Sources of Placebo-Induced Relief From Nausea: The Role of Instruction and Conditioning

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ABSTRACT

Objectives: It is well documented that expectancies alter the nauseous response. However, the lack of integration in research examining sources of expectancy has limited our understanding of how expectancies are formed and, consequently, our ability to intervene. The present study explored the role of both instructions and conditioning in placebo-induced relief from nausea.

Methods: The study used a 2 × 2 between-subjects design with instruction and conditioning as factors with 56 healthy volunteers. The instruction manipulation involved randomizing participants to receive information that a sham treatment (a peppermint essence vapor) would reduce nausea or no such instructions. The conditioning manipulation involved further randomizing participants to have the first administration of this sham treatment paired with a surreptitious reduction in galvanic vestibular stimulation (GVS) intensity or no prior pairing. Nausea was induced through GVS. On test, all groups received the same level of GVS with the sham treatment present.

Results: On test, participants who received instruction had significantly lower nauseous response scores than those who did not ($F(1,46) = 6.71$, $p = .013$), and those who received conditioning also reported less nausea than those who did not ($F(1,46) = 5.20$, $p = .027$), with the interaction between the two not reaching statistical significance ($F(1,46) = 2.33$, $p = .13$).

Conclusions: These findings indicate that placebo responding in nausea can be induced both through positive instructions and as little as one pairing of a treatment with a reduction in nausea, as well as their combination. This suggests that using placebo effects to complement antiemetic therapy may offer an important method of further reducing nausea in the clinic.

Key words: expectancy, placebo, nausea, instruction, conditioning.

INTRODUCTION

Nausea and vomiting are problematic in a wide range of settings, including in oncology, surgery, and obstetrics. Not only are they inherently physically and emotionally unpleasant, but also they can also lead to a variety of other undesirable outcomes, including extended hospital stays and readmissions (1), treatment discontinuation (2), and increased health care costs (3). Despite recent improvements in the efficacy of pharmacological antiemetics, the control of nausea and vomiting remains incomplete (4,5), with nausea being particularly resistant to intervention (6). This suggests that psychological factors may contribute to nausea and serve as a potential point of intervention.

The placebo effect is one such phenomenon that can contribute to nausea (7). The placebo effect is a psychobiological phenomenon whereby improvement occurs in response to the expectancies activated by the treatment context (8). In the case of nausea, it seems that expecting nausea can increase its severity (9,10). As one of the few potentially malleable patient characteristics predictive of the nauseous response, patient expectancies have therefore been a growing area of interest for intervention (11,12). However, one outstanding question impeding the development of a successful intervention to reduce nausea concerns how expectancies about nausea are formed.

Verbal instructions and conditioning have been the main sources of learning implicated in producing the expectancies that drive the placebo effect. Instructions may induce placebo responding by creating explicit expectancies that generate the expected response themselves (13). Pavlovian conditioning–based models of placebo responding instead propose that contextual features, such as the treatment setting or ritual of administration, function as conditioned stimuli (14). After becoming associated with an antiemetic (or nauseating) drug or procedure, these stimuli can in turn independently elicit a conditioned reduction (or increase) in nausea. In other areas, for example, pain, it has largely been accepted that both of these sources of learning contribute to

GVS = galvanic vestibular stimulation

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the placebo effect (15,16). In nausea research, however, these two aspects of placebo responding have rarely been considered together (7). Prior research in nausea has largely focused either solely on instructions (17–19) or solely on conditioning (20,21). Although one study (22) used a conditioning manipulation to enhance instructions in an interesting integration of the two sources of expectancy, the design of that study did not allow for comparison of placebo effects between instruction alone, conditioning alone, or the two combined. This means that there is a current lack of understanding concerning the way instruction and conditioning independently and in combination affect the nauseous response, which limits our ability to develop interventions to reduce nausea in the clinic.

