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 = 5,069). The side effects examined were nausea (anticipatory and post-treatment), vomiting, fatigue, pain, problems with concentration, and skin reactions. Meta-analyses indicated significant and 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 conditioned side effects in patients with previous treatment experience ($r = 0.211 – 0.476$). 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.

Keywords: cancer, cancer treatment, conditioning, expectancies, expectancy, side effects

1. 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 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 and Montgomery [6] paper in order to re-evaluate the evidence for a systematic relationship between cancer patients' expectations, duration of exposure to treatment, and experience of cancer-treatment-related side effects. The current review builds upon their analysis by comparing the

relationship between patients with no prior treatment experience (where the effect must raise from cognitive expectations) and those with some prior treatment experience (where the response may include a conditioned response) for each side effect. The treatment side effects included in the review replicate and extend those reported by Sohl, Schnur and Montgomery [6], and include nausea (anticipatory and post-treatment), post-treatment vomiting, fatigue, pain, skin reactions, and problems with concentration. It was hypothesised that associations between side effects and experience would be greater in patients with some treatment experience (conditioned side effects with and without a possible contribution from expectations) than in patients without prior treatment experience (response expectancy effects only; no conditioning).

2. Methods

2.1. Search strategy

The first author (CF) conducted an extensive systematic search of the literature published up to and including November 2016 using MEDLINE, PubMed, SCOPUS, PsycINFO, Informit, Web of Science, and CINAHL databases. The following search string was used: (expectation OR expectations OR expectancy OR expectancies OR expect* OR anticipatory OR anticipations OR anticipat* OR somatic OR somatisation OR somati* OR nocebo) AND ("side effects" OR "adverse effects" OR "treatment side effects" OR outcomes OR "adverse outcomes" OR nausea OR emesis OR vomit* OR fatigue OR cognitive OR cognition OR memory OR attention OR concentration OR hair loss OR alopecia OR neuropathy OR anxiety OR depression OR survival OR morbidity OR mortality OR breathlessness OR dyspnoea OR libido OR appetite OR constipation OR diarrhoea OR pain) AND (radiotherapy OR chemotherapy OR surgery OR treatment) AND (cancer OR neoplasm OR oncology). Searches were limited to studies conducted with human participants and

published in English. Reference lists of extracted articles were manually searched for additional, potentially eligible studies that were not retrieved from the database searches.

The initial search was conducted on the 26th of July 2015. A total of 11,343 citations were identified through the search (11,339 from electronic database searches and four through manual searching of reference lists). Duplicate articles were removed (n = 2,868) and the first and fourth authors (CF and EG) independently reviewed the remaining 8,475 titles for relevant articles. There was almost perfect (99%) agreement between reviewers (Kappa = 0.74, $p < 0.001$). Abstracts of potentially eligible articles (n = 225) were reviewed independently by the first and second authors (CF and CW). Reviewers agreed on 70% of decisions (Kappa = 0.33, $p < 0.001$) with final agreement negotiated, where required. The full-text of the remaining articles (n = 107) were obtained and screened against the inclusion criteria and a further 76 articles were excluded as they did not meet the eligibility criteria (see Figure 1 for the PRISMA flow diagram for reasons for exclusion). Any disagreements about inclusion were resolved through discussion among the research team.

The remaining 31 articles met the inclusion criteria and were included in the meta-analysis. This included one article that described two separate studies and another two articles describing the same study (these data were included only once). An updated search was conducted on the 23rd of November 2016 to identify articles published since the initial search was conducted. An additional 1,609 citations were identified; however none of the studies met the inclusion criteria. The meta-analysis included all of the studies analysed by Sohl, Schnur and Montgomery [6], except for two studies that did not include a measure of anticipated response to treatment [7, 8] and an additional 14 studies identified in the literature search.

2.2.Selection criteria

Studies were eligible for inclusion if they examined the relationship between patient anticipation of side effects and their subsequent occurrence, duration, frequency, or severity in patients undergoing cancer-related treatment. This included patients with no previous treatment experience (potential "cognitive expectations" effect) or with some previous treatment experience (potential "conditioned response"). The side effects included were nausea, vomiting, fatigue, pain, skin reactions, and problems with concentration.

Eligible studies were required to meet the following criteria:

1) included participants undergoing curative treatment for cancer;
2) employed a measure of anticipated response to treatment;
3) examined the relationship between anticipation and experience of cancer treatment-related side effects; and
4) reported quantitative data (either an effect size or enough statistical information to calculate an effect size).

Studies were excluded during the screening process if; anticipation of treatment-related side effects was not measured, the study was a review or meta-analysis of the literature, the associations between anticipated and experienced side effects were not reported, the sample was not cancer patients, the study focussed on mental health issues, or if treatment was palliative or **involved** complementary **and alternative therapies (i.e., not adjuvant therapies used for curative purposes)**.

