and the placebo effect were less than additive.⁴⁰ Thus, although the additivity assumption seems to be challenged, further large scale studies that directly test the additivity assumption, preferable in patients, are needed before final conclusions can be drawn. Still, the studies may shed new light on the discussion of whether the reduction of the placebo response may improve the assessment of pharmacological treatments. In the study that found that the drug effect and the placebo effect were less than additive, sub-additivity was only found in participants with a high placebo effect. It can, therefore, be speculated that assay sensitivity may be improved by reducing the placebo effect, for example by giving negative verbal suggestions for pain relief as done in one of the studies outlined above,⁴¹ in which patients were told that the treatment was a placebo treatment although it was an active medication. Although this strategy may be problematic in clinical practice from an ethical standpoint the results also show that it may not be helpful. In this study the therapeutic gain was investigated and it was found that although the difference in pain-free outcome between the active drug and placebo was reduced by negative information, the reduced therapeutic gain appeared to reflect a decrease in the efficacy of the drug rather than an increase in the efficacy of the placebo treatment. This is in line

with the tendency toward a lower drug effect in participants with a low vs. high placebo effect and with a correlation between the drug effect and the placebo effect,⁴⁰ the latter also seen in meta-analyses.^{5,5} Furthermore, in anti-depressant studies placebo run-in did not lower the placebo effect nor did it increase the difference between drug and placebo.^{51,52} Thus, although an elimination of placebo responders at first glance appears to improve drug-placebo comparisons, this strategy may run the risk of reducing the drug effect, which could also influence the overall conclusions from the trial. Hence, as pointed out,^{41,42} it may not be recommendable to reduce the placebo component of a trial.

Not only verbal suggestions for pain relief but also verbal suggestions for pain *increase* may influence the outcome of a trial. From the nocebo mechanism literature it is well known that verbal suggestions for pain increase may enhance the nocebo effect.^{12,53} Also,

one landmark study has shown that verbal suggestion for hyperalgesia (i.e., heightened levels of pain) may fully negate the analgesic effect of the well-known pain medication, remifentanyl, in healthy volunteers exposed to heat pain stimuli.³⁹ Although verbal suggestions for hyperalgesia are unlikely to be deliberately given in RCTs, the situation may resemble a condition where a patient, due to previous experiences, general information about the treatment, and verbal/non-verbal suggestions stemming from the interaction between the healthcare provider and patients, comes to expect that the administered treatment will not be effective. *Thus it will be important to find ways to account for how verbal suggestions for pain reduction influence the outcome of future trials.*

THE INFLUENCE OF VERBAL SUGGESTIONS ON EXPECTATIONS AND EMOTIONS: VARIABILITY

As verbal suggestion in relation to pain treatment greatly influence the placebo effect and the drug effect, variability in RCTs may not only arise from patients and illness characteristics, but also from the verbal suggestions given in relation to the treatment and especially from patient perceptions of these suggestions. In RCTs patients are typically given uncertain verbal suggestions for pain relief like “this may be an active or an inactive agent” but there may be important differences in the exact wording of the informed consent as well as in the actual verbal and non-verbal suggestions given during the conduct of the trials. Investigators may unintentionally or subconsciously convey information about the treatment to the patients,⁵⁴ not only on treatment efficacy but also on adverse events (AEs) or negative outcomes.³³ Such verbal suggestions have been shown to influence patients’ expectations of pain relief as well as their emotions. Sometimes the term “verbal suggestion” is even replaced by “expectation” perhaps assuming that verbal suggestions for pain relief directly leads to expectations of low pain levels.^{39,42,55,56} However, in order to understand how the treatment context and the verbal suggestions given in relation to pain may influence patients expectations and emotions it is essential to directly ask the patients about their expected pain levels, their desire for pain relief and emotions that are about the treatment.^{29,57}

In placebo analgesia research, participants have been asked about their expected pain levels and their desire for pain relief by posing the following questions: “*what do you expect your pain*

levels to be?" and "How strong is your desire for pain relief" right after the treatment (placebo and active) has been given and before it has taken effect.^{28,29,36,49,56,58,59} Participants have rated expected pain levels on the same VAS that is used to rate actual pain. The patients have also rated their desire for pain relief on a VAS anchored "no desire" to "the most intense desire for pain relief." The combination of expected pain levels and the desire for pain relief has been shown to account for up to 77% of the variance in pain levels following placebo administration and 81% of the variance in pain levels following lidocaine administration.³⁴ In subsequent analyses, changes in expectancy and desire ratings predicted changes in pain ratings across natural history and placebo conditions (i.e. placebo responses). These findings indicate, along with several other studies on expect-

ancy^{39,49,56,59,60} that the expected pain levels and the desire for pain relief are central placebo factors, and they not only contribute to the efficacy of placebo treatments but also add to the efficacy of active treatments.

