



Shaping placebo analgesic responses on the Internet: a randomized experimental trial

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Abstract

Background: The field of Internet-based treatments is expanding. However, little is known about placebo effects in online therapeutic settings. The aim of this study was to test if placebo analgesia could be induced via online communication. Exploratory analyses tested if different communication styles (empathetic/neutral) would influence the placebo effect.

Methods: In this double-blind experiment, 30 healthy participants were randomized to either empathetic or neutral online communication. After completing the online modules, a face-to-face placebo analgesia experiment was performed. An independent experimenter (blinded as to communication type) performed the pain testing and treatment with a sham analgesic device (placebo).

Results: Overall, there was a significant placebo effect, as participants rated the pain lower when the sham analgesic device was turned on, compared to off. An additional control experiment ($n = 17$) confirmed that pain testing with the sham analgesic device per se, without any prior communication, was not enough to induce placebo effects. Exploratory analyses indicated a significant difference in perception of the online communication between participants randomized to the empathetic and neutral groups because the empathetic group rated the interaction as more positive. Also, there was a significant difference in online compliance. Yet, exploratory analyses did not suggest any difference in placebo pain ratings between the empathetic and neutral communication groups.

Conclusion: The results in this study suggest that placebo effects can be created even when information about an analgesic treatment is delivered online. This is the first indication of a novel research line that investigates placebo effects in online treatment.

Keywords: Placebo effect, Internet, Expectancy, Analgesia, Patient–physician interaction

1. Introduction

Since 2005, the World Health Organization has encouraged member states to implement eHealth in services and health systems.¹⁸ Today, Internet-based treatments (IBTs) have started to replace traditional face-to-face therapy for a wide range of clinical problems, such as depression, substance abuse, and pain management, and is expected to flourish in the future.¹³ In contrast to pharmacological trials, where placebo controls are the gold standard for estimating the contextual effects of a treatment,⁷ little is known about the placebo component of IBT or the role of

patients' perception of online therapeutic relationships.^{3,11} Here, we tested if placebo analgesia could be induced through suggestions given via online patient–clinician communication. A double-blind placebo experiment was performed, using an authentic clinical platform for IBT, combined with a face-to-face visit in our laboratory where participants' placebo effect was assessed in response to a sham analgesic device. To explore the patient–clinician relationship, participants were randomized to “empathetic” or “neutral” online communication. The empathetic condition was hypothesized to yield higher placebo effects because previous studies have shown that factors such as empathy and warmth significantly affect clinical outcomes.^{8,9,16} To control for the possibility that the mere exposure to the sham analgesic device could lead to placebo effects, we also performed a control experiment where participants were not given any suggestions about the analgesic properties of the device. By using a randomized experimental design with controllable variables, this study aimed at elucidating the potential influence of placebo components in a naturalistic IBT setting.

2. Materials and methods

2.1. Participants

Healthy participants were recruited through online advertisement and informed over telephone that the study aim was “to explore

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the relation between different types of communication and pain sensitivity.” Inclusion criteria were: generally healthy, aged 18 to 55 years, and understand Swedish. Participants ($n = 30$, 12 male) had a mean age of 27 ± 9 years, and 7 of 10 had higher education. The 30 participants were randomized to either “empathetic” or “neutral” online communication using an online list randomizer (random.org). After the randomization and completion of the main experiment, new participants ($n = 17$, 9 male) were recruited to a control experiment through online advertisement (mean age 27.6 ± 5 years, 10 of 10 had higher education). The participants in the control experiment were not randomized to any of the 2 experimental conditions “empathetic” or “neutral” because they did not receive any online communication before the experiment. All participants provided oral and written consent to participate in the study, which was approved by the Regional Ethical Review Board in Stockholm, Sweden (#2016/1210-31). All participants, including those who were recruited for the control experiment, were compensated €20 for participation in the study and debriefed at study end.

2.2. Procedure

2.2.1. General information

Our experiment consisted of 3 steps: (1) Preexperimental phase: participants communicating with experimenter over the Internet starting 3–4 days before the experiment; (2) experimental phase: face-to-face placebo test including calibration of thermal pain temperatures and testing participants’ pain sensitivity and response to the sham analgesic device; and (3) postexperimental phase: questionnaires and debriefing session. The participants in the control experiment underwent only the second step of the experiment, ie, the placebo test.

The preexperimental communication was performed using a secure clinical platform designed to deliver IBT.¹² Online modules were completed on 2 consecutive days, including writing tasks (about prior experiences of pain) and reading tasks (experimenter feedback). The communication was designed to give the impression that they communicated with the experimenter they were scheduled to meet face to face for pain testing the same week. Hence, this study was double blind because the experimenter who performed the placebo test did not know to which condition the participants had been randomized, and the participants were unaware of the 2 different conditions until the study was over.

