The Role of Response Expectancies in Cancer Treatment

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Abstract

Cancer incidence continues to grow gradually yet mortality rates have decreased, warranting research on methods of predicting and reducing treatment-related toxicities. This research project explored the influence of *response expectancies*, individuals' expectations of their automatic reactions to stimuli (i.e., cancer treatment), on side effect experiences.

Although research has supported associations between response expectancies of cancer treatment-related toxicities and subsequent experience, outcomes have not been consistent. Furthermore, whether response expectancies are equally influential in under-investigated patient groups is unknown, and exploration into patients' side effect reduction through response expectancy-based interventions is still in its infancy. The current project addressed these gaps through a meta-analysis and three empirical studies.

Meta-analysis aims (*Study 1*) were threefold; to replicate the relationship between expectancies of cancer toxicities and subsequent experiences, to explore if association strength differed between individual toxicity expectancies, and to investigate methodology differences on outcomes. In a pooled analysis of 27 quantitative studies, results revealed a moderate relationship between expectancies of all measured side effects and their experience. Further analyses revealed significant differences between individual toxicities, with expectancies of hair loss demonstrating the strongest relationship with subsequent experience. Measurement and sample differences were associated with varying levels of effects, explored more comprehensively using a psychometric design (*Study 2*).

In *Study 2,* the inclusion of a midpoint representing patients being 'unsure' whether they would experience a toxicity, and differences between the two most

commonly used scales (5-point and visual analogue scales; VAS), were investigated. Forty-five men scheduled for radiotherapy for prostate cancer completed measures of side effect expectancies on both 5-point scales and VAS. Analyses revealed patients often selected 'unsure' on the 5-point scale, which appeared a less sensitive measure of response expectancies than VAS. For most toxicities, responses on the two scales were not highly related. Based on *Study 1* and *2,* careful consideration is essential when designing and pooling studies.

Study 3 collected longitudinal data from the same homogenous sample of patients with prostate cancer (N = 35, *Study 2)*. This prospective study found that baseline response expectancies significantly and uniquely predicted 6 of the 18 radiotherapy toxicities 2-weeks into treatment (where toxicities are not yet medically expected). This signified the influence of response expectancies early in radiotherapy. Seven-weeks into treatment, response expectancies (measured at 2-weeks) predicted 7 of the 16 experienced side effects. Expectancies of sexual toxicities demonstrated moderate-to-strong associations with experience, throughout, and thus should be a clinical and research focus in the future.

Study 4 explored whether pre-treatment side effect information presented in different valence frames could influence response expectancy formation and subsequent experience. A healthy sample of 134 university students was randomised to receive information about an experimental pain induction task framed in a positive or negative format. Results revealed that although response expectancies consistently and independently predicted subsequent experience, framing had minimal impact on response expectancies and experience. Social influences through media and social media channels, were found to impact participants' pain experiences, suggesting a clear direction for future research.

Declaration

I, Elise Devlin, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Last but certainly not least, to all the patients who participated in the clinical study, for taking time out during an already busy morning to complete the measures. Your contribution to this thesis is recognised and sincerely appreciated. Similarly, to all the students who participated in the somewhat scary experimental study, thank you!

Chapter 1: Introduction

'Just as I expected': An exploration of response expectancies and their influence on cancer treatment side effects

1. Background

Before beginning treatment for a cancer diagnosis, patients develop expectations about whether they will experience side effects, and to what degree (Roscoe et al., 2006). These specific expectations, termed *response expectancies* (Kirsch, 1985), refer to an individual's anticipation for how they will automatically (non-volitionally) respond to stimuli or behaviours. Such responses include treatment-related side effects (toxicities), symptomatic improvement, emotional states, and arousal levels. The impact of response expectancies on subsequent toxicity experience can be substantial. In a study of 194 women undergoing chemotherapy for breast cancer, Roscoe et al. (2004) found patients who rated it 'very likely' they would experience nausea were five times more likely to report severe nausea than those who indicated it 'very unlikely'. More generally, side effect expectancies are often, but not universally, found to be moderately related to later toxicity experiences (Colagiuri & Zachariae, 2010; Sohl, Schnur, & Montgomery, 2009). Consequently, response expectancies have potential utility for explaining different reactions to cancer treatment regimens, predicting those patients at increased risk of severe toxicity experiences, and informing potential non-pharmacological side effect reduction interventions.