2.3.Quality assessment

The first and third authors (CF and AH) assessed the methodological quality of studies included in the meta-analysis using the Qualsyst tool [9], which was developed for assessment of the quality of both qualitative and quantitative studies that employ any study

design. The Qualsyst tool for assessment of the quality of quantitative studies is comprised of 14 items that are scored as yes, partial, no or not applicable. Examples of the items are; is the question/objective sufficiently described, is the sample size appropriate, and have they controlled for confounding. A summary score was calculated for each paper and then a final score was calculated by dividing the summary score by the total possible score (determined by subtracting the Not Applicable responses). Mean quality score for each paper was calculated by averaging the scores given to each paper by the two assessors. These scores are documented in Supplementary Table 1 (range: 0.66 to 1.0). The scores assigned by the first assessor ranged from 0.59 to 1.0 (mean: 0.81, standard deviation: 0.09). The scores assigned by the second assessor ranged from 0.64 to 1.0 (mean: 0.85, standard deviation: 0.10). Both assessors assigned the same score to six studies (19%). Good inter-rater reliability was observed ($r = 0.60$). Discrepancies in the scores of the remaining studies ranged from 0.01 to 0.18 and were resolved through discussion. Articles were not excluded from the meta-analysis based on a threshold Qualsyst score.

2.4.Data extraction

The first author (CF) extracted key descriptive data and effect sizes for the relationship between anticipated response and subsequent experience of side effects. Descriptive data extracted related to the study design (e.g., cross-sectional, longitudinal/prospective, experimental), sample size, sample characteristics (e.g., gender, cancer type, treatment type), whether participants had previous experience of cancer treatment, instrument used to measure anticipation of treatment-related side effects, when anticipation of side effects was measured (e.g., before first treatment, before treatment other than the first, before multiple treatments), which side effects were experienced, and whether occurrence, duration, frequency, or severity (or combination) of side effects were assessed. Reported effect sizes or statistical information needed to compute effect sizes for the

relationship between anticipated response and subsequent experience of side effects were also extracted.

2.5.Data analysis

2.5.1. Effect size

The effect size correlation coefficient (ESr) was used as the outcome in the meta-analysis. Positive values indicated an association between anticipated response and subsequent experience of the side effect measured by indices including, duration, frequency, and severity. Effect sizes (Pearson's r) were directly available in many of the studies [10-21]. In cases where a correlation coefficient was not reported, mean side effects scores and standard deviations [22], t-tests [23], number of side effect events and non-events [24], chi-square statistics [25-27], odds ratios [28-31], change in *R* square [23], or Beta-coefficients [32-39] were used to estimate effect sizes utilizing formulas suggested in the literature [40, 41].

Several studies reported results for multiple indices of side effects (e.g., nausea duration, nausea severity, and nausea unpleasantness) or multiple time-points (e.g., cycles of chemotherapy). In these cases, an average effect size was calculated for each separate side effect so that each study contributed only one effect size for each side effect to the meta-analysis.

2.5.2. Meta-analysis

The meta-analysis was conducted using Comprehensive Meta-Analysis Software V3 [42]. Analyses were conducted separately for each side effect and for patients with and without prior treatment experience. Overall effect sizes were calculated when relevant data were available from at least three studies. Following recommendations by Borenstein and colleagues [40], a random-effects modelling approach was used to account for variation in

sampling in the included studies. *Q* tests were conducted to investigate differences in effect sizes in patients with no prior treatment experience versus some prior treatment experience.

2.5.3. Heterogeneity

The I^2 statistic was calculated for each analysis to assess the consistency of the results of included studies. The I^2 statistic describes the percentage of total variation between study results that is due to genuine underlying differences (heterogeneity) rather than chance [43]. It is a measure of inconsistency of results. According to Higgins and colleagues [43], levels of heterogeneity can be described as low ($I^2 = 25\%$), moderate ($I^2 = 50\%$), and high ($I^2 = 75\%$), with a lower level indicating less inconsistency in results.

2.5.4. Publication bias

Publication bias was assessed using Rosenthal's [44] Classic Fail-Safe N (N_{fs}), Orwin's [45] N_{fs}, and Egger's test [46]. Rosenthal's N_{fs} estimates the number of unpublished studies reporting null results that would be needed to increase the P-value for the meta-analysis to above 0.05. Orwin's N_{fs} takes a more conservative approach to estimate the number of studies needed to reduce the effect size to a specified level other than zero (defined in the present meta-analysis as $r \leq 0.05$). An effect size was considered to be robust if Rosenthal's N_{fs} was larger than $5k + 10$, where k is the number of studies included in the analysis. Rosenthal's N_{fs} of less than the recommended criterion ($5k + 10$) indicated potential publication bias, which was further investigated using Egger's test. Where Egger's test confirmed a publication bias, an adjusted effect size was estimated using Duval and Tweedie's [47] trim-and-fill method, which uses imputations of missing results to recalculate the effect size.