Expectations of a certain goal, i.e., pain relief, have been shown to interact with the desire for fulfillment of this goal in the prediction of a range of positive and negative emotional feelings.^{57,61} The placebo effect has been related to low levels of negative emotions including anxiety^{37,62,63} as well as high levels of positive emotions.^{58,62} Moreover, high levels of negative emotions such as fear have been shown to block the placebo effect.^{64,65}

Less is known about the contribution of expectations, desires, and emotions to nocebo hyperalgesic effects. However, one study has shown that participants expect high pain levels and that the expected pain levels account for 37% of the variance in the subsequent pain ratings.⁵⁶ Another study has found that participants have significantly higher anxiety levels in the nocebo compared with the no-treatment condition,⁶⁶ and although this finding was not supported by a subsequent study,⁵⁶ it was in agreement with neuropharmacological studies showing that levels of cortisol increased during nocebo effects, thereby suggesting that anxiety and stress responses related to hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis are implicated in nocebo effects.^{67,68}

As indicated above, using direct ratings to assess the influence of proximate mediating factors such as expectation, desire for relief, and emotions (e.g., anxiety) could reflect a novel and useful means of predicting and accounting for placebo and nocebo effects and the variability of individual responses. For example, the validity of VAS as ratio scale measures of both experimental and clinical pain might be very useful,^{69,70} especially since the same VAS would be used to measure both actual and expected pain.^{36,37} The VAS has also been validated as a ratio scale measurement of desire, expectations, and emotions in studies of emotions and decision behavior.^{61,71,72} Although other types of scales and brief assessment methods could also be considered, such as the numerical rating scale and brief pain questionnaires, a ratio scale level of measurement would more optimally account for high amounts of variance in responses during placebo analgesic conditions as well as during hyperalgesic conditions (e.g., **28,36,37,63** nocebo).

In clinical trials, patients are seldom asked about their expected pain levels, their desire for pain relief, or emotions. Yet, by

including these few questions and providing simple ratings of these factors, it may be possible to achieve an understanding of how patients perceive the treatment and of the contribution of placebo factors to the overall treatment outcome. Thus, one way of accounting for the variations in patients' perceptions of a treatment is by directly asking them and having them rate their expected pain levels and desire for pain relief. As exemplified above, if ratings of patients' levels of pain, expectancy, and desire are obtained before the treatment it may be possible to accurately predict the post-treatment pain levels and then calculate the projected change scores that reflect placebo (and possible nocebo) effects. Using this approach it may be possible to deduce the placebo component of active and inert placebo treatments and thereby estimate the drug effect more precisely. This method is well-validated and it may furthermore help overcome some of the ethical concerns about exposing patients to inert placebo treatments as it may allow for an estimation of the placebo component of a drug without including inert treatments.

VERBAL SUGGESTIONS FOR ADVERSE EVENTS: THE RISK OF UNBLINDING

Although verbal suggestions in clinical trials are often related to pain relief, information and suggestions in relation to AE are also given. Recent meta-analyses have shown that in clinical trials a large number of patients experience AEs in the placebo arm of the trial, although there is no pharmacological basis for these AEs.^{33,34} Hence, the experiences of AEs are most likely related to the information given in the informed consent. In fact, the frequency and type of AEs have been shown to correspond with the AEs in the active arm, so that a higher number of AEs were experienced in the placebo arm of anti-convulsant trials as compared to the non-steroidal anti-inflammatory trials and triptans trials. Also, there was a higher drop-out rate in the placebo arm of the anti-convulsant drugs as compared to the non-steroidal anti-inflammatory drugs and triptans trials.³³ A recent meta-analysis of clinical trials in irritable bowel syndrome has further shown that irritable bowel syndrome therapies with a higher incidence of AEs were related to a higher subjective patient-reported efficacy in clinical trials, thereby suggesting that AEs may unmask the blinded active treatment.²⁴ Thus, verbal suggestions and experiences of AEs may un-blind the study and influence the treatment outcome and thereby further complicate the information that can be obtained from clinical trials.

A simple way of testing if the trial is double-blind is by directly asking patients and investigators about their perception of the treatment: "which treatment do you think that you/the patients received?" In studies that test double-blinding in this manner it has been found that approximately 80% of patients and investigators can correctly identify treatment allocation, thereby showing that the studies are not truly double-blind. Researchers have sought to overcome this problem by using "active" placebos where the placebo treatments have side-effects that mimic the side-effects of the active medication. Still, the active placebos are often difficult to develop and even in studies using active placebos, high rates of correct treatment identification have also been seen in both patients (50%-70%) and investigators (73%-75%).⁷⁴

Thus, at present the most precise way of obtaining information about patients' perceptions of the treatment, and hence of the blinding, appears to be by directly asking them about which treatments they think they have or have not been given and having them rate critical factors.

CONCLUDING REMARKS

Patient perception of a treatment and especially the verbal suggestions given in relation to pain may greatly influence the magnitude of the placebo effect, the nocebo effect, the drug effect and hence the overall outcome of the trial. However, knowledge of the underlying mechanisms will make it easier to account for these effects in the design, conduction, and interpretations of clinical trials. It has been suggested that one way of improving the information that can be drawn from clinical trials may be to minimize the placebo and nocebo components of clinical trials. Yet as exemplified above, this approach may be practically difficult, it may question ecological validity, and it may not necessarily improve drug-placebo comparisons. An additional or alternative approach may be to tap into patients' perceptions of a treatment and their expectations and desires toward the treatment in order to understand to what extent these factors influence the outcome of the study. This can be done by adding three simple questions to standard clinical analgesia trials: (1) "What do you expect your pain levels to be (once the treatment takes effect)?" (2) "How strong is your desire for pain relief?" and (3) "Which treatment do you think that you received (active, placebo)?" These questions may help overcome problems with unintentional un-blinding, and they may constitute additional or alternative measures of the placebo component of inactive and active treatments, thereby allowing a more precise estimation of the true drug effect.^{28,29,36-38,73}

Hence, in the future, the information from clinical trials may be enhanced by interfacing knowledge of placebo and nocebo mechanisms with improvements in clinical trial designs thereby allowing for better ways of testing and approving new pharmacological treatments.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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