In this introductory review, I explore how response expectancies are formed and the mechanisms through which they are proposed to influence side effects. A summary of research on response expectancies of cancer treatment side

effects is then presented, specifically introducing measurement and methodology, correlates (covariates) of response expectancies, and expectancy-based intervention strategies. The overall aim is to clarify what is currently understood about expectancies of cancer treatment side effects, and what remains to be discovered. The chapter then concludes with an outline of the research aims and questions at the core of this thesis and research project.

1.1   An overview of response expectancies

Response expectancies were first conceptualised by Kirsch (1985) as a unique form of expectancy, not previously explicitly recognized in the literature (Bandura, 1977; Rotter, 1954). This specific type of expectancy refers to individuals' anticipations for how they will react to stimuli (or behaviour) in an automatic and unintentional way, such as expecting to become fearful when boarding a flight, to become angry when held up in traffic, or to become nauseous during chemotherapy. Because response expectancies are internal states, they are proposed to be directly related to subsequent responses, "the perception is not just *of* the experience, it *is* the experience" (Kirsch, 2000, p. 280). Accordingly, these subjective states can produce associated objective responses. For example, expectancies of alertness following the ingestion of decaffeinated coffee are associated with higher blood pressure (Kirsch, 1997).

The associations between response expectancies and subsequent side effects depend on both the strength of the expectancy and the magnitude of the expected response; strong expectancies for weaker responses generally have the greatest influence (Kirsch, 1999a). However, response expectancies do not usually predict an experience in isolation (Kirsch, 1999a). For example, the

severity of nausea a patient experiences during chemotherapy is likely due to the emetic potential of the dosage given to a patient. This is known as a *specific effect* because it is a direct consequence of the treatment. However, other *non-specific effects* (non-pharmacological effects) also contribute to an individual's experience of nausea, including previous experience with a treatment (conditioning effects), coping style, demographic factors, distress, meaning, social and instructional learning, and the relationship between patients and healthcare workers (Andrykowski & Gregg, 1992; Colloca & Miller, 2011c; Kirsch, 1985, 2013; Moerman, 2002b; Voudouris, Peck, & Coleman, 1990; Whitford & Olver, 2012). Consequently, a holistic understanding of response expectancies needs to incorporate these, and possibly other novel, untested variables to gain a full picture of the impact of all relevant effects on a patient's experience.

Moreover, although response expectancies and subsequent experiences can consciously and unconsciously occur (Benedetti et al., 2003), they can only influence what is physically available to someone's body, and do not influence all processes. For example, response expectancies can increase levels of a naturally occurring neurotransmitter (dopamine), thus reducing symptoms of Parkinson's disease (Lidstone, Schulzer, Dinelle, & et al., 2010). However, they do not appear to alter the hormone cortisol (Colloca & Miller, 2011), nor can they replace insulin or any other hormone that is missing in the body (Benedetti et al., 2003; Kaptchuk & Miller, 2015; Miller & Colloca, 2011).

1.1.1 The formation of response expectancies

Theory and research have established a number of predictors of response expectancies. Direct (conditioning), and vicarious (social learning and verbal

influence) experiences have been posited to produce response expectancies (Colagiuri, Schenk, Kessler, Dorsey, & Colloca, 2015; Kirsch, 1985, 1997) and this has been supported through a range of experiments and observations (Benedetti, 2013; Colagiuri et al., 2015; Mazzoni, Foan, Hyland, & Kirsch, 2010).