3. Results

3.1.Study Characteristics

The meta-analysis included the results of 31 studies with a total of 5,069 participants. Studies had an average sample size of 164 (ranging from 20 [16] to 911 [29]). Fifteen of the studies included participants with breast cancer [11, 13-17, 20, 22, 25, 26, 28, 30, 32, 35, 36]. Other cancers studied included ovarian [23] and mixed cancer types [10, 12, 18, 19, 21, 23, 24, 29, 31, 33, 34, 37-39]. One study did not specify the types of cancer that participants were diagnosed with [27]. The most commonly studied side effect was post-treatment nausea (77% [10-12, 14, 15, 17, 19-25, 27, 29-31, 33-39]), followed by post-treatment vomiting (39% [11, 17, 20, 23, 24, 27, 28, 31, 34, 36-38]), fatigue (29% [11, 13-15, 20, 24, 33, 37, 38]), pain (23% [11, 14-16, 24, 37, 38]), anticipatory nausea (16% [12, 13, 26, 30, 32]), skin reactions (13% [18, 24, 37, 38]), and problems with concentration (6% [37, 38]).

Study designs were predominantly prospective and longitudinal. Several studies were randomised controlled trials, comparing antiemetic regimens [39], or testing whether the assessment of patients' expectations of side effects were related to their experience of side effects [33], the effectiveness of a pre-surgery hypnosis session in reducing post-surgery pain [16], and the effectiveness of educational or informational interventions to reduce post-treatment nausea [19, 21]. Another study analysed data collected from participants in the control arm of a larger randomised controlled trial [17]. Studies used a variety of instruments to measure patients' anticipation of side effects, including the Side Effect Expectancy Questionnaire [10, 12, 18, 19, 21-26, 30, 32], the Symptom Experience and Expectation Interview Schedule [27], visual analogue scales [11, 13-16, 20, 29, 31, 37, 38, 48], and other Likert-type scales [17, 33-36, 39]. The actual experience of side effects was assessed using the Morrow Assessment of Nausea and Emesis [12, 30, 34, 36], the Brief Pain Inventory [15], the Rhodes Index of Nausea and Vomiting [27], the MASCC Antiemesis Tool [31], patient report diaries [17, 19-23, 28, 29, 39, 48], symptom checklists [32, 35], visual analogue scales [10, 11, 13, 14, 16, 18, 29, 33, 37, 38], and other Likert-type scales [13, 17, 19-21, 23-25, 48].

Most studies included participants undergoing chemotherapy (80% [10-13, 17-20, 22-33, 35-39]). The remaining studies included participants undergoing surgery [14-16] and radiotherapy [18,

[21]. Twenty-six of the studies measured *anticipation of side effects prior to the first treatment,* two studies measured *anticipation prior to each of multiple cycles of treatment* (one of which also measured anticipation prior to the first treatment), and the final three studies measured *anticipation prior to any treatment session but not the first*. Experience of the side effect was measured after the first treatment in 13 of the studies, after each of multiple treatment sessions in 13 of the studies, and any treatment other than the first in five studies.

3.2. Association between anticipation and experience of side effects

Analyses were conducted to investigate the overall effect of anticipation on each of the seven side effects: anticipatory nausea, post-treatment nausea, post-treatment vomiting, fatigue, pain, skin reactions, and problems with concentration (Table 1). Analyses were also conducted to investigate differences in effect sizes for each side effect in patients with and without previous treatment experience (Table 2). An insufficient number of studies meant that analyses could not be conducted for anticipatory nausea in patients with no prior treatment experience and for pain, problems with concentration, and skin reactions in patients with some previous treatment experience.

3.2.1. ***Overall effect*** *of anticipation on side effects*

Results indicated significant, medium, positive associations between anticipated effects of treatment and experience of anticipatory nausea (ESr = 0.442), fatigue (ESr = 0.325), pain (ESr = 0.364), and problems with concentration (ESr = 0.431). Significant, small, positive associations were found between anticipation and experience of post-treatment nausea (ESr = 0.230), vomiting (ESr = 0.181), and skin reactions (ESr = 0.290). Findings for anticipatory nausea, post-treatment nausea, vomiting, fatigue, pain, and problems with concentration appeared to be robust, with Rosenthal's N_{fs} exceeding the recommended criterion, $5k + 10$. This was not the case for the effect size for skin reactions,

where Rosenthal's N_{fs} ($N = 20$) was less than the recommended criterion ($N = 30$). This indicated a potential publication bias, however this was not confirmed by Egger's test ($p = 0.122$). Only two studies investigated the relationship between anticipation and problems with concentration therefore the potential for publication bias could not be assessed.

