



## Systematic or Meta-analysis Studies

# The relationship between anticipated response and subsequent experience of cancer treatment-related side effects: A meta-analysis comparing effects before and after treatment exposure



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## ABSTRACT

**Objective:** To review the evidence for a systematic relationship between cancer patients' pre-treatment expectations (anticipated side effects) and subsequent experience of treatment-related side effects, and to compare this relationship in patients with no prior treatment experience (cognitive expectations) and with some prior treatment experience (conditioned response).

**Methods:** A total of 12,952 citations were identified through a comprehensive search of the literature published on or before November 2016 and screened against inclusion criteria. Studies were eligible if they included participants undergoing curative treatment for cancer, measured a treatment side effect, examined the relationship between anticipation and experience of side effects, and reported quantitative data.

**Results:** Thirty-one studies were included in the review and meta-analysis (total N = 5069). The side effects examined were nausea (anticipatory and post-treatment), vomiting, fatigue, pain, problems with concentration, and skin reactions. Meta-analyses indicated positive associations between anticipation and subsequent experience for all included side effects in patients with no prior treatment exposure ( $r = 0.153$ – $0.431$ ). Stronger associations were found for all included side effects in patients with previous treatment experience ( $r = 0.211$ – $0.476$ ), except for fatigue ( $r = 0.266$ ) and pain ( $r = 0.235$ ). No significant differences were found when overall effect sizes for patients with and without prior treatment exposure were compared for each side effect, except for anticipatory nausea ( $p = 0.012$ ).

**Conclusion:** These results may have implications for future interventions that target patients' expectations of cancer treatment-related side effects. Future research could explore patient reports of messages received about likely treatment effects both before and during treatment.

## Introduction

Cancer patients report experiencing a range of treatment-related side effects including pain, fatigue, nausea and vomiting, and even cognitive decline, although the nature and extent of these can vary between individuals undergoing the same treatment [1]. Some side effects, such as nausea, may be more common depending on the type of chemotherapy that the patient receives. Other individual differences contribute to the experience of these side effects, above and beyond variations in the specific treatment provided. These effects have been variously described as expectancy, conditioning and nocebo effects with considerable overlap in theorising around each [2,3]. Response

expectancies could be described as largely cognitive and reflect anticipation of subsequent experience prior to any treatment. In general, the side effects that a patient experiences are attributed to exposure to information about possible negative experiences of treatment. By contrast, it is possible to interpret some of the negative side effects of treatment as arising from conditioning. According to this interpretation, exposure to treatment (i.e., the unconditioned stimulus), which results in a negative experience (i.e., the unconditioned response), may become paired with contextual cues, such as attendance at the infusion suite (i.e., the conditioned stimulus), and result in a similar negative response (i.e., the conditioned response; nausea). This response may be experienced either before or after treatment but requires at least one