The present study therefore examined the role of instructions and conditioning in placebo-induced relief from nausea simultaneously using a novel experimental model of nausea that we recently developed (23). This model involves inducing nausea through galvanic vestibular stimulation (GVS) under the guise of examining the effects of stimulation on spatial awareness. The model has important advantages over previous research using rotation chairs: demand characteristics are less likely, and experimental control over the experience of nausea is increased, as is the potential for other stimuli in the environment to be conditioned (as rotation chairs tend to dominate the experimental context). In the current study, we examined whether instruction alone, conditioning alone, or their combination could induce placebo effects for nausea. The sham treatment was a vapor containing low concentrations of peppermint essence. Experimental participants were given placebo instructions, suggesting that the vapor was effective for reducing nausea, a surreptitious reduction in stimulation timed with the vapor to condition a decrease in nausea, or both.

It was hypothesized that the three experimental groups, who received instructions designed to reduce nausea (the "instruction" group), conditioning without explicit instruction (the "conditioning" group), or both (the "'combined" group), would show reduced nausea on test with the sham treatment relative to controls who received this sham treatment in isolation. The factorial design also meant that we could test whether instruction and conditioning were additive in any placebo-induced reductions in nausea that they generated. To our knowledge, this is the first attempt to condition a *reduction* in nausea in humans in the absence of any instructions, as well as to simultaneously explore both instruction and conditioning and their effect on nausea.

METHODS

Design

Table 1 illustrates the 2 × 2 (instruction by conditioning) design. All groups received high-intensity stimulation on Day 1, low-intensity on Day 2, and moderate-intensity on Day 3, with the presentation of the vapor and instructions manipulated between groups. The instruction intervention was termed as such because the first time the vapor was presented, it was accompanied with a suggestion that it would reduce nausea. The conditioning intervention was instead that the first time the vapor was presented, it was paired with a simultaneous reduction in stimulation, known as a surreptitious reduction procedure, which is often used in pain research (24–26).

Participants

Participants were 56 undergraduates from the University of Sydney who received partial course credit for their involvement. They had an average (standard deviation [SD]) age of 19.7 (2.3) years, and 32 were female. Recruitment occurred from March 2014 to August 2014. The project received approval from the University of Sydney Human Research Ethics Committee.

Apparatus

GVS was used to induce nausea in participants, in a method similar to Quinn et al. (23). GVS involves passing small electrical currents to the vestibular end organs via surface electrodes over the mastoid processes (27). This alters the firing rate of vestibular afferents which causes individuals to detect a mismatch between their vestibular input and their visual system that is known to produce nausea (28). Rather than using the placebo setting of the device as performed previously (23), the current study manipulated the intensity of stimulation by varying the peak amplitude of the pseudorandom sine wave that participants experienced. The device has a dial to manipulate the amplitude, so that at 80% stimulation, the peak wave has amplitude of ±4 mA, 60% has ±3 mA, and 40% has ±2 mA. These settings were selected after pilot testing indicated that 80% generally led to severe nausea; 60%, moderate nausea; and 40%, mild or no nausea.

Sham Treatment

The vapor was scented with peppermint, a common home remedy and aromatherapy used to treat nausea (29). This was achieved using peppermint essence, which does not contain menthol—the only proposed active component of real peppermint oil (30,31). The essence still exhibits a strong peppermint odor, however, making it an ideal and salient placebo. The vaporizer was a 5.8-L aroma air humidifier and diffuser with 0.5 ml of peppermint essence added per 7 L of water, dispensed at a rate of 8 ml/min. The device was 34 cm (tall) × 25 cm (wide) × 15 cm (deep) and was seated directly in front of participants.

Procedure

The study was conducted at the same time of day on three nonconsecutive days within a fortnight for each participant. Participants were given a cover story that the study aimed to determine the effects of a motion simulator on spatial and reasoning ability, with nausea only mentioned briefly as a possible adverse effect. Also designed to reduce the likelihood of demand characteristics, participants were informed that ratings would be taken to ensure a detailed record of their experience of adverse effects from GVS, which would be important for their own safety to determine their tolerance. This scale, used previously by our group (23), included six nausea-related symptoms (urge to vomit, stomach awareness, nausea, headache, fatigue, and dizziness) and two bogus adverse effects added to divert attention from nausea, which they were asked to rate on a visual analog scale from 0 (not at all) to 10 (severe), resulting in a total maximum score of 60.