*3.2.2. Effect of anticipation on side effects in patients **with no prior treatment experience***

Significant associations were found between anticipation and experience of each of the side effects, with medium, positive associations for fatigue (ESr = 0.337), pain (ESr = 0.366), and problems with concentration (ESr = 0.431) in patients with no previous treatment experience. Small, positive associations were found for post-treatment nausea (ESr = 0.200), post-treatment vomiting (ESr = 0.170), and skin reactions (ESr = 0.278). There was evidence of potential publication bias in the finding for post-treatment vomiting, with the recommended criterion ($N = 45$) exceeding Rosenthal's N_{fs} ($N = 42$). Egger's test supported the presence of a publication bias ($p = 0.012$). Therefore, imputations of missing results were used to calculate an adjusted effect size (ESr = 0.153), which was considerably smaller than the unadjusted effect for post-treatment vomiting. The recommended criterion ($N = 25$) also exceeded Rosenthal's N_{fs} ($N = 12$) indicating potential publication bias in the finding for skin reactions, however this was not supported by Egger's test ($p = 0.220$) and an adjusted effect size was not calculated.

*3.2.3. Effect of anticipation on side effects in patients **with prior treatment experience***

Significant, medium, positive associations were found between anticipation and experience of anticipatory nausea (ESr = 0.476) and post-treatment nausea (ESr = 0.288) in patients who had some prior treatment experience. Significant, small, positive associations were also found for post-treatment vomiting (ESr = 0.211) and fatigue (ESr = 0.266). The effect size for pain was medium in size (ESr = 0.235), but was not significant. Overall effect

sizes could not be calculated for problems with concentration and skin reactions because there were not enough data to run the meta-analysis. Rosenthal's N_{fs} (N = 13) was less than the recommended criterion (N = 35) for post-treatment vomiting, indicating a potential publication bias. Egger's test was conducted, but did not provide evidence of a publication bias (p = 0.881). Rosenthal's N_{fs} also indicated potential publication bias in the finding for fatigue, however this was not supported by Egger's test (p = 0.933).

3.2.4. Differences in effect in patients with and without prior treatment experience

Contrary to the main hypothesis, no significant differences in effect sizes were found in patients with and without prior treatment experience for post-treatment nausea, post-treatment vomiting, fatigue, pain, problems with concentration, and skin reactions (Table 4). The difference between effect sizes for the relationship between anticipation of side effects and the experience of anticipatory nausea in patients with and without prior treatment experience was significant (p = 0.012), with a greater effect size for patients with prior treatment experience (ESr = 0.476). However, only one study examined anticipation of side effects and the experience of anticipatory nausea in patients with no previous treatment experience with results indicating only a non-significant, small, positive association (r = 0.036 [12]), so this result should be interpreted with caution.

4. Discussion

Results of the meta-analysis confirmed those of Sohl, Schnur and Montgomery [6]; a medium effect size which varied with previous treatment experience. Our results extend these previous results by analysing additional treatment side effects and side effects based on prior or no prior experience of treatment separately. When studies that measured side effects in patients with and without previous treatment exposure were analysed together (See Table 1), the largest effect sizes were reported for anticipatory nausea and problems with

concentration, although the conclusiveness of the latter is mitigated by the fact that only two studies were included. Nonetheless, future research in the area of anticipated cognitive impairment following cancer treatment is required, particularly given the rising report of this form of potential impact from treatment in both the scientific (e.g., Janelsins et al. [49]) and non-scientific media (e.g., the New York Times [50]) including non-government cancer support organizations around the world (e.g., MacMillan in the UK [51], the Breast Cancer Network in Australia [52], and the Fred Hutchinson Center in the US [53]).

It is also interesting to note that although all side effects were positively associated with anticipation, post-treatment vomiting had the smallest effect size. Subsequent analysis separated studies where side effects were measured in patients who had not been previously exposed to treatment (see Table 2), from those where patients had previous treatment exposure (see Table 3). In the first case, the mechanism is hypothesised to involve response expectancies based upon information obtained directly or indirectly from expert or lay sources, whereas for the second conditioning could be at least part of the explanation. In both of these, post-treatment nausea remained the smallest effect, and was actually reduced to non-significance in patients with no prior treatment experience after adjusting for publication bias. This result could reflect real or anticipated effects of any anti-emetics provided, an issue future research might address.