The calibration and placebo experiment was conducted in a room with a comfortable treatment chair in a hospital environment (Karolinska Hospital, Stockholm, Sweden). The heat stimulations were administered using a 3×3 cm heat probe using the Medoc Pathway ATS model, a pain and sensory evaluation system (Medoc Advanced Medical Systems Ltd, Ramat Yishai, Israel). The sham analgesic device consisted of an electronic box that made a beeping sound when “turned on” and an electrode that was placed on the participant’s volar forearm next to the heat probe. Verbal communication during the experiment was reduced to a minimum because the online modules were designed to represent as much of the patient–clinician communication as possible. All administrative and practical information regarding the study was given by a research assistant.

To ensure that the experiment would be double blind, the experiment required 2 staff who could work independently from each other, ie, one experimenter performed the placebo experiments and one administered the online communication. In the

control experiment, there was no randomization to different conditions and therefore, the experimenter was not blinded.

2.2.1.1. Preexperimental communication online

Participants were randomly assigned to empathetic or neutral online communication, based on a validated checklist for patient–clinician communication.⁸ The randomization list was prepared by an independent researcher with no connections to the study participants. The empathetic checklist included, for example, using the participant’s own vocabulary in experimenter responses, asking open-ended questions, provide reflections, validating emotions, and avoiding medical jargon. The neutral communication included only prewritten, nonpersonalized messages with closed questions, no reflections, and frequent use of medical jargon. The same actual facts and information was presented but framed with different type of language (empathetic/neutral). A validation procedure, consisting of a questionnaire asking about the communication online, confirmed that the different communication versions were perceived as intended. The questionnaire included questions such as: “Please rate how positive you perceived the communication you had over the Internet with the experimental leader in this study (0 = not positive at all, 100 = completely positive).”

The aim of the online communication was to convey positive information about the analgesic device and create an alliance between the participant and the person communicating online with them. The sham analgesic device was described as a tool that can lower the perception of pain through electrical activation of peripheral nerves in the skin, similar to a transcutaneous electrical nerve stimulator. The participants answered personal questions about their previous experiences of pain and read information about the sham analgesic device. Because the answers contained personal reports of previous pain experiences, the experimenter was given an opportunity to validate and express empathy in the empathetic condition.

2.2.1.2. Experimental phase

After giving informed consent, the participants were asked to sit in the chair and the experimenter placed the heat probe and sham analgesic electrode on the participant’s volar forearm. To find a temperature that was moderately painful for each participant (approximately 60 out of 100 on a numeric response scale [NRS] ranging from 0 = no pain, 100 = worst imaginable pain), the participants were given a series of ascending temperatures. After each temperature, the participants were asked to rate the pain from 0 to 100 NRS. The heat stimulations started at 38 degrees Celsius and increased until the participant rated 60 NRS or until the maximum temperature (49°C). Each participant’s pain threshold and maximum pain were noted. The participants’ pain threshold was the first heat stimulation rated above 0 NRS, and maximum pain was the first heat stimulation rated above 60 NRS.

After this, a placebo experiment with a sham analgesic device was performed. Verbal communication during the experiment was reduced to a minimum. The experimenter explained: “*Since this is a study assessing the use of online communication in health care, we would like the online information to speak for itself, which means that I will not talk to you much during this session, only ask for your pain ratings.*” Before the heat stimulations, the participants were told: “*This is the analgesic device you have read about on the Internet.*” No further verbal information was given at this point. Each participant was administered their high temperature (60 NRS) 3 times: one time while the sham analgesic device was turned “off,” one when the device was “on,” and then when

the device was “off” again. As the same temperature was administered during each of the 3 stimulations, any difference in pain rating would represent a placebo effect. After each trial, participants rated how painful it was on the 0 to 100 NRS.

The procedure in the control experiment was identical, except that the following explanation was given at the beginning: “Because you did not receive any online information, some aspects of this experiment might not be understandable to you at this point but we will give you all details as soon as the test is over. The whole purpose of this control experiment is to perform testing when participants are naive, and compare that to the results of those who received information online.” When it was time to use the sham device, the experimenter did not mention that the device was analgesic. Instead, the experimental leader explained: “Now I am going to attach an electrode to your skin and ask you to rate pain while the electrode is either turned on or off.” Just as in the main experiment, the device was properly turned on (with beep and light indicating it was on) or off.

2.2.1.3. Postexperimental phase

After the placebo experiment, participants filled out standardized questionnaires and a study-specific questionnaire regarding how they perceived (1) the sham analgesic device, (2) the experimenter, and (3) the online communication. Finally, the participants were fully briefed about the 2 different types of online communications (empathetic/neutral) and the deception used in the study (sham device).