On the first day, all participants provided consent, filled out a demographics questionnaire, and then completed baseline symptom ratings. They were then attached to the device and experienced nauseating (80%) stimulation for 25 minutes, during which they completed a range of spatial tasks both to support the cover story and to enhance the coriolis effect. A full description of the GVS stimulus and spatial tasks can be found in Quinn et al. (23). After the first day, participants were stratified into groups based

TABLE 1. Experimental Design: Intervention and Stimulation Type for the Four Groups Across the 3 Days

	Intervention		
Group	Day 1 (80%)	Day 2 (40%)	Day 3 (60 %)
Controls (n = 14)	—	—	Peppermint vapor (no instructions)
Instruction (n = 14)	—	—	Peppermint vapor (instructions)
Conditioning (n = 14)	—	Peppermint vapor (no instructions)	Peppermint vapor (no instructions)
Combined (n = 14)	—	Peppermint vapor (instructions)	Peppermint vapor (instructions)

% refers to the percentage amplitude of the wave used in galvanic vestibular stimulation, where 100% is a ±5-mA current.

on their symptom scores. This was achieved by classifying participants as either responders (>6-point change between baseline and poststimulation ratings) or nonresponders (<6-point change), and randomly allocating participants within each stratum to the four groups. This classification was used for stratification purposes only to ensure that an even number of participants who were sensitive or insensitive to GVS were allocated to both groups, and all participants were included in the final analyses. On the next 2 days, the procedure was replicated, except for the difference in stimulation level, presence of vapor, and the instructions provided, as depicted in Table 1. On the second day, stimulation at the nonnauseating level of 40% was delivered, and for the conditioning groups, this reduction (relative to Day 1) was paired with the first presentation of the vapor. The combined instruction and conditioning group also received the instructions that the vapor reduced nausea. The control and instruction-only groups experienced this 40% stimulation in the absence of the vapor. On Day 3, 60% stimulation was delivered and all groups received the vapor, with the instruction group now receiving the instructions that the vapor reduced nausea.

The instructional manipulation consisted of both a written and verbal component. Participants were informed that the researchers had now received approval to use an antiemetic vapor commonly used in vestibular research to reduce nausea by relaxing the stomach muscles. They were asked about any allergies or adverse drug reactions they had ever experienced, and then read an information sheet about the vapor, which they had to sign to give consent. The control group and conditioning group received no instructions about the vaporizer, and it was switched on surreptitiously while the GVS electrodes were being attached. After poststimulation ratings were made on the test day, participants underwent a manipulation check asking them what they thought the aims of the experiment were, and if they were given instructions, whether they had believed them, and were then fully debriefed.

Analysis

One participant was excluded ad hoc as she had an extreme response to the GVS, and averaged across the 3 days, her symptoms rating difference was more than 3 SD above the mean and 1 SD above the next highest scoring participant. For all analyses, the dependent variable was the difference between a participant's poststimulation and baseline nausea ratings, termed the nauseous response. However, to ensure that no baseline differences existed on any day, a between-subject analysis of variance was conducted on the baseline ratings, before calculating the response scores. Sex was added as an independent variable for all analyses, as three previous experiments (20,21,32) discovered that men and women might respond significantly different to instructions and conditioning.

Training data were analyzed to ensure that on Day 1, there were no differences between the groups in their response to the high-intensity stimulation using a one-way between-subject analysis of variance across the four groups. A post hoc analysis was also undertaken on Day 2 nausea ratings to determine if the sham treatment had any unconditioned effect, as it has been suggested previously that the controlled breathing that may naturally occur in response to the presence of a scented vapor may itself be nausea reducing (33). Using contrast analysis, we compared the Day 2 nauseous response for the conditioning group, who received the vapor without nausea reducing instructions, with the control and instruction groups who did not receive the vapor that day.

The primary analysis was on the test day (Day 3) nauseous responses, which were analyzed using a 2 × 2 × 2 (instruction by conditioning by sex) between-subject analysis of covariance with Day 1 nauseous response scores included as a covariate to attempt to control for overall susceptibility to motion sickness. All analyses were conducted using SPSS (V20), and results were considered statistically significant when $p < .05$.

