

Drug-Related Information Generates Placebo and Nocebo Responses That Modify the Drug Response

MAGNE ARVE FLATEN, DR PSYCHOL, TERJE SIMONSEN, CAND MED, AND HARALD OLSEN, DR MED

Objective: Administration of the muscle relaxant carisoprodol and placebo was crossed with information that was agonistic or antagonistic to the effect of carisoprodol. It was investigated whether information alone induced physiological and psychological responses, and whether information modified the response to the drug. **Methods:** Half of the subjects received capsules containing 525 mg carisoprodol together with information that the drug acted in a specific way (Groups Relaxant/C, Stimulant/C, and No Information/C). The other half of the subjects received lactose (Groups Relaxant/L, Stimulant/L, and No Information/L). Dependent variables were blink reflexes and skin conductance responses, subjective measures of tension and sleepiness, and serum carisoprodol and meprobamate concentrations. Recordings were made between 15 and 130 minutes after administration of the capsules. **Results:** The Stimulant/L group reported more tension compared with the other two groups, and carisoprodol increased tension even more in the Stimulant/C group. The Relaxant/C group displayed higher levels of carisoprodol serum concentration compared with the other groups that received carisoprodol. **Conclusions:** Reported tension was modulated in the direction suggested by the stimulant information. The effect of carisoprodol on tension was also modulated by stimulant information. Increased carisoprodol absorption in the group that received relaxant information could be a mechanism in the placebo response. **Key words:** placebo response, nocebo, blink reflex, skin conductance response, carisoprodol.

ANOVA = analysis of variance; EMG = electromyography; SCR = skin conductance response; kPa = kilopascal; VAS = visual analog scale.

INTRODUCTION

A placebo or nocebo may be defined as an inactive substance or a procedure that is administered with suggestions that it will modify a symptom or sensation (1). The placebo and nocebo response is the response to the inactive substance or procedure. Placebo responses may be observed as, eg, a reduction in pain or swelling after tooth extraction (2). Nocebo responses may be regarded as negative placebo responses, eg, as increases in pain or in other unpleasant symptoms (3).

Information about drug effects may induce placebo responses. Flaten (4) gave three groups of subjects information that they received a relaxant, a stimulant, or an inactive agent, whereas all groups received an inactive agent. Stress was reduced in the group that received information that it received a relaxant drug, whereas arousal increased in the group that received information that it had ingested a stimulant. These

findings, as well as other findings reviewed by Flaten (4), indicate that information about drug effects generates responses that are similar to the drug's expected effect.

Drug-related information has also been shown to modify the magnitude of the physiological drug response. In one study (5) asthmatics were told that they received either a bronchodilator or a bronchoconstrictor, and this information was crossed with administration of either a bronchodilator or bronchoconstrictor. The results showed that the bronchodilator was more effective in decreasing airway resistance when the subjects were told that they received a bronchodilator, and the bronchoconstrictor was more effective in increasing airway resistance when the subjects were told that they received a bronchoconstrictor. Thus, when information about drug effects matched the pharmacological drug effect, an increased drug response was seen. A mismatch between information and drug decreased the drug response. Similar findings were obtained by Lyerly et al. (6) and Penick and Fisher (7).

Because of these findings, we wanted to investigate whether a) different forms of information differentially affected psychological and physiological responses, and b) whether the information-induced response modified the drug effect. To test these hypotheses, three groups of subjects were informed that they received a relaxant, a stimulant, or were not given any information about the drug effect. Half of the subjects in each group received carisoprodol, and the other half received lactose. Carisoprodol is a centrally acting muscle relaxant drug known to inhibit the polysynaptic transmission of the blink reflex (8, 9) and induce drowsiness, and is metabolized into meprobamate (10). It was expected that relaxant information should decrease psychological and physiological indices of arousal and tension, whereas stimulant information

From the Department of Psychology (M.A.F.), University of Tromsø, and Department of Clinical Pharmacology (T.S.), Tromsø University Hospital, Tromsø, Norway; and Department of Psychiatry (H.O.), University of Oslo, Oslo, Norway.

Address reprint requests to: Magne Arve Flaten, Prof Dr Psychol, Department of Psychology, SVT, Norwegian University of Science and Technology, N. 7491 Trondheim, Norway. E-mail: magne.flaten@svt.ntnu.no

Received for publication July 7, 1998; revision received November 2, 1998.