We undertook a direct comparison between studies reporting data after a single treatment exposure (where the opportunity for classical conditioning of response was eliminated) with studies where side effect experience was measured after the patient had received multiple treatment cycles (where effects were likely a combination of expectations raised before treatment (i.e., cognitive expectancies) and reactions learned though experience (i.e., conditioned responses), **as well as potential residual toxicity resulting from the cumulative effects of some treatments**). The findings for anticipatory nausea confirmed

those of Sohl, Schnur and Montgomery [6]. The experience of anticipatory nausea was more strongly related to anticipation among patients who had some previous treatment experience, in comparison to patients with no treatment experience, therefore highlighting a potential influence from classical conditioning. Contrary to the hypothesis, all other results (i.e., post-treatment vomiting and fatigue), trended in the other direction. The one exception was post-treatment nausea, where the effect size documenting the relationship between anticipation and side effects in patients with no prior treatment experience was $r = 0.200$ and $r = 0.288$ in patients with prior treatment experience. Although non-significant, this result suggests that further research might usefully consider the anticipated effectiveness of anti-emetic treatments. A small number of the studies included in the meta-analysis did control for the use of anti-emetic treatments or describe the relationship between anti-emetic use and subsequent nausea and vomiting [10, 22, 23, 29-31, 34, 35], however none specifically examined patients' anticipation of the effectiveness of anti-emetic treatments.

The implications of the findings for clinical practice should be considered. Several studies included in this review recommended providing patients with information prior to treatment in order to alter patient expectations. Although intervention studies provided some support for the use of acupressure bands for reducing nausea [21] and hypnosis for reducing post-surgery pain and distress [16], manipulations of the information given to patients did not result in changes in side-effects [16]. Shelke et al. [19] found that providing information about the effectiveness of an antiemetic successfully altered patient expectations. However, pre-intervention anticipation and not post-intervention anticipation was predictive of subsequent side effects. This suggests that simply changing patient education regarding side effects may not be effective in reducing expectancy effects.

The data presented here are subject to significant limitations. The most significant of these is the inability to account for variance arising from an array of variables likely to impact

both the predictor variable, anticipated effect of treatment, and the outcome variable, report of side effects. For example, it is possible that variables like education, IQ, depression, anxiety, locus of control and optimism would all impact ratings of anticipation and the side effects experienced, and the extent to which these are positive or negative, irrespective of messages received about likely effects or any conditioning experienced. There is some support for this from an experimental study of pain expectancies, which found that pain expectancies played a mediating role between catastrophizing and depression and the actual pain experienced [54], although further research is required to test this. Furthermore, the nature and intensity of the chemotherapy regime and the medication provided to alleviate side effects are all potential confounds of reported side effects. **There may also be a differentiated impact of the type of treatment on the side effects that patients experience. This was not examined in the present study due to the small number of studies that included participants undergoing treatment other than chemotherapy. More research is needed to examine the relationships between anticipation of side effects and actual experience of side effects in patients undergoing radiotherapy and surgery before meta-analysis can be conducted to provide meaningful insight.**

Our results confirm existing findings; anticipation of side effects positively predict the experience of these. In addition, our findings extend those of others by demonstrating their impact in a reasonably recent area of research in side effects of cancer treatment; cognition. Importantly, they highlight the potentially "additive" effects of conditioning following treatment on the impact made from expectations generated before any treatment, but only for anticipatory nausea. The failure to find an additive influence from treatment experience for other side effects suggests an important role for cognition in predicting treatment experience.

Future research could usefully explore patient reports of messages received about likely treatment effects both before and during treatment, and from whom these messages originate.

In terms of conditioned responses, interview data could identify cues (i.e., the conditioned stimulus) that precede anticipatory nausea and vomiting in an attempt to develop strategies that could mitigate these associations. Further exploration of the anticipated outcomes attached to preventive therapies for side effects might also usefully identify strategies for minimisation of adverse treatment events. An increasing focus on the importance of measuring patient reported outcomes in cancer patients and survivors bodes well for increased concern about patient reported side effects and improved commitment from health providers to assist in their mitigation.

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Competing Interest Statement

The authors have no competing interests to report.