RESULTS

Training Days

The nausea ratings for the four groups across the 3 days are presented in Table 2. There was no significant difference between the four groups in their baseline nausea ratings on Day 1 ($F(3,51) = 1.18$, $p = .33$, $\eta_p^2 = 0.070$) or in nauseous response scores (poststimulation-prestimulation; $F(3,51) = 0.10$, $p = .96$, $\eta_p^2 = 0.006$), indicating that stratification had been successful.

An analysis of baseline nausea ratings on Day 2 found that controlling for Day 1 nauseous response, there was again no significant difference between the four groups ($F(3,51) = 0.74$, $p = .53$, $\eta_p^2 = 0.047$). There was no difference between groups in nauseous response scores either ($F(3,51) = 1.63$, $p = .20$, $\eta_p^2 = 0.096$), and a contrast comparing the conditioning group (who received the vapor without instructions) with the instruction and control groups (who did not receive the vapor that day) found no statistically significant evidence that the presence of the vaporizer itself (in the absence of instructions and conditioning) had affected nauseous response ($F(1,51) = 2.04$, $p = .16$, $\eta_p^2 = 0.042$).

Test Day

An analysis of baseline nausea ratings on test found that there were no differences between groups $F(3,51) = 0.38$, $p = .77$, $\eta_p^2 = 0.024$, and so nauseous response scores were again computed and are depicted in Figure 1. Controlling for Day 1 nauseous response, those who received the instruction intervention had significantly smaller nauseous response scores than those who did not ($F(1,46) = 6.71$, $p = .013$, $\eta_p^2 = 0.127$), and those who received the conditioning intervention also had significantly smaller nauseous response scores than those who did not ($F(1,46) = 5.20$,

TABLE 2. The Mean (SD) Nausea Symptom Ratings of the Four Groups Across the 3 Days of the Experiment

	Day 1		Day 2		Day 3	
Group	Baseline	Post	Baseline	Post	Baseline	Post
Full cohort (n = 55)	4.98 (4.85)	21.15 (11.51)	4.93 (5.45)	11.00 (8.51)	4.16 (5.02)	11.49 (8.89)
Controls (n = 14)	4.29 (4.25)	22.64 (11.08)	4.43 (3.39)	14.43 (9.95)	3.50 (4.57)	16.79 (11.60)
Instruction (n = 13)	4.08 (4.79)	19.16 (11.58)	3.31 (3.68)	8.77 (8.45)	3.92 (5.51)	9.69 (8.60)
Conditioning (n = 14)	4.43 (3.13)	20.21 (12.04)	5.17 (7.38)	9.86 (7.42)	4.14 (4.29)	10.07 (7.04)
Combined (n = 14)	7.07 (6.51)	22.43 (12.25)	6.23 (6.34)	10.77 (7.79)	5.07 (5.98)	9.29 (5.94)

SD = standard deviation.

$p = .027$, $\eta_p^2 = 0.1020$. The interaction between instructions and conditioning did not reach statistical significance ($F(1,46) = 2.33$ $p = .13$, $\eta_p^2 = 0.048$). There was no overall difference between men and women in terms of their nauseous response scores on test ($F(1,46) = 0.67$, $p = .42$, $\eta_p^2 = 0.014$), but there was a significant instruction by sex interaction where it seemed that the effect of instructions on nauseous response was larger for men than for women ($F(1,46) = 5.01$, $p = .030$, $\eta_p^2 = 0.098$). All other interactions were not significant.

Sex Analysis

To further explore the instruction by sex interaction, a post hoc analysis was undertaken, which examined the effect of instruction and conditioning separately for men and women. As illustrated in Figure 2A, men who received the instruction intervention had significantly smaller nauseous response scores than those who did not receive the intervention ($F(1,19) = 13.16$, $p = .002$, $\eta_p^2 = 0.409$), whereas there was no significant effect of the conditioning intervention ($F(1,19) = 1.11$, $p = .31$, $\eta_p^2 = 0.055$). A post hoc contrast comparing the nauseous response scores in men for the control and conditioning groups individually approached but did not reach statistical significance ($F(1,19) = 3.56$, $p = .075$, $\eta_p^2 = 0.158$). In contrast, as depicted in Figure 2B, for women, the effect of the instruction intervention was not significant ($F(1,26) = 0.15$, $p = .70$, $\eta_p^2 = 0.006$), but women who received the conditioning intervention had significantly smaller nauseous response scores than those who did not receive conditioning ($F(1,26) = 4.25$, $p = .049$, $\eta_p^2 = 0.141$).