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should increase responses. It was, furthermore, expected that relaxant information should augment the drug response, whereas stimulant information should reduce the drug response.

METHOD

Subjects

Sixty-six drug-free subjects (30 women, 36 men, aged 18–38 years), without previous or present illness or injuries, and with clinical chemistry parameters revealing normal liver and renal function, were included in the study. The subjects were either students of or employed in social, natural, and humanistic sciences (non-health professions). A preliminary recruitment procedure informed the subjects that the study tested the effect of drug administration on physiological and psychological responses. They were also informed that some subjects would receive capsules containing placebo, whereas others would receive an active drug. The data from one subject was excluded because she fell asleep, and the physiological data from two additional subjects were excluded because of experimenter error. Two subjects, both in the Relaxant/C group, were excluded from the pharmacological analyses because the carisoprodol to meprobamate ratio was unusually high, indicating a genetic disposition for slow carisoprodol metabolism (11).

Chemicals

Carisoprodol was from Dumex, and lactose was from Norsk Medisinaldepot (Oslo, Norway). The capsules were hard gelatin size 1 capsules from Davcaps (Hertfordshire, England). The capsules, containing either 175 mg carisoprodol or lactose, were packed by the pharmacy at Tromsø University Hospital. Carisoprodol, meprobamate, and nortriptyline for analytical purposes were from Norsk Medisinaldepot. Other chemicals were reagent grade.

Apparatus and Stimuli

The experiment was conducted in a room at the Clinical Research Unit at Tromsø University Hospital. The equipment for airpuff presentation and data collection was placed in the same room, but out of sight of the subject. This equipment consisted of a 486 PC, a Coulbourn stack-a-rack with modules for response signal preparation, a voltage transformer, and a solenoid valve controlling delivery of the airpuff. The valve was covered with sound-dampening fabric so the subjects could not hear its operation. The airpuff used to elicit blink reflexes and SCRs had a duration of 50 msec and an intensity of 27.6 kPa (4 psi), and was delivered to the medial canthus of the right eye. The R² component of the blink reflexes was recorded via EMG as in Flaten (12) and skin conductance responses were recorded as in Flaten (13). The subjects were asked to indicate, on a VAS consisting of two 100-mm long lines, their present status on two dimensions. At the poles of the first dimension were written "sleepy" and "awake"; at the poles of the second dimension were written "tense" and "relaxed."

Blood samples were taken from an indwelling Veneflon in the left median basilic or cubital vein continuously infused with a solution of isotonic sodium chloride. At sampling time the infusion was stopped. After discharging the first 2 ml of blood from each sampling, 10 ml of blood was collected in gel-free glass tubes four times during the experiment. Serum was prepared 30 minutes after sampling by spinning the sample tubes at 1500g for 10 minutes. The serum samples were pipetted off and kept frozen at -20°C in 2-ml plastic tubes until analyzed.

Each subject received one of three types of drug-related information. The Relaxant group received the following information: "You will receive three capsules that contain a prescription drug that acts as a relaxant. The drug is used as a relaxant and against muscle pain, since it reduces muscle tension. The drug will make you feel relaxed and drowsy." The Stimulant group received the following information: "You will receive three capsules that contain a prescription drug that acts as a stimulant. The drug is used to increase the metabolism of the body and the activity in bodily organs. The drug will make you feel alert." The No information group received the following information: "You will receive three capsules that contain a prescription drug. Because we are interested only in the biological effects of the drug, you cannot be told anything about the drug's effects." The participants were instructed not to speak to anyone else about the experiment.

All administration of drug and lactose was double-blind, and was performed by uniformed nurses. Both substances were given as three white capsules that were swallowed with a glass of water. For half of the subjects, each capsule contained 175 mg carisoprodol, ie, a total of 525 mg (Groups Relaxant/C, Stimulant/C, and No Information/C). For the other half of the subjects, the capsules contained an equal amount of lactose (Groups Relaxant/L, Stimulant/L, and No Information/L).

Procedure

The subjects were allocated to groups according to a semi-random procedure (Table 1).

The subjects met in the laboratory at either 8:30 AM or 12:00 noon, one subject at a time. Those who met at 8:30 AM were asked not to eat or drink coffee on the day of the experiment. They received one or two slices of bread with orange marmalade, and a glass of apple juice. The subjects who met at 12:00 noon had been asked not to drink coffee on the day of the experiment, and to eat a light breakfast. They received one or two slices of bread with orange marmalade, and a glass of apple juice.