Specific to expectancies of cancer treatment side effects, Hoffman (2012) found younger age, being female, a higher level of education, diagnosis, and scheduled treatment predicted the number of expectancies of side effects formed across chemotherapy and radiotherapy, and that pre-existing levels of side effects (measured at baseline) were significantly related to expectancies of those toxicities. Further, Schnur (2007) found that pre-surgery expectancies of pain were predicted by trait anxiety, younger age, and greater distress, whereas expectancies of fatigue were predicted by a previous history of surgery, baseline (pre-existing) fatigue, and a higher level of education. Thus, it is evident that although some variables more commonly predict response expectancies in general, differences existed for certain cancer treatment-related side effects, highlighting the complexity of response expectancy research in the treatment of cancer.

1.1.2 How response expectancies influence experiences

The mechanisms through which response expectancies relate to subsequent experience has been theorized at philosophical, cognitive, and neurobiological levels. Response expectancies are proposed to be self-fulfilling prophecies that automatically elicit responses. This is based on monist mind-body philosophical theories (Kirsch & Hyland, 1987), which propose that cognitions correspond with physical states, or that "there is a physiological substrate for any

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experiential state" (Kirsch, 2000, p. 280). Just as emotional feelings are automatically generated by related cognitions (e.g., feeling happy corresponds with happy thoughts), and volitional intentions automatically generate responses (e.g., standing up is directly related to the intention of standing), response expectancies are sufficient to create the corresponding experience; thus, the expectancy of pain is also the perception of pain. The same occurs for other experiences, such as fatigue and nausea. This *theory of automaticity* has been theorised to occur through schema activation (Kirsch & Lynn, 1999).

Cognitive schemas are knowledge structures through which stimuli are interpreted and perceived (Bartlett & Burt, 1933; Piaget, 1923). Schemas are built though previous experiences (direct and indirect), and allow immediate (automatic) perceptions and reactions to the environment. This speed is a product of schemas being automatically prepared, or 'primed' for activation by stimuli in the environment. Kirsch and Lynn (1999) posit that patients' response expectancies can be the stimuli that prepare certain schemas for activation. This has been supported with research, with Schagen, Das, and van Dam (2009) finding that priming patients with a stereotypical 'chemo-brain schema' resulted in their making more complaints of cognitive impairment (than other participants not primed with that information). Once a schema is activated, it has been widely and consistently evidenced in research (Cobeanu, 2013) that attention is directed to information which matches it. Thus, individuals who have stronger expectancies of experiencing a side effect have a reduced threshold for noticing that toxicity (Roscoe et al., 2006). Furthermore, schemas can influence perception of ambiguous stimuli. A treatment reaction could be interpreted as 'nausea' if this fits with an individual's pre-existing schema, or alternatively the same stimulus

could be interpreted as 'abdominal cramps' if that is more congruent with their schema. This also explains evidence that more ambiguous (subjective) stimuli often show the strongest relationship with their response expectancies (Roscoe et al., 2006), because these would more easily be misinterpreted. For example, expectancies of nausea have been shown to have stronger relationships with subsequent nausea experience than the relationship between expectancies of vomiting and its corresponding experience (Olver, Taylor, & Whitford, 2005; Roscoe, Hickok, & Morrow, 2000a).

With increasingly powerful technology such a functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), and high resolution electroencephalography (EEG), novel research in pain research is also beginning to uncover neurobiological bases to response expectancies. Much of this research is based on *nocebo effects*; negative responses (i.e., side effects) produced or worsened from expectancies of their occurrence (Colloca & Miller, 2011b; Freeman et al., 2015), rather than an active (physical or pharmacological) treatment. Research on nocebo effects has found increased activation of the hypothalamic-pituitary-adrenal (HPA) axis in healthy volunteers during a ischemic pain induction task, with the hippocampus playing a vital role in this process (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006). The hippocampus has also shown brain activation in subsequent investigations of nocebo effects (Bingel et al., 2011; Kong et al., 2008). The secondary anterior cingulate, somatosensory cortex, insular cortex, thalamus, and amygdala have also been found to be activated during nocebo responding (Schmid et al., 2015; Scott et al., 2008). However, although response expectancies have been shown to be major components of nocebo effects (Berna et al., 2017; Colloca & Finniss, 2012;