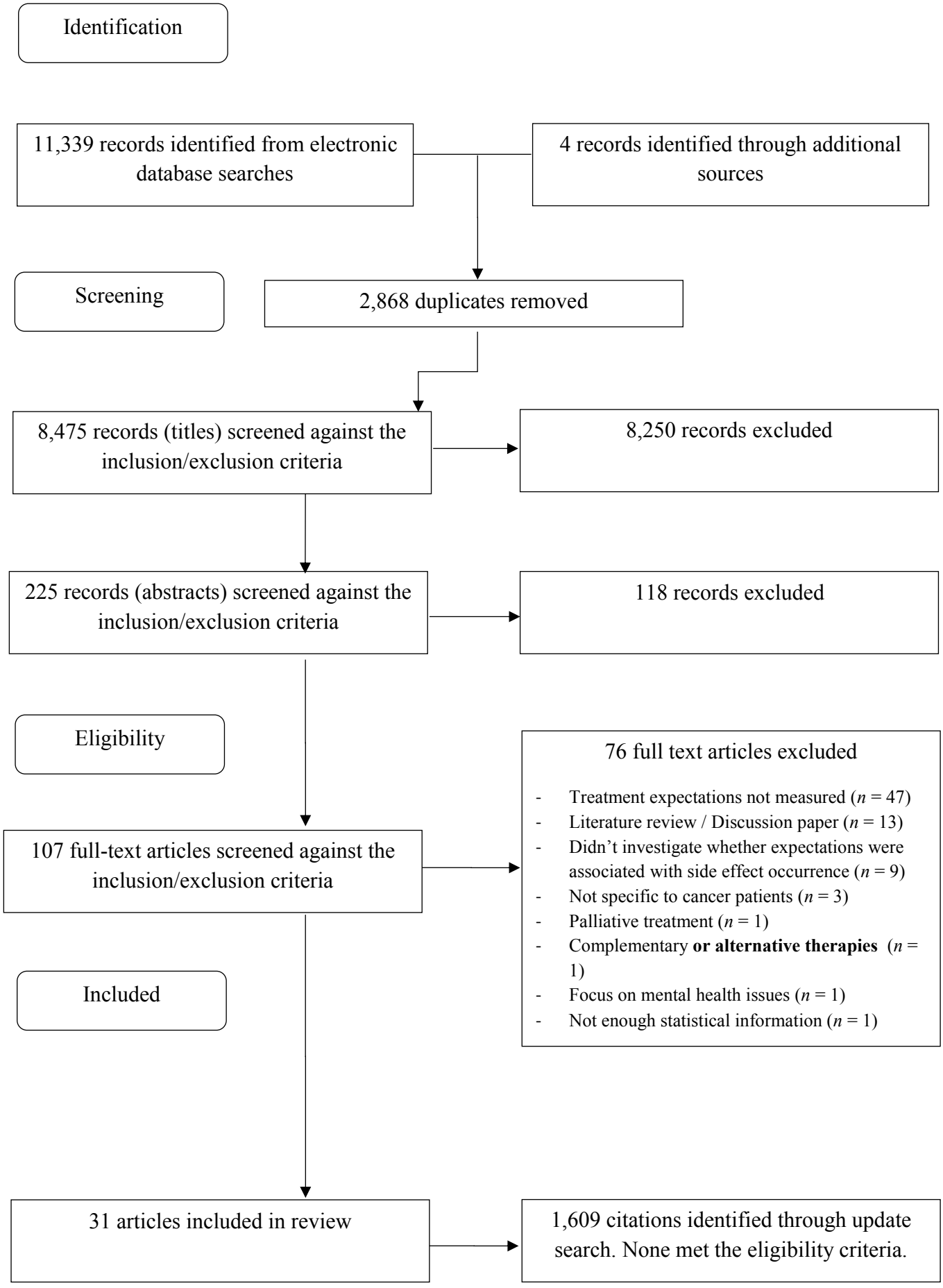

Figure 1. Study flow diagram for systematic review.

Table 1. Meta-analysis results for the relationships between expectations of side effects and actual experience of side effects in patients receiving treatment for cancer.

Side effect			**Effect size**	**95% CI**		**Rosenthal's**	**Orwin's**	I^2
	k	***N***	***r***	**Lower**	**Upper**	N_{fs}	N_{fs}	**%**
Anticipatory nausea	5	359	0.442**	0.173	0.649	74	42	84.24***
Post-treatment nausea	25	4,054	0.230***	0.161	0.297	827	53	75.520***
Post-treatment vomiting	11	1,166	0.181***	0.123	0.238	91	30	0.00
Fatigue	9	672	0.325***	0.196	0.443	140	51	64.07**
Pain	6	386	0.364***	0.174	0.528	67	38	71.26**
Problems with concentration	2	146	0.431***	0.287	0.556	-	-	0.00
Skin reactions	4	858	0.290*	0.003	0.534	20	4	87.913***

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

k; number of studies; *N*, Number of participants; *r*, Pearson correlation coefficient; CI, Confidence Interval; I^2, I^2 statistic; N_{fs}, Fail-Safe N; %, Percentage.

Table 2. Meta-analysis results for the relationships between expectations of side effects and actual experience of side effects in patients who had *no previous treatment experience*.

Side effect			**Effect size**	**95% CI**		**Rosenthal's**	**Orwin's**	I^2
	k	***N***	***r***	**Lower**	**Upper**	N_{fs}	N_{fs}	**%**
Anticipatory nausea[a]	1	-	*0.036*	-	-	-	-	-
Post-treatment nausea	17	3,553	0.200***	0.121	0.277	372	30	78.726***
Post-treatment vomiting	7	901	0.170***	0.104	0.234	42	17	0.00
Adjusted effect size [b]			0.153	0.092	0.213			
Fatigue	6	526	0.337***	0.180	0.477	87	35	72.636**
Pain	5	330	0.366**	0.141	0.554	50	32	76.975**
Problems with concentration[c]	2	146	0.431***	0.287	0.556	-	-	0.00
Skin reactions	3	802	0.278	-0.065	0.562	12	3	91.243***

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, [a] Only one study examined expectancies and experience of anticipatory nausea prior to any treatment, therefore there were not enough data to run the meta-analysis. [b] Egger's test confirmed a publication bias, therefore adjusted effect size calculated using Duval and Tweedie's trim-and-fill method. [c] Only two studies examined the relationship between response expectancies and problems with concentration, therefore publication bias analysis could not be conducted. Results should be interpreted with caution.

k; number of studies; *N*, Number of participants; *r*, Pearson correlation coefficient; CI, Confidence Interval; I^2, I^2 statistic; N_{fs}, Fail-Safe N; %, Percentage.