The subjects sat in a comfortable armchair. After having had breakfast or lunch, the electrodes, the equipment for airpuff presentation, and the indwelling Veneflon were fitted to the subject. The first reflex test was performed 30 minutes after arrival in the laboratory, the first blood sample was taken 40 minutes after arrival, and the first VAS was administered 45 minutes after arrival. These data constitute the pretests.

TABLE 1. Schematic Representation of the Composition of Each of the Six Groups in the Experiment

	Lactose	Carisoprodol
Relaxant information	Relaxant/L ^a group 7 men 4 women	Relaxant/C ^a group 6 men 4 women
Stimulant information	Stimulant/L group 7 men 5 women	Stimulant/C group 6 men 5 women
No information	No Information/L group 6 men 5 women	No Information/C group 5 men 5 women

^a The C indicates that the subjects in three of the groups received carisoprodol, the L indicates that the subjects in three of the groups received lactose.

Sixty minutes after arrival in the laboratory, the subjects received information about the drug, and the capsules were administered.

Eight reflex tests were performed at 15, 30, 45, 60, 75, 90, 105, and 120 minutes after administration of the capsules, and blink reflexes and SCRs were sampled during these tests. Each reflex test consisted of 10 airpuffs, and the intertrial interval varied between 23 and 27 seconds. Blood samples were taken at 40, 80, and 125 minutes after administration of the capsules. Six VASs were administered 20, 35, 50, 65, 95, and 130 minutes after ingestion of the capsules. The subjects were allowed to read between the tests.

Response Scoring and Data Treatment. Blink reflexes were scored as the integral of the EMG response from 20 to 140 msec after airpuff onset. Data are expressed in analog-to-digital units. Skin conductance response amplitudes were scored as the maximum deviation from baseline 1 to 7 seconds after airpuff onset. The responses on the VAS were scored in millimeters. For all of these dependent variables, the data from the first test were subtracted from the data in each of the tests conducted after administration of the capsules.

Design and Statistics. The general design was a 2 Drug (carisoprodol, lactose) \times 3 Information (Relaxant, Stimulant, No information) \times 8 Posttests mixed design, with the first two factors treated as between-groups factors, and the last factor treated as a within-subjects factor. Statistical analyses were performed by ANOVA. For analyses involving repeated measurements the Geisser-Greenhouse correction was used. A priori planned tests were performed by contrast analyses, where the α level had been corrected by the modified Bonferroni procedure; a posteriori tests were performed by the Newman-Keuls test. The Statistica package was used, and an α level of .05 was chosen.

RESULTS

Carisoprodol and Meprobamate Serum Concentrations

After carisoprodol administration, the serum concentration of carisoprodol increased in all groups (Figure 1) ($F(3,78) = 30.02$), and carisoprodol was converted into meprobamate (Figure 1).