Colloca & Miller, 2011c), such responses are also uniquely predicted by other variables including previous direct experience (classical conditioning), social cues (observations and interpersonal interactions), anxiety, catastrophisation, and somatisation (Benedetti, Lanotte, Lopiano, & Colloca, 2007; Colloca, 2014; Colloca & Miller, 2011c; Wilson, Dworkin, Whitney, & LeResche, 1994). Therefore, the evidence based on nocebo effects may not always represent the independent mechanisms underpinning response expectancies alone. Nonetheless, in one empirical investigation, Bingel et al. (2011) gave the same pain analgesic, remifentanil to 22 healthy participants undergoing thermal stimulation (i.e., heat on the skin causing a painful sensation). When this treatment was paired with negative response expectancies the remifentanil did not provide any analgesic effect, but when it was paired with positive response expectancies its analgesic effect was doubled. Importantly, fMRI scans indicated the activation of different neural regions under each condition. The positive response expectancies were associated with activation of the endogenous opioid system, and again, the negative response expectancies were associated with activation on the hippocampus. Because the treatment was the same across conditions, this study revealed that these neural activations were associated with response expectancies alone, suggesting the activation of this hippocampus in nocebo research was likely produced to some degree by negative response expectancies.

The hormone cholecystokinin (CCK) has also been implicated in patient experiences based on response expectancy modifying information (Benedetti et al., 2006). When patients reporting postoperative mild pain were given a saline solution, those that were told the inert solution would increase pain reported more pain (i.e. a nocebo effect). However, some groups received the same information,

but were also given proglumide, a drug that blocks the effects of CCK (a CCK antagonist). In the groups that received proglumide, an increase in pain was no longer reported (Benedetti et al., 2006), suggesting CCK mediated the link between response expectancy and pain.

Brain imaging and psychopharmacologic studies of negative response expectancies and nocebo effects are a novel area of investigation, however the important discoveries found to date indicate a biological basis to these responses, as opposed to patients only reacting accordingly to please practitioners or researchers (Hróbjartsson & Gøtzsche, 2001), or misattributing existing symptoms to treatment (Barsky, Saintfort, Rogers, & Borus, 2002). Having explained the contextual basis for the formation of response expectancies, and the mechanisms through which they shape experiences, I will next provide a review of the current published research on how response expectancies specifically influence cancer treatment side effects, then summarise gaps in the existing literature.

1.2   The problem of cancer treatment-related side effects

Cancer is a disease caused by mutations in a cell's genome (Stewart & Wild, 2014), whereby cells grow, multiple, and can spread (if the cancer is malignant) in an uncontrolled way (Cancer Council Australia, 2016). Because 'cancer' is an umbrella term encompassing a collection of over 100 related but different diseases (Cancer Council Australia, 2016), there are substantial differences in the occurrence of individual diagnoses over time. Furthermore, incidence differs in different geographic locations; however, general trends are evident. In America, the incidence of cancer remained stable for women over a

five year period until 2013, but decreased in men (Jemal et al., 2017), yet remains the second most common cause of mortality in that region of the world (Center for Disease Control and Prevention, 2017). Worldwide, in 2012 8.7 million people (over 15 years of age) had been diagnosed with cancer within one year and 326 million within five years of measurement (Jemal et al., 2017). Thus, cancer is a significant universal burden.

Fortunately, based on improvements in cancer prevention, detection, and treatment, overall death rates are decreasing for men, women, and children by an average of 1.6% (between 2010 and 2014; Jemal et al., 2017). Furthermore, the rates of patients surviving cancer up to 5-years post-diagnosis have increased from 50% in 1977 to 66% in 2012 (Jemal et al., 2017) and projections from the American Cancer Society estimate the number of cancer survivors will increase from 15.5 million to 20.3 million by 2026 (an increase of 31%; Miller et al., 2016). With this comes a new set of challenges; most importantly, the need for supportive long-term care for a growing number of patients experiencing the unpleasant side effects (toxicities) created by cancer treatment, and research into how to minimise these effects.