Table 3. Meta-analysis results for the relationships between expectations of side effects and actual experience of side effects in patients who had s*ome previous treatment experience*.

Side effect			**Effect size**	**95% CI**		**Rosenthal's**	**Orwin's**	I^2
	k	***N***	***r***	**Lower**	**Upper**	N_{fs}	N_{fs}	**%**
Anticipatory nausea	5	359	0.476***	0.237	0.660	90	46	81.44***
Post-treatment nausea	11	707	0.288***	0.184	0.386	142	49	46.38*
Post-treatment vomiting	5	390	0.211***	0.096	0.320	13	17	12.99
Fatigue	4	271	0.266**	0.090	0.427	11	18	36.20
Pain[a]	2	86	0.235	-0.072	0.500	-	-	32.31
Problems with concentration[b]	0	-	-	-	-	-	-	-
Skin reactions[c]	1	-	-	-	-	-	-	-

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. [a] Only two studies examined the relationship between response expectancies and pain, therefore publication bias analysis could not be conducted. Results should be interpreted with caution. [b] None of the included studies examined the relationship between response expectancies and problems with concentration in patients with previous treatment experience. [c] Only one study examined expectancies and experience of skin reactions in patients with previous treatment experience, therefore there was not enough data to run the meta-analysis.

k; number of studies; *N*, Number of participants; *r*, Pearson correlation coefficient; CI, Confidence Interval; I^2, I^2 statistic; N_{fs}, Fail-Safe N; %, Percentage.

Table 4. Between groups analysis for the relationships between expectations of side effects and actual experience of side effects in patients with and without previous treatment experience

Side effect	**Heterogeneity**		
	Q	***df***	***p***
Anticipatory nausea[a]	6.353	1	0.012*
Post-treatment nausea	1.817	1	0.178
Post-treatment vomiting	0.772	1	0.380
Fatigue	0.375	1	0.540
Pain	0.516	1	0.472
Problems with concentration[b]	-	-	-
Skin reactions	0.079	1	0.778

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

[a] Only one study examined response expectancies and experience of anticipatory nausea in patients with no previous treatment experience ($r = 0.036$ [12]), therefore result should be interpreted with caution. [b] None of the included studies examined response expectancies and experience of problems with concentration in patients with previous treatment experience.

Supplementary Table 1: Study characteristics

Study	n	Side effect type	Cancer type	Treatment type	Treatment experience	Expectancies measured before treatment no.	Side effect measured after treatment no.
Andrykowski, 1988 [32] Qualsyst score: 0.82	77	Anticipatory nausea	Breast	Chemotherapy	No previous treatment experience	First	First and subsequent
Andrykowski, 1992 [10] Qualsyst score: 0.89	65	Post-treatment nausea	Mixed	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at subsequent treatments	First	First and subsequent
Booth, 2007 [28] Qualsyst score: 0.91	143	Post-treatment vomiting	Breast	Chemotherapy	Some previous treatment experience	Multiple treatments	Cessation of chemotherapy or maximum of 6 treatment cycles
Cassileth, 1985 [24] Qualsyst score: 0.66	56	Post-treatment nausea Post-treatment vomiting Fatigue Pain Skin reactions	Mixed	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at second treatment	First	First and second (analyses conducted using side effects reported following second treatment)
Cobeanu, 2013 [11] Qualsyst score: 0.69	30	Post-treatment nausea Post-treatment vomiting Fatigue Pain	Breast	Chemotherapy	Some previous treatment experience	Treatment other than the first	Treatment other than the first
Colagiuri, 2008 [39] Qualsyst score: 0.82	671	Post-treatment nausea	Mixed	Chemotherapy	No previous treatment experience	First	First
Colagiuri, 2013 [33] Qualsyst score: 0.75	91	Post-treatment nausea Fatigue	Mixed	Chemotherapy	No previous treatment experience	First	First