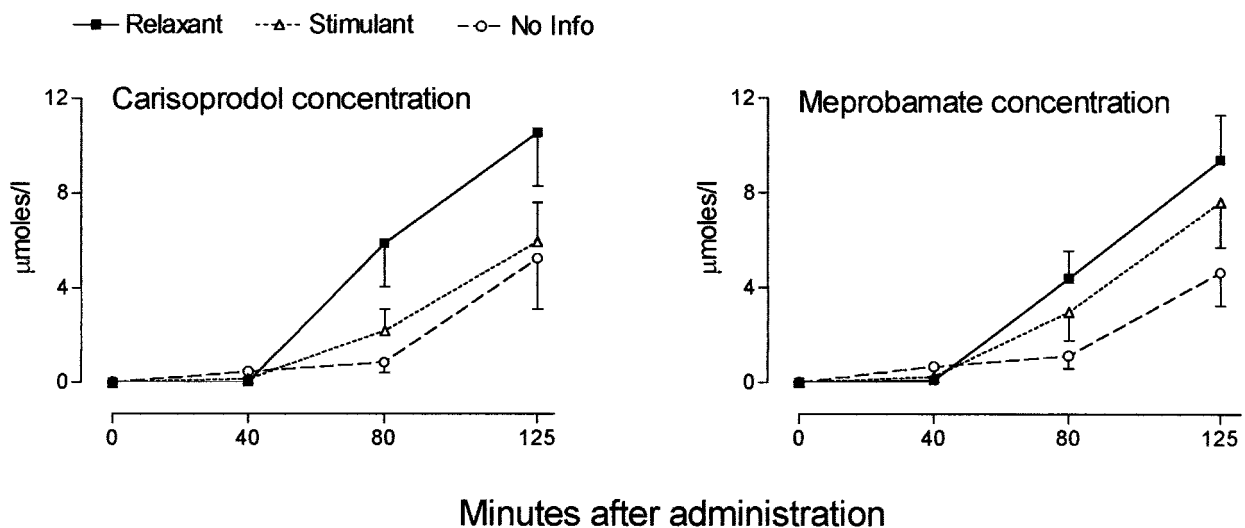


Fig. 1. Mean carisoprodol and meprobamate serum concentration in the blood sample taken before carisoprodol administration (0), and in samples collected 40, 80, and 125 minutes after administration. Error bars indicate ± 1 SE.

Relaxant information was associated with increased levels of carisoprodol serum concentration, and this is supported by the significant main effect of Information ($F(2,26) = 3.45$, $p < .05$). Follow-up tests (Newman-Keuls) showed that concentration of carisoprodol was significantly higher in the Relaxant/C group compared with the Stimulant/C group ($p = .046$), whereas there was no significant difference between the Relaxant/C and No Information/C group ($p = .051$).

Blink Reflexes

Blink reflexes (Figure 2) decreased across tests ($F(3.68,209.69) = 24.44$, $p < .05$). The Relaxant/L and Relaxant/C groups had smaller blink reflexes across all tests (sign test, $p < .0001$), but the interaction of Information by Test was not significant ($F(7.36,209.69) = 1.87$, $p = .072$). No other main effects or interactions were significant in the overall ANOVA.

Skin Conductance Responses

Skin conductance responses decreased across tests ($F(3.68,209.69) = 7.29$) (Figure 3). No other main effects of interactions were significant.

Sleepy-Awake Dimension

The significant interaction of Drug by Tests ($F(5,295) = 3.22$) (figure not shown) shows that carisoprodol induced sleepiness, and follow-up tests showed increased sleepiness at 95 and 130 minutes in the groups that received carisoprodol, compared with the groups that received lactose ($F(1, 59) = 5.23$). No other main effects or interactions were significant.

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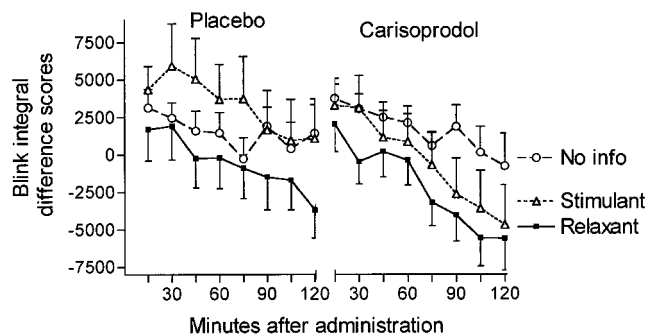


Fig. 2. Blink reflex integrals across tests for each group. The left part of the figure displays responses to information about the drug. The right part displays responses to information and carisoprodol. The integrals are expressed as the difference from the pretest, performed before administration of the capsules. Thus, scores below zero indicate reduced blink reflex integrals compared with the pretest. Error bars indicate ± 1 SE.

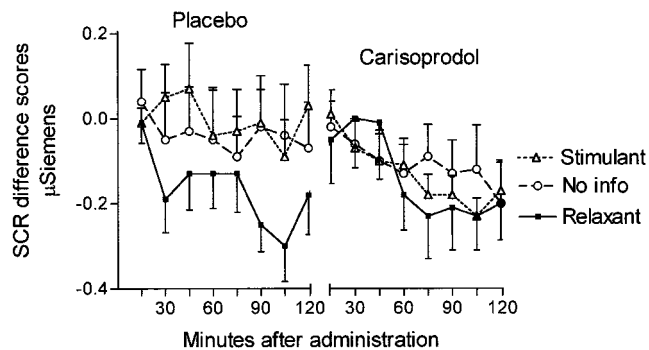


Fig. 3. Skin conductance responses across tests for each group. The left part of the figure displays responses to information about the drug. The right part displays responses to information and carisoprodol. The SCRs are expressed as the difference from pretest, performed before administration of the capsules. Thus, scores below zero indicate reduced SCRs compared with the pretest. Error bars indicate ± 1 SE.