Side effects can occur during treatment and be acute, termed *early effects,* or continue beyond treatment, considered chronic toxicities. They can also begin post-treatment and occur for months, or many years, termed *late effects* (Bentzen et al., 2003). Some toxicities have been consistently linked to a reduced quality of life (Davis et al., 2014; Genre et al., 2002), can lead to treatment nonadherence (Barsky et al., 2002), and the need to lower treatment doses (Olver, Eliott, & Koczwara, 2014). This is often related to the prevention of normal day-to-day

activities such as household chores, food preparation, and social activities (Curt et al., 2000).

Side effects also impact both direct medical costs, such as extended inpatient hospitalisation and emergency room visits, and indirect costs including days absent from work for both survivors and caregivers (Carlotto, Hogsett, Maiorini, Razulis, & Sonis, 2013). For example, in a study of 406 male and female patients, more than half of whom had completed treatment (chemotherapy and/or radiotherapy) more than 2 years prior, 67% of the survivors still experienced fatigue more than a few days per month (and 30% experienced fatigue on a daily basis). In this group, 88% of the survivors indicated their fatigue altered their day-to-day lives, and of those who were employed, 75% had changed employment status. Their caregivers were also absent an average of 4.5 days per month (Curt et al., 2000).

In summary, improvements in cancer detection and treatment have led to an increase in survivorship that is steadily climbing, and the overall incidence of cancer is gradually declining at best, but remains stable in some groups (depending on diagnosis, sex, and geographic location). Thus, more individuals will require treatment in the future and consequentially, will experience a degree of cancer treatment-related side effects. Toxicities, especially long-term, can be costly for society and for individuals. Thus, strategies to prevent and/or reduce the severity of side effects are vital. Specific pharmacological treatments can be beneficial for side effect control; however, these are also usually costly, and come with risks of their own side effects, and/ or interactions with primary treatment (Lokiec, 2013). Non-pharmacological methods of side effect reduction, such as those based on expectancy modification, may be highly valuable in this area,

especially for those toxicities found to be impacted by patient response expectancies to a meaningful degree.

1.3 Expectancies of cancer treatment side effects

The first influential study measuring the influence of response expectancies on side effect experience concluded that expectancies of 16 chemotherapy side effects were not related to toxicity experience, in a sample of 56 treatment-naïve patients with cancer (Cassileth et al., 1985). Using chi-square analyses, the authors found significant matches between expectancies of side effects and experiences (and likewise between side effects not expected or experienced), for only 6 of the 16 toxicities measured. They explained these few significant results as artefacts of matches between very low levels of response expectancies and experiences, and concluded that expectancies of side effects did not impact subsequent experiences. Using the same response expectancy measure as in the original seminal study (Cassileth et al., 1985), a 5-point scale known as the Side Effect Expectancy Questionnaire (SEEQ), other researchers similarly concluded that response expectancies did not influence chemotherapy-related nausea (Andrykowski & Gregg, 1992), or chemotherapy and radiotherapy-related skin reactions (Ryan et al., 2007). Moreover, side effect response expectancies measured on a 3-point scale showed no relationship with subsequent nausea (Higgins, Montgomery, & Bovbjerg, 2007), and the univariate relationships identified between expectancies of nausea and vomiting and their experience no longer remained in multivariate models (Molassiotis, Stamataki, & Kontopantelis, 2013). A potentially important commonality among these studies failing to find

an association between response expectancies and experience, is that all but one (Higgins et al., 2007) involved patient samples with mixed cancer diagnoses.