Manipulation Check

Of the 55 participants analyzed, only 2 participants correctly identified nausea as the dependent variable, one who was in the control group and one in the instruction only group. One participant in the conditioning group wrote that the experiment was designed to trial the vapor. There were also 14 participants who did mention nausea, but who thought that it might be an independent variable along with the experience of motion rather than realizing that it was a dependent variable. The number who reported this did not differ significantly between the groups ($\chi^2 = 3.07$, $p = .80$). Of the 28 participants who were given the instructional manipulation, 3 participants reported not believing the instructions, 2 of whom were in the combined group

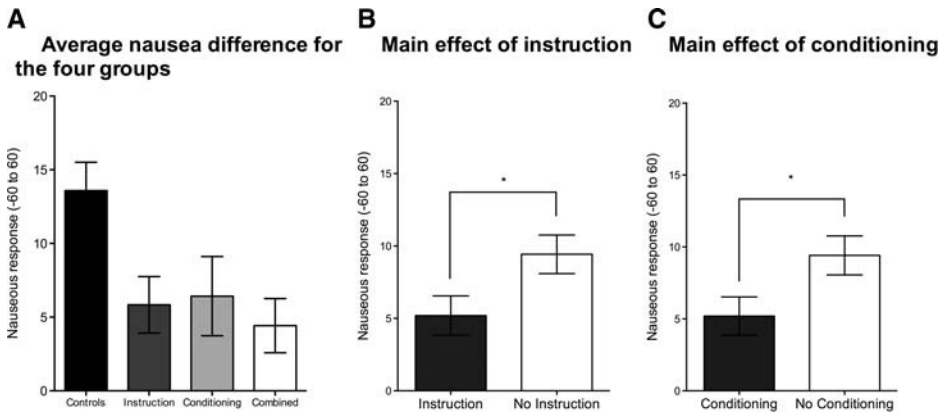

FIGURE 1. Covariate adjusted mean (SEM) nauseous response scores (poststimulation–baseline stimulation ratings) on test (n = 55) for the four groups (A), averaged across levels of instruction and no instruction (B), and conditioning and no conditioning (C). SEM = standard error of the mean. * $p < .05$.

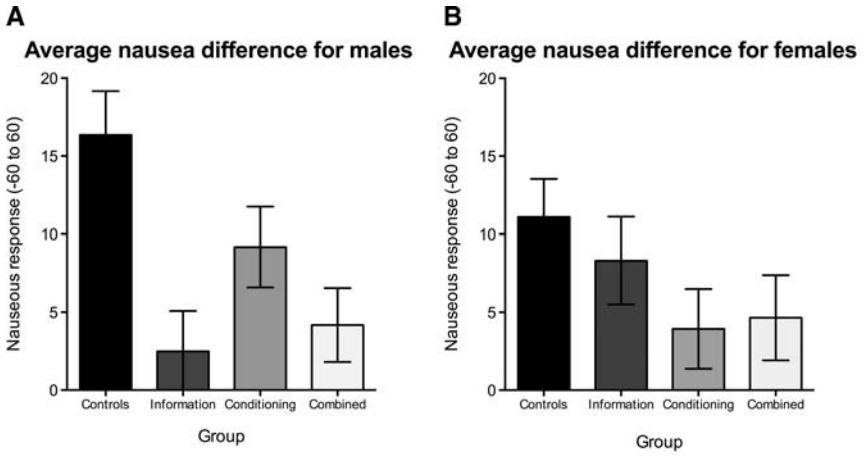

FIGURE 2. Covariate adjusted mean (SEM) nauseous responses on test for (A) male ($n = 24$) and (B) female participants ($n = 32$) across the four groups. SEM = standard error of the mean.

and 1 in the instruction group. Removing participants who were aware of the true purpose of the experiment or did not believe the instructions did not change the outcome of any main or interaction effects.