Relaxed-Tense Dimension

The significant main effect of Information ($F(2,59) = 7.20$) was due to more reported tension in the Stimulant groups compared with the Relaxant and No information groups ($F(1,59) = 10.34$ and 10.94 , respectively) (Figure 4).

The significant interaction of Information by Tests ($F(6.69,197.19) = 4.62$, $p < .05$) was followed-up by the Newman-Keuls test. There was increased tension in the subjects who received stimulant information compared with the subjects who received relaxant information and no information across all tests (p values $< .004$ and $< .006$, respectively).

Contrast analyses showed significantly increased tension in the Stimulant/L group compared with the Relaxant/L group across tests ($F(1,59) = 4.22$, $p = .041$). Increased tension was seen even at 20 minutes

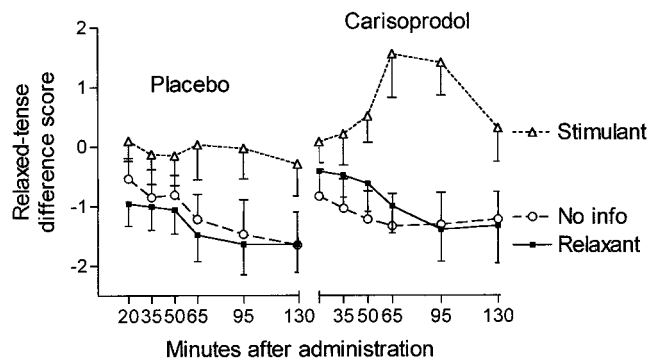


Fig. 4. Reports on the tense-relaxed dimension across tests for each group. The left part of the figure displays responses to information about the drug. The right part displays responses to information and carisoprodol. The data are expressed as the difference from the pretest, performed before administration of the capsules. Thus, scores below zero indicate reports of increased relaxation. Error bars indicate ± 1 SE.

after administration ($F(1,59) = 4.87$, $p = .031$). There was no significant difference between the Stimulant/L and No Information/L groups ($F(1,59) = 2.91$, $p > .05$). Linear trend analyses indicated decreased tension across tests in the Relaxant/C and No Information/C groups (F values $(1,59) = 4.21$ and 7.64 , respectively, p values $< .05$).

There was increased tension in the Stimulant/C group compared with the Relaxant/C and No Information/C groups across tests (F values $(1,59) = 6.17$ and 8.67 , p values $< .016$, respectively). Tension increased across the first 65 minutes in the Stimulant/C group, before a decrease was seen at 95 and 130 minutes after administration (quadratic trend, $F(1,59) = 13.49$, $p < .01$). Tension decreased across tests in the Relaxant/C group (linear trend, $F(1,59) = 6.87$, $p = .011$), whereas there was no trend in the No Information/C group ($F = 1.02$).

DISCUSSION

Information that the subjects received a stimulant drug increased feelings of tension, and carisoprodol increased tension even more in the Stimulant/C group. The interaction of Drug by Test was not significant for the blink reflex. The inhibitory effect of carisoprodol on the blink reflex has only been tested and seen in humans with a 700-mg dose (9). Thus, the 525-mg dose may have been too small to reliably inhibit blink reflexes.

Tension increased in the Stimulant/L group compared with the Relaxant/L and No Information/L groups across tests. There was no difference between the Relaxant/L and No Information/L groups, and ten-

sion decreased across tests in both groups. Thus, information that the subjects received a relaxant did not modulate reported tension. There were tendencies in the blink reflex and SCR data that relaxant information reduced these responses, but the results failed to reach acceptable levels of statistical significance. The hypothesis was not confirmed for the sleepy-awake dimension.

The Stimulant/C group reported increased tension across tests. Serum carisoprodol concentration increased from 40 to 80 minutes in all subjects, and an increase in tension was seen from 50 to 65 minutes after administration in the Stimulant/C group. Thus, the information modulated the drug response in the direction of the information, even though carisoprodol, to our knowledge, has no stimulating effect. It is possible that the perception of the response to carisoprodol was labeled according to the subjects' expectation, ie, the information provided by the experimenter. Finally, the hypothesis was not supported for the blink reflex and SCR data. In summary, the hypothesis was partly confirmed for the tense-relaxed dimension, but not for the blink reflex and SCR.