2.2.2. Outcome measures

Placebo effect was defined as decreased pain when the device was turned “on” vs “off” (3 pain ratings). Credibility of the sham analgesic device was rated on a 0 to 100 NRS and was also rated anonymously in a postexperiment questionnaire. Participants’ perception of the online communication (how positive it felt) was rated on a 0 to 100 NRS. The participants’ rating of their relationship with the experimenter was assessed using the “bond” dimension of the Working Alliance Inventory (WAI),⁵ a validated instrument used to assess the working alliance between patients and clinicians. The bond dimension represents the strength of the empathetic bond that can develop between a patient and clinician.

2.3. Statistical analyses

Placebo effect and interaction effects of communication type were analyzed using a mixed-effects model of participants’ pain ratings. Other measures were analyzed using independent-samples *t* test or Pearson’s *r*; statistical significance threshold $P < 0.05$, 2-tailed (SPSS 23). Sample size was calculated based on the effect size obtained with a similar placebo experiment in healthy participants in our previous study.⁶ Overall, required sample size was 13 participants in each group, given a power of 80% and an alpha level of 0.05, 2-tailed.

3. Results

Fifteen participants were randomized to the empathetic condition and 15 to the neutral condition. Overall, there was a significant placebo effect ($F = 9.552$, $P = 0.003$, $df = 58$, 95% confidence interval [CI]: -6.31 to -1.35), as pain ratings were lower when the sham analgesic device was turned “on,” compared to “off” (Figure 1). In the control experiment ($n = 17$), where participants had not been informed about the meaning of the device placed

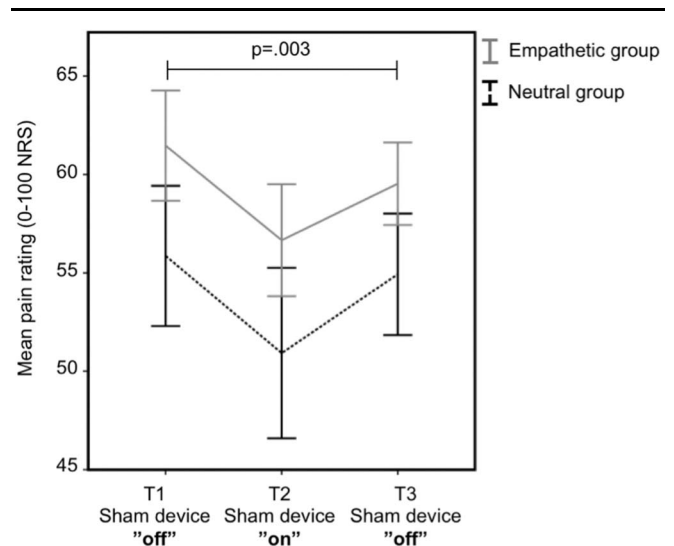


Figure 1. Pain ratings during the placebo experiment. Mean pain ratings (0–100 NRS) during subjectively calibrated high-intensity heat while the sham analgesic device was turned “off” (T1), turned “on” (T2), and turned “off” (T3). The same absolute temperature (°C) was used during T1 to T3 within subjects. The difference between machine “on” and “off” across groups was analyzed using a mixed-effects model of participants’ pain ratings ($P = 0.003$). Error bars represent 1 intrasubject SD. NRS, numeric response scale.

next to the thermode (ie, the sham analgesic device), there was no significant placebo effect [$F = 0.194$, $P = 0.662$, $df = 33$, 95% CI: -5.12 to 3.3].

Our exploratory analyses showed a significant difference in perception of the online communication between participants randomized to the empathetic and neutral groups [$t(28) = -2.957$, $P = 0.006$, 95% CI: -54.17 to -9.83], as the empathetic group rated the interaction as more positive. Also, there was a significant difference in online compliance, as participants receiving empathetic communication completed the online tasks and read the experimenter feedback more often compared with the neutral group [$t(28) = -2.153$, $P = 0.04$, 95% CI: -22.76 to -0.56]. Participants who rated the online communication as positive also gave high ratings for the patient–clinician alliance (WAI bond), $r = 0.410$, $P = 0.024$ (Table 1). Yet, our exploratory analysis suggests that there was no significant difference in placebo effect between the empathetic/neutral communication groups [$F = 0.464$, $P = 0.501$, $df = 28$, 95% CI: -20.42 to 10.22].

The quality of the face-to-face therapeutic alliance during pain testing was measured with the “bond” dimension of the WAI questionnaire. Here, we found that participants’ perception of the online communication correlated significantly with WAI bond ($P = 0.024$), as those who had a positive online experience subsequently had a positive face-to-face experience during the pain experiment (Table 1).

