Original Research

Different Disclosed Probabilities to Receive an Antiemetic Equally Decrease Subjective Symptoms in an Experimental Placebo Study: To Be or Not to Be Sure

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ABSTRACT

Purpose: The purpose of this study was to examine whether the disclosed probability of receiving an antiemetic affects nausea.

Methods: Forty-eight healthy participants (mean [SD] age, 26.8 [5.4] years; 50% female) were exposed to 5 × 2 minutes of nauseogenic body rotations on 2 days. On day 2, participants were randomized to 3 experimental groups that were given different instructions concerning the probability of receiving an antiemetic remedy (100%, 50%, or 0% probability), whereas all received an inert substance. Subjective symptoms, behavioral (rotation tolerance) measures, and physiologic (electrogastrogram) measures of nausea were assessed and mediator and moderator analyses performed for effects of expectations and psychological characteristics on outcomes.

Findings: Disclosed probabilities of both 100% and 50% significantly reduced subjective symptoms of nausea in an equal manner compared with the 0% probability group from day 1 to day 2. This effect was found for neither rotation tolerance nor myoelectric gastric activity. Expectations and psychological characteristics did not affect the results found. Post hoc analyses revealed that women only seem to be susceptible to this placebo effect.

Implications: Nausea is susceptible to placebo effects independent of the disclosed probability of receiving a drug and of explicit expectations. In line with placebo research, this effect is probably attributable to central mechanisms, and it is speculated that it could be related to the reward circuitry and social interactions. (*Clin Ther*. 2017;39:487–501)

Key words: expectancy, motion sickness, nausea, placebo effect, uncertainty.

INTRODUCTION

Research about placebo effects aims to further our understanding of the underlying mechanisms, to minimize their influences in clinical trials, but to harness and maximize them in clinical practice.[1] In general, placebo effects arise from expectations and learning through conditioning and social observation, but it is still difficult to explain the large interindividual variance of placebo responses between persons[2] and conditions.[3,4] Furthermore, one of the important questions is whether and how results from experimental placebo research can be transferred to clinical trials and

Accepted for publication November 22, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.11.022
0149-2918/$ - see front matter

practice.[5] This question is linked to effects of the perceived probability of receiving a potent drug or a placebo in clinical trials.[6] Two fundamental differences have been pointed out between double-blind randomized clinical trials (RCTs) with patients and experimental studies with healthy volunteers that bear difficulties for this translation. First, in classic RCTs, participants are randomized with a 50% probability to a drug or a placebo group not knowing in which group they are, whereas in most placebo mechanism studies participants are told convincingly (or conditioned) that they receive "a potent drug" with a 100% probability of inducing a placebo effect. This conceptual difference may have led to a significant difference in effect sizes for placebo analgesia among 23 RCTs (mean effect size = 0.15) and 14 experimental studies (mean effect size = 0.95) in a meta-analysis.[7] Second, the desire and motivation for symptom relief could be different between patients with a disease or disorder, maybe even a chronic condition, and healthy volunteers who take part in an experimental study in which a symptom is induced for some minutes or hours only and who are paid for their participation or receive credit points.[8,9]

Reviews and meta-analyses of RCTs and experimental studies have repeatedly found that placebo effects vary based on the probability of being randomized to an active drug or a placebo group. As far as we know, Diener et al[10] were the first who pointed to the problem that an unbalanced randomization of more patients to drug groups than to the placebo group may inflate placebo effects in migraine RCTs. They compared a study with a randomization of 16:1 for drug to placebo with other RCTs with ratios of 1:1 to 8:1, which also tested the same drugs for migraine treatment. They found that the drug responses were nearly the same but placebo responses increased up to fourfold, probably because of higher expectations of patients to receive a drug. This association between the disclosed probability of receiving a drug or placebo has also been found for other conditions, such as RCTs for depression,[11–13] schizophrenia,[14,15] and Parkinson disease.[16] Furthermore, increased placebo responses may also account for higher drug responses in comparator studies, in which all patients know they receive a drug either way, compared with placebo-controlled trials, in which patients know that they could receive a placebo only. This association between the probability of receiving a drug and placebo effects has been found for clinical trials of depression[17,18] and anxiety disorders.[19]

Only a few experimental studies, mostly using pain paradigms, have examined differences among disclosed probabilities. For example, healthy participants received an inert infusion with instructions of a 100%, 50%, or 0% probability of receiving an analgesic drug in a visceral pain paradigm.[20,21] Participants of the first study reported a significant pain reduction in the 100% compared with the 0% probability condition only,[20] whereas participants in the second study reported a significant pain decrease in the 100% versus 0% and in the 100% versus 50% probability conditions.[21] In a heat pain paradigm, participants received a nasal spray again with the instructions of a 100%, 50%, or 0% probability of receiving an analgesic drug and experienced a significantly higher pain decrease in the 100% versus 0% probability groups and a trend between the 50% versus 0% groups.[22]

Nausea is a very common symptom, particularly in oncology and surgery. It is a side effect of many drugs and can occur in otherwise healthy persons as motion sickness in everyday situations, such as traveling by car, bus, or ship. Meta-analyses by Hrobjartsson and Gotzsche[23–25] revealed no significant group-based placebo effect compared with no treatment in RCTs for the treatment of nausea. However, susceptibility of nausea symptoms to placebo (for symptom decrease) and nocebo (for symptom increase) manipulations were noted as early as the 1950s, when Wolf et al[26] found nausea induction and inhibition with placebo applications in their patient with fistulas.[27] Since then, studies about the occurrence of nausea in chemotherapy treatments found that, on the one hand, negative expectations and personal experiences of patients increase anticipatory nausea before chemotherapy[28] and after chemotherapy.[29] On the other hand, experimental studies manipulating positive expectations concerning a treatment with an acupressure band[30] and conditioning with an overshadowing manipulation[31] elicited a decrease in postchemotherapy nausea. Furthermore, experimental studies on motion sickness induced by optokinetic drum or rotation chair repeatedly found that placebo effects elicited through verbal suggestions[32–34] and through conditioning procedures[35–38] can affect nausea.

Overall, there seems to be a difference in the magnitude of placebo effects on nausea in RCTs compared with experimental studies that could be attributable to the disclosed probability of receiving drug or placebo and to the symptoms' relevance to the participants. Therefore, we investigated whether the disclosed probability of receiving a drug differentially affects