There was significantly increased carisoprodol and meprobamate serum concentration in the Relaxant/C group compared with the Stimulant/C group. This was found even when two subjects in the Relaxant/C group had been removed from the data because of unusually high concentrations of carisoprodol relative to meprobamate. This finding indicates that carisoprodol absorption was slower in the Stimulant/C group. Stimulant information seemed to increase sympathetic activation somewhat, although the effect of information on the SCR did not reach significant levels. Increased sympathetic activation reduces the secretion of hydrochloric acid, with the consequence that dissolving the capsules could have taken longer. Increased sympathetic activation could also reduce motility in the gastrointestinal tract, and this would slow down the mixing of the capsules with hydrochloric acid, bile and digestive enzymes, and thus lead to slower absorption. It is not clear, however, whether this would reduce the total amount of drug absorbed. These two processes, changes in the secretion of hydrochloric acid and changes in motility in the gastrointestinal tract, could be mechanisms in the placebo response that, to our knowledge, has not been reported previously.

The behavior of the No Information group was more variable than the behavior of the other two groups. It reported relaxation to the same degree as the Relaxant/L group, whereas the SCRs were similar to the Stimulant/L group, and the blink reflex data were similar to the Relaxant/L group in the first 75 minutes, and

similar to the Stimulant/L group for the last 30 minutes of the experiment. An earlier study (4), where the subjects in the control group were told that they received placebo capsules, also reported variable control group behavior. Not receiving any information about drug effects could generate nervousness and arousal, which should make the control group more similar to the Stimulant group. This suggests that other procedures should be used in the control group.

For the tense-relaxed dimension, placebo or nocebo responses could be seen at 20 minutes after administration of lactose. Because this was the first test of the subjective effects, the placebo or nocebo response could have occurred even earlier. Flaten (4) found reduced stress and arousal at 15 minutes after placebo administration. The subjects did not receive any information about when the drug effects could be expected. Future studies could, therefore, manipulate the expectancy of when drug effects should occur and how long they should last, to generate specific predictions and test the role of expectancy in placebo and nocebo responding.

Placebo and nocebo effects are most likely not specific psychological processes, but must be understood as special cases of known processes. Classical conditioning and expectancy have been put forth as explanations of placebo and nocebo responses (14, 15). The present data suggests that subjects who expect a stimulant drug become more tense. There was, thus, a match between the subject's expectancy and the subjective and physiological state induced in the subject. Earlier studies have yielded similar findings (4, 6). However, there is also evidence that the opposite may occur. Studies of human and animal pharmacological classical conditioning have shown that a conditioned stimulus that signals the administration of a drug may elicit conditioned responses that are antagonistic to the drug response (9, 16). Such responses are interpreted as nocebo responses. It seems reasonable to assume that a pharmacological classical conditioning procedure induces the expectancy that, in the presence of the conditioned stimulus, the drug is soon to be administered. Why drug antagonistic, or nocebo, responses are so often seen in classical conditioning research, and not when expectation is induced through verbal information, is not clear.

From this viewpoint, the increased tension in the Stimulant/C group is especially interesting. Stimulant information alone increased reported tension, and reported tension was augmented by carisoprodol, a drug that does not induce tension. Thus, a mismatch between information and drug response increased tension.

Kirsch and Weixel (17) gave two groups of subjects

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decaffeinated coffee. One group was led to believe that they got caffeinated coffee, whereas the other group was told that they might receive coffee or decaffeinated coffee. The results indicated that the expectancy effects were stronger in the group that was led to believe that they got caffeinated coffee. This indicates that placebo effects could be enhanced if the subject has no reason to believe that he or she is not receiving an inactive agent. In the present study, all participants were told that they might receive an inactive agent, and this could have reduced placebo and nocebo responding.

In conclusion, the present study yielded support to the notion that placebo and nocebo responses may be generated by information about the effects of a drug. The information-generated response was associated with modulation of absorption of the drug.

The study was approved by the Committee for Medical Research Ethics in Health Region V in Norway (49/93), and was supported by The Council for Psychiatric Health (94036/19).

The authors thank the staff at the Research Unit at Tromsø University hospital for their assistance.

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ANNOUNCEMENT

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