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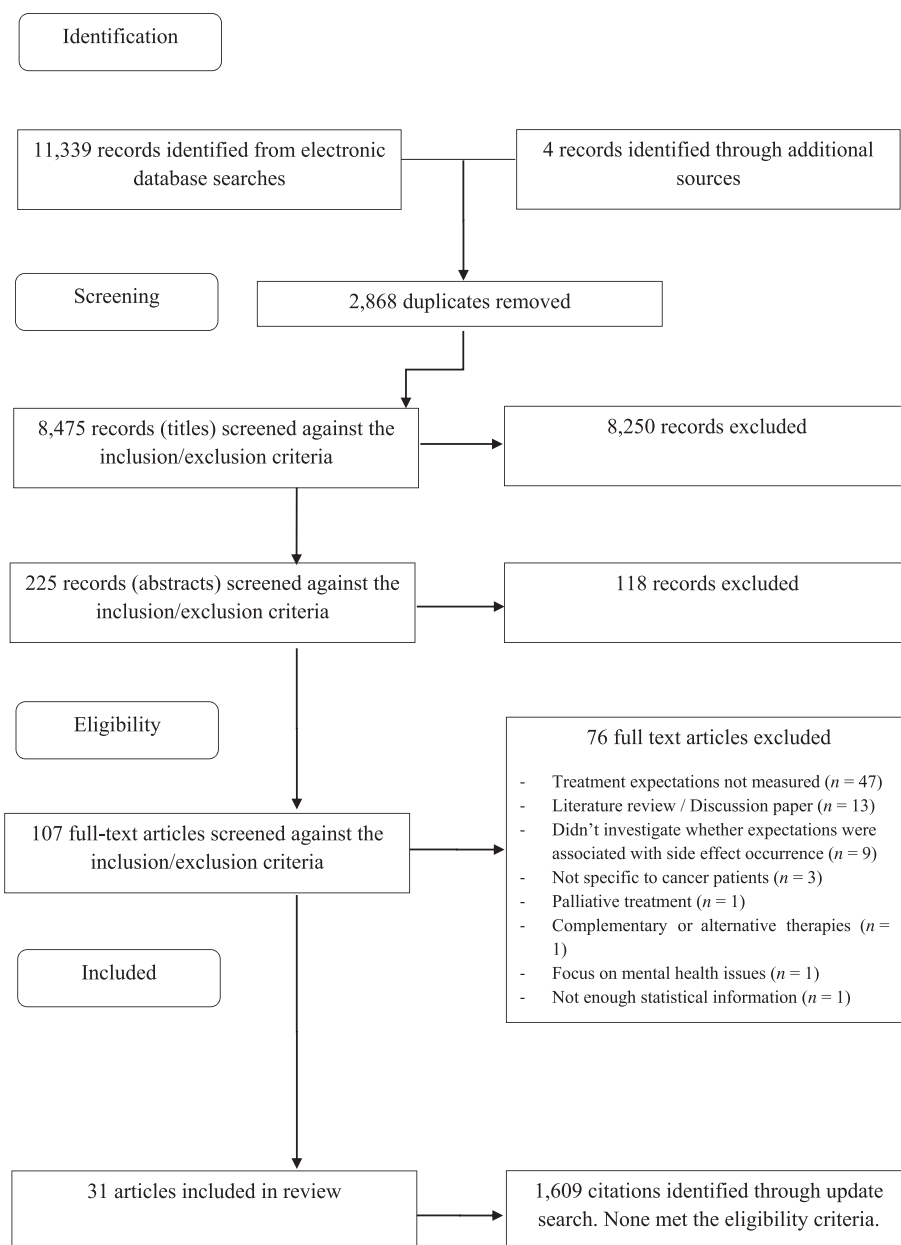


Fig. 1. Study flow diagram for systematic review.

trial that pairs treatment with side-effects.

By contrast, nocebo effects (the negative equivalent to the placebo effect) have been described as being mediated by both expectations (i.e., response expectancies) and previous experience (i.e., conditioning). Stewart-Williams and Podd [4] suggest that although conditioning and direct information provision can each shape conscious expectations, classical conditioning without changed expectations (i.e., without conscious learning), can also produce negative outcomes.

One possible strategy for discriminating between a non-conditioned (“expected”) and a conditioned side effect is to note the incidence of the side effect before and after exposure to any treatment. “Side effects” generated before the patient has received any treatment (e.g., anticipatory nausea before attendance for first chemotherapy session) are likely due to expectations (also called “response expectancies”). Comparable side effects experienced after one or more treatment cycles may reflect learning via conditioning, or response expectancies, or both. The finding that “repeated exposure to chemotherapy increases risk for the development of Anticipatory Nausea and Vomiting (ANV)

conforms to a classical conditioning model, wherein repeated pairings of unconditioned (i.e., chemotherapy) and conditioned stimuli (e.g., the clinic, the nurse) produce nausea and vomiting even before administration of emetogenic agents” (p. 173) [5]. This observation confirms the importance of identifying the stage of treatment at which side effects are first reported, and whether these change over the treatment course.

A recent meta-analysis of cancer treatment side effects was undertaken by Sohl, Schnur and Montgomery [6]. The study aimed to determine the size of the relationship between “expectations for non-volitional responses” (p. 775) (response expectancies) associated with cancer treatment and patients’ experiences of these side effects. On the basis of 14 included studies, results confirmed a medium-sized association ( $r = 0.36$ ) between response expectancies and experienced side effects. Importantly, treatment exposure resulted in stronger associations supporting the potential importance of the contribution of classical conditioning.

The current review aims to replicate and update the Sohl, Schnur

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