Other studies have reported significant relationships between response expectancies and experiences of some side effects, but not others (Colagiuri et al., 2013; Montgomery & Bovbjerg, 2004; Olver et al., 2005; Rhodes, Watson, McDaniel, Hanson, & Johnson, 1995; Roscoe et al., 2000a; Whitford & Olver, 2012; Zachariae et al., 2007b). However, the majority of research using the original 5-point SEEQ has found response expectancies predict a wide variety of subsequent side effects (Andrykowski et al., 1988; Colagiuri et al., 2008; Haut, Beckwith, Laurie, & Klatt, 1991; Hickok, Roscoe, & Morrow, 2001; Jacobsen et al., 1988a; Roscoe et al., 2004; Shelke et al., 2008). Significant relationships have also been found in studies using Visual Analogue Scales (VAS; Cobeanu, 2013; Montgomery & Bovbjerg, 2001; Montgomery, Schnur, Erblich, Diefenbach, & Bovbjerg, 2010b), and other response expectancy measures, including 3-point categorical scales; dichotomous scales; and 10-point scales (Booth et al., 2007; Molassiotis, Yam, Yung, Chan, & Mok, 2002; Montgomery & Bovbjerg, 2000, 2003; Montgomery et al., 1998; Watson, Meyer, Thomson, & Osofsky, 1998). Relationships between expectancies of fatigue, pain, vomiting, and nausea, and subsequent experience have been further established, with two meta-analyses revealing small to moderate relationships (Colagiuri & Zachariae, 2010; Sohl et al., 2009).

Thus, the evidence to date is not entirely consistent. Expectancies of side effects are associated with subsequent toxicities in some contexts, but not all. Differences in response expectancy measurement methods, and interactions

between, or shared explanatory power with other psychological variables, may help explain these apparent inconsistencies.

1.3.1 The influence of methodology and measurement of response expectancies on reported associations with cancer treatment side effects

Most studies investigating response expectancies have measured the same toxicities, generally nausea and vomiting, less often pain and fatigue, and very rarely any other common cancer treatment-related side effects. In their 2009 meta-analysis, Sohl and colleagues compared individual effect sizes for studies investigating nausea, vomiting, pain, and fatigue across 14 studies, only finding significant differences between effect sizes for expectancies of pain and experience, and expectancies of vomiting and experience. Although there were very few studies investigating pain, fatigue, or vomiting (two or three studies for each), this tentatively indicated response expectancies influence may be somewhat, but not entirely, consistent across treatment side effects. There is evidence that placebo effects (effects resulting from positive response expectancies; explained in detail in Section 1.3.3), occur through different neural mechanisms for different responses (Benedetti, Carlino, & Pollo, 2011; Finniss, Kaptchuk, Miller, & Benedetti, 2010b). Accordingly, it is important for future research to determine whether this is also the case for response expectancies themselves. Thus, further investigation is required into whether there is one general effect of response expectancies on all future cancer treatment toxicities, or whether the effects of response expectancies differ between individual side effects, or toxicity clusters.

The observed inconsistencies between study findings may also reflect the use of different response expectancy measurement methods. Two reviews have found no impact of the response expectancy measurement scales utilised on effect sizes (Colagiuri & Zachariae, 2010; Sohl et al., 2009). However, when they were conducted, there were few studies using measures other than the side effect expectancy questionnaire (SEEQ). In a novel study, Colagiuri et al. (2008) investigated the linearity of nausea expectancies, by separating the data provided by 671 chemotherapy-naïve patients into four equal quartiles, labelled not expectant, slightly expectant, somewhat expectant, and highly expectant. They found that being highly expectant predicted significantly more severe nausea (on average and a greater peak level of nausea), whereas there was no difference between the other categories. This not only implied that response expectancies might only be problematic for people with the strongest expectancies, but also that they might be non-linear predictors, and thus, categorical measurement may most accurately capture their effects on subsequent toxicities. Furthermore, although it has been shown that effects are stronger if response expectancies are measured after a treatment has begun and toxicities have already been experienced (Colagiuri & Zachariae, 2010; Sohl et al., 2009), other potentially important variables are yet to be explored. These include the use of different recording methods (including patient report diaries that are completed at home versus survey packs completed at the hospital) and the timing of the follow-up measurement of side effects during cancer treatment. Given that individual studies are often considered interchangeably, and their findings are not consistent, these are all important considerations in clarifying the research on expectancies of cancer treatment toxicities.