DISCUSSION

The current study provides new evidence that instruction, conditioning, and their combination can induce placebo effects for nausea. In terms of instruction-alone effects, previous research has found that negative instructions can induce nausea (Experiment 2 (32)), but this experiment is the first laboratory evidence that positive suggestions in isolation can reduce nausea, with one experiment finding no symptom improvement (18), and another finding that positive instructions actually led to more severe nausea than negative instructions (19).

As we have argued previously, it may only be possible to reduce nausea with instructional manipulations via the placebo effect in individuals with high expectancies (7). In the current study, the experience with nauseating stimulation on the first day likely has the effect of both creating high expectancies for nausea and more desire for relief than in previous designs, both factors that have been found to mediate the placebo response (12,34). The current study would likely better mimic a clinical scenario in which a patient often seeks help precisely because he/she is currently experiencing an aversive symptom. It may also be that the 3-day design we used encourages a rapport or trust between participant and experimenter that is absent in shorter experiments, which has also been found to increase placebo responding clinically (35). This rapport is arguably a closer approximation of the relationship present between a patient and clinician than in standard laboratory experiments and may be a better way to study placebo effects in the laboratory.

We also found that conditioning alone, that is, pairing the sham treatment with a surreptitious reduction in stimulation, also led to less nausea on test overall. Three previous laboratory demonstrations showed that neutral stimuli could acquire nauseating properties through conditioning (23,32 [Experiment 1],36), but this is the first that has shown that a *reduction* in nausea can be conditioned to a stimulus without instructions and that only a single conditioning trial is needed to produce this effect. Importantly, the effect of conditioning alone is not assumed to occur without expectancy. In fact, it seemed from both informal and formal feedback that many participants in the conditioning group had reasoned that the vapor might have been introduced to reduce nausea. Indeed, it is difficult to obtain evidence of human conditioning without propositional reasoning, and learning may be dependent on these reasoning processes (37). Instead, the placebo-induced nausea relief in the conditioning alone group indicates that an explicit instruction is not necessary to establish a placebo effect via conditioning. The direct experience of an effective treatment, simulated here via the surreptitious reduction in nausea on Day 2, is sufficient to produce placebo relief from nausea at test.

A comparison of the η_p^2 between the instruction and conditioning effects suggested a similar effect size for the two methods of reducing nausea via the placebo effect. This may suggest a discrepancy between the way that instruction and conditioning alter expectancies for nausea compared with other conditions, as it has been found previously that in placebo analgesia, conditioning manipulations typically produce stronger placebo effects than instruction does (38).

It was interesting to note that the effects of instruction and conditioning seemed to be additive in their ability to reduce nausea via the placebo effect, as indicated by the lack

of a statistically significant instruction by conditioning interaction. This suggests that combining multiple sources of placebo responding produces the largest placebo reduction in nausea. However, some caution is required here, because despite the statistically nonsignificant interaction, the pattern of means seemed to suggest subadditivity. There are two things to consider about this result. On the one hand, the lack of significant interaction could have been a Type II error due to a lack of power to detect a significant interaction effect in the current study. On the other hand, the fact that both instruction alone and conditioning alone almost entirely eradicated nausea may have meant that there was a floor effect in which an enhanced placebo effect in the combined group was artificially suppressed, as this group would have had to have reported no, or even negative levels of, nausea to show perfect additivity. To address this, one could test the effects of instruction, conditioning, and their combination with higher-intensity stimulation, which should reduce the possibility of any floor effects.