Study	n	Side effect type	Cancer type	Treatment type	Treatment experience	Expectancies measured before treatment no.	Side effect measured after treatment no.
Haut, 1991 [34] Qualsyst score: 0.84	36	Post-treatment nausea Post-treatment vomiting	Mixed	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at subsequent treatments	First	First and subsequent
Hickok, 2001 [12] Qualsyst score: 0.80	63	Anticipatory nausea Post-treatment nausea	Mixed	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at third treatment	First	First and third
Higgins, 2007 [22] Qualsyst score: 0.91	56	Post-treatment nausea	Breast	Chemotherapy	No previous treatment experience	First	First
Jacobsen, 1988 [35] Qualsyst score: 0.83	45	Post-treatment nausea	Breast	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at subsequent treatments	First	First six treatments
Molassiotis, 2002 [36] Qualsyst score: 0.95	71	Post-treatment nausea Post-treatment vomiting	Breast	Chemotherapy	No previous treatment experience	First	First
Molassiotis, 2013 [31] Qualsyst score: 0.96	286	Post-treatment nausea Post-treatment vomiting	Mixed	Chemotherapy	No previous treatment experience	First	First, second, and third cycles
Molassiotis, 2014 [29] Qualsyst score: 0.88	Cycle 1: 911 Cycle 2: 888 Cycle 3: 769	Post-treatment nausea	Mixed	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at second and third treatments	First	First, second, and third cycles (data only for first cycle)
Montgomery, 1998 [26] Qualsyst score: 0.88	59	Anticipatory nausea	Breast	Chemotherapy	No previous treatment experience	First	Sixth

Study	n	Side effect type	Cancer type	Treatment type	Treatment experience	Expectancies measured before treatment no.	Side effect measured after treatment no.
Montgomery, 2000 [25] Qualsyst score: 0.77	52	Post-treatment nausea	Breast	Chemotherapy	No previous treatment at first treatment Some previous treatment experience at subsequent treatments	Multiple treatments	Multiple treatments
Montgomery, 2001 [13] Qualsyst score: 0.80	60	Anticipatory nausea Fatigue	Breast	Chemotherapy	Some previous treatment experience	Third	Third
Montgomery, 2002 [16] Qualsyst score: 0.72	20	Pain	Breast	Surgery	No previous treatment experience	Pre-surgery	Post-surgery
Montgomery, 2004 [14] Qualsyst score: 0.89	63	Post-treatment nausea Fatigue Pain	Breast	Surgery	No previous treatment experience	Pre-surgery	Post-surgery
Montgomery, 2010 [15] Qualsyst score: 0.93	101	Post-treatment nausea Fatigue Pain	Breast	Surgery	No previous treatment experience	Pre-surgery	Post-surgery
Olver, 2005 [37] Qualsyst score: 0.89	87	Post-treatment nausea Post-treatment vomiting Fatigue Pain Skin reactions Problems with concentration	Mixed	Chemotherapy	No previous treatment experience	First	First
Rhodes, 1995 [27] Qualsyst score: 0.78	329	Post-treatment nausea Post-treatment vomiting	Not specified	Chemotherapy	No previous treatment experience	First	First
Roscoe, 2000 (study 1) [23] Qualsyst score: 0.77	29	Post-treatment nausea Post-treatment vomiting	Ovarian	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at second	First	First and second

Study	n	Side effect type	Cancer type	Treatment type	Treatment experience	Expectancies measured before treatment no.	Side effect measured after treatment no.
					treatment		
Roscoe, 2000 (study 2) [23] Qualsyst score: 0.77	81	Post-treatment nausea	Mixed	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at third treatment	First	First and third (data only for third treatment)
Roscoe, 2004 [17] Qualsyst score: 0.73	201	Post-treatment nausea Post-treatment vomiting	Breast	Chemotherapy	No previous treatment experience	First	First
Roscoe, 2009 [21] Qualsyst score: 0.72	88	Post-treatment nausea	Mixed	Radiotherapy	Some previous treatment experience	Other than first	Fifth treatment since study commencement
Ryan, 2007 [18] Qualsyst score: 0.80	656	Skin reactions	Mixed	Chemotherapy and/or radiation therapy	No previous treatment experience	First	First
Shelke, 2008 [19] Qualsyst score: 0.85	358	Post-treatment nausea	Mixed	Chemotherapy	No previous treatment experience	First	First
Watson, 1998 [30] Qualsyst score: 1.0	100	Anticipatory nausea Post-treatment nausea	Breast	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at subsequent treatments	First	First and subsequent
Whitford, 2012 [38] Qualsyst score: 0.82	59	Post-treatment nausea Post-treatment vomiting Fatigue Pain Skin reactions Problems with concentration	Mixed	Chemotherapy	No previous treatment experience	First	First

Study	n	Side effect type	Cancer type	Treatment type	Treatment experience	Expectancies measured before treatment no.	Side effect measured after treatment no.
Zachariae, 2007 [20] Zachariae, 2007 [48] Qualsyst score: 0.91	125	Post-treatment nausea Post-treatment vomiting Fatigue	Breast	Chemotherapy	No previous treatment experience at first treatment Some previous treatment experience at subsequent treatments	First	First, fourth, sixth, and last (seventh or ninth)

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