Credibility of the sham analgesic device was rated orally on a 0 to 100 NRS, ranging from 0 = “will not reduce pain at all” to 100 = “will reduce pain completely.” In line with previous placebo research, we found that participants’ credibility in the analgesic treatment correlated with the placebo outcome ($P = 0.001$, Table 1). To test if positive placebo effects may have been an effect of social desirability,² the credibility was also rated anonymously in a post-experiment questionnaire. There was a very high correlation (>0.9) between the credibility ratings given orally and the ratings given anonymously ($P = 0.001$), indicating that responses were likely not affected by response bias (Table 1).

Table 1
Correlations between credibility, therapeutic alliance, and placebo outcome.

Correlation	<i>r</i>	<i>P</i>
Credibility sham device/placebo outcome	0.78	0.001
Credibility sham device/anonymous credibility sham device	0.948	0.001
WAI bond/communication positive	0.410	0.024

The aim of the online communication was to convey positive information about the analgesic device and create an alliance between the participant and the person communicating online with them. Credibility of the sham analgesic device was rated orally on a 0 to 100 NRS, ranging from 0 = "will not reduce pain at all" to 100 = "will reduce pain completely." The credibility was also rated anonymously in a postexperiment questionnaire. Placebo outcome was defined as the difference in pain rating when the sham analgesic device was "off" minus "on." Perception of the online communication was rated on a 0 to 100 NRS, ranging from 0 = not positive at all to 100 = completely positive. The quality of the face-to-face therapeutic alliance was measured with the "bond" dimension of a validated scale called the Working Alliance Inventory (WAI). NRS, numeric response scale.

4. Discussion

Here, we were able to demonstrate how placebo analgesia was induced through information communicated via an online patient–clinician platform. It is well known that the patient–clinician interaction is important for placebo responses⁸; yet, we are unaware of previous trials examining placebo effects in IBT, where the alliance between patient and clinician is created online. Our study could thus be the first account of how placebo effects can be formed through online communication. Previously, placebo experiments have included written information as a medium to induce different expectations in placebo experiments¹⁷ but, to the best of our knowledge, placebo suggestions have not been tested in an online context.

In line with our hypothesis, we found that the perception of the online communication (how positive it felt) correlated significantly with the participants' perception of the alliance with the experimenter during pain testing. The experimenter did not know if participants had been randomized to neutral or empathetic online communication; yet, participants were led to believe that the experimenter was the same person they had interacted with online. This means that the perception of an online alliance may transfer to the face-to-face situation, which has important clinical implications.

As part of an exploratory approach, this study assessed the difference in placebo effects between 2 different communication types. In this small and exploratory analysis, we did not find any significant effects of communication type (empathetic/neutral); however, there was a significant difference in how the communication was perceived (how positive it felt) and how the participants behaved online. The empathetic online condition was associated with more positive ratings and higher compliance regarding online tasks. Based on these observations in healthy participants, we hypothesize that patients may show better treatment results in an enhanced online treatment context, not only because there is an emotional and motivational potential from empathetic online communication but also through increased treatment compliance. Yet, this study was not powered to detect the subtle differences in placebo outcomes between our 2 different online conditions and therefore, the results should be interpreted with caution.

Previous evidence has shown that clinicians in face-to-face treatments characterized by warmth and empathy are more effective than clinicians who are formal and impersonal.^{4,9,14,16} Yet, there is evidence that the perceived alliance between patient and clinician in IBT affects the clinical outcome to a smaller extent than face-to-face treatment.^{1,10} This suggests that the patient–clinician relationship might not be as important for IBT as it is for face-to-face treatment. Future studies should explore

the difference in influence of the patient–clinician relationship between online and face-to-face communication.

The scope of this study was to test if placebo effects can be created through online information and not to compare the online condition to a face-to-face condition. This study could thus not determine if placebo effects created on the Internet are more or less powerful than traditional face-to-face interactions. However, previous data from our laboratory,¹⁵ using the same placebo manipulation in a face-to-face context, suggest that the effect size is the same, as pain was reduced by approximately 10 NRS during placebo analgesia, compared to the control condition. It is therefore possible that the placebo response in an experimental setting is not sensitive as to the medium of the treatment suggestion. Yet, clinical studies may find that a face-to-face interaction with a clinician enhances the placebo effect. This should be investigated in future randomized studies, comparing online vs face-to-face placebo suggestions. We therefore suggest that further studies are needed to test these preliminary findings in larger populations and in clinical settings. The health care improvements expected from current investments in eHealth¹⁸ will not be fully realized unless we learn more about the placebo components of online therapeutic relationships and interventions.

Limitations to this study include the fact that the control experiment was performed separately from the randomization of participants to the empathetic or neutral conditions. A random assignment to all 3 groups had been preferable. Another limitation is the small sample size and limited power to detect differences in placebo responses between the empathetic and neutral groups. A future experiment, with fully randomized groups and larger sample size, would be preferable to validate the findings in this study.

5. Conclusion

Here, we provide preliminary data to suggest that placebo effects can be created even when information about the analgesic treatment is delivered online rather than face to face.

Disclosures

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