It was also interesting that sex seemed to moderate placebo responding for nausea. Here, it seemed that male participants responded to the instructional manipulation and female participants did not, whereas the reverse was true for conditioning. Although this was a post hoc analysis, interestingly this pattern has replicated several findings in the literature for similar paradigms, discussed later. Given that our study involved testing a reduction in nausea, our findings in isolation could be interpreted in line with evidence that men tend to underreport symptoms in the presence of a female experimenter (39,40). However, Klosterhalfen et al. (32, Experiment 2) found that men, but not women, showed enhanced nausea after a suggestion that consuming an oral strip would worsen rotation-induced nausea. The presence of both placebo and nocebo responding after instructions in men only, combined with the overall absence of sex differences in reported symptoms in our experiment, seems to suggest that this effect is not due to a systematic underreporting of symptoms by men. The sex difference in responsiveness to conditioning is also consistent with previous literature, where it has been found that women were more sensitive to a latent inhibition manipulation (20), conditioned nausea to a flavored oral strip (32, Experiment 1), and had lower levels of cortisol and an immunological correlate of nausea after overshadowing (21).

However, it is important to note that rather than these differences being purely a product of a participant's sex, it may be an experimenter-participant interaction. In all of the abovementioned studies and the current one, the experimenters were female. Thus, it is quite possible that the critical factor is whether there is a sex match or mismatch between the participant and experimenter, rather than an effect of the participant's sex per se. It would therefore be interesting to see whether these effects would hold with a male experimenter, or reverse as was found by Kallai et al. (39) in a pain tolerance study. Regardless, future studies should take sex into account in analyses, as it seems that the way individuals respond to stimuli is influenced by their sex, and this may aid our understanding of the nature of this difference.

The current results have important clinical applications. Understanding how to harness and optimize placebo effects ethically and with limited compromise to patient autonomy has been a key goal of placebo research over the last decade (41). The finding that the instruction intervention led to a reduction in nausea indicates that information communicated about antiemetic medications may moderate their efficacy. As such, clinicians could attempt to reduce nausea in the clinic by emphasizing the efficacy of these medications as appropriate to the medication. In addition to enhancing our understanding of how placebo effects in nausea may occur naturally, the lower nausea ratings after the conditioning manipulation also offer a method of intervention. If as little as one pairing of the sham treatment with a reduction in nausea can lower the subsequent experience of nausea, a method of combining a placebo with a potent antiemetic or a day of lower treatment toxicity may offer another inexpensive and low-risk method of reducing nausea and reliance on antiemetics during subsequent treatments. Finally, these results may suggest a reason for the continued popularity of several complementary treatments in treating nausea (42) despite limited scientific evidence for their efficacy, as both the positive information available combined with the conditioned reduction in nausea experienced through coincidental natural symptom improvement may produce placebo responding.

There are also some potential limitations that should be noted here. A problem inherent with using self-report data in placebo research is that participants provided with the instructions may be inclined to lower their symptom ratings consistent with what they believe the researchers are trying to achieve. Although efforts were made to reduce any such demand characteristics by diverting attention away from nausea as an experimental variable and explaining the symptom ratings as a safety requirement, it is possible that these demands were still perceived. This could be resolved in future designs by including a behavioral assessment such as stimulation tolerance or physiological assessments such as electrogastrogram, although these types of outcomes are not without their own limitations (7,43). It is also important to mention that our post hoc assessment of the vapor's unconditioned efficacy may not have been sufficiently sensitive due to the low ratings of nausea on Day 2. Although the dosage provided to participants would be "subtherapeutic" even if we had used peppermint oil rather than essence (44), without a control group receiving no vapor on test, we cannot rule out that the vapor itself had some effect on nausea. However, this effect could not account for the group differences observed here. Lastly, for the post hoc exploratory analyses by sex, the lower sample size for men may

have reduced statistical power for subgroup analysis, and the effect of conditioning may have reached significance for men if men had a comparable sample size to the women.

Overall, these findings make three important additions to the existing literature concerning placebo effects in nausea. First, if delivered in the right circumstances, positive instructions in isolation can produce placebo-induced relief of nausea. Second, classical conditioning procedures can be used to condition a reduction in nausea to a previously neutral stimulus (i.e., the placebo), and only a single conditioning trial is required to induce a placebo effect. Third, a potentially interesting sex effect suggested that the way in which sources of expectation lead to placebo responding may be different for men and women. Together, these findings suggest that taking advantage of placebo effects (45) in the clinic could offer an important method of intervening to reduce nausea.

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