Another potential issue is the homogeneity of the research field. In a multi-institutional study involving 938 patients, Hofman and colleagues (2004) investigated the formation of expectancies of a variety of cancer treatment toxicities. They found that the patients who formed the most expectancies of side effects were (1) women, (2) younger than 60 years of age, (3) had a tertiary education, and (4) were scheduled for chemotherapy. This demographic profile resembles that of most samples participating in the current literature, with a review of 14 studies finding 89% of patients across the studies were female, with an average age of 53.4 (SD = 5.81), just under half (44%) had graduated from college, and 86% of studies recruited patients treated with chemotherapy (Sohl et al., 2009). Thus, the majority of research in this area has been similar, likely because of the high numbers of women diagnosed with breast cancer (Torre et al., 2015), enabling recruitment of adequate sample sizes for individual empirical studies. Although the resulting knowledge is beneficial for this patient population, it is difficult to determine the scope of association between response expectancies and toxicities, particularly given that this subgroup of patients has been shown to form the most response expectancies (Hofman et al., 2004) – potentially inflating overall effect sizes of the response expectancy and side effect association, and limiting the generalisability of results.

1.3.2 Correlates of response expectancies

Although response expectancies have been shown to be unmediated predictors of subsequent side effects, they are not theorised to account for side effects in isolation. In fact, they frequently share explanatory power with other variables (Kirsch, 1999a). Thus, understanding the degree to which response

expectancies uniquely predict subsequent side effects (above and beyond other individual differences between patients), is necessary to establish whether they have prognostic value in assessing which patients are most at risk of developing severe side effect experiences. This could assist the design of education strategies, and prioritising preventative care to patients at greatest risk. Two of the most commonly measured covariates of expectancies of side effects and subsequent toxicities are anxiety and a patient's previous history of side effects.

1.3.2.1 Anxiety

Anxiety is associated with many cancer treatment toxicities (Andrykowski, 1990; De Vries, Van der Steeg, & Roukema, 2009; Zachariae et al., 2007a). It can predict response expectancy formation (Schnur et al., 2007) and in turn, can be influenced by response expectancies (Schoenberger, 1999). Roscoe et al. (2004) suggested that many studies linking anxiety to nausea might actually be measuring the impact of response expectancies; however, studies investigating both response expectancies and anxiety have produced mixed results.

Based on data that are now more than 30 years old (1982-1984), Andrykowski and Gregg (1992) accrued 65 patients with mixed cancer diagnoses scheduled for chemotherapy, they reported that post-treatment nausea was predicted by state anxiety, but not by nausea expectancies. However, research using multivariate models has found expectancies of vomiting independently predicted vomiting, but anxiety did not (Zachariae et al., 2007b). Another study of 101 breast cancer patients found that pre-surgery expectancies of pain, nausea, and fatigue not only uniquely predicted those experiences when tension-anxiety (measured through the Profile of Mood States) was also in the model, but also

partially moderated the effect of anxiety on all three toxicities (Montgomery et al., 2010b). Thus, it appears that anxiety and side effects response expectancies generally influence subsequent toxicity experience independently; however, expectancies of toxicities can also strengthen the relationships between anxiety and experience.

To investigate further, Whitford and Olver (2012) recruited a sample of 59 patients scheduled to receive chemotherapy. Univariate correlations revealed significant associations between response expectancies and anxiety for only 2 of the 20 measured side effects. The authors also investigated a specific cancer coping style, *anxious preoccupation*, as a correlate. The anxious preoccupation subscale in the Mental Adjustment to Cancer (MAC) scale (Watson et al., 1988), measures attendance to maximal (positive and negative) information in the face of a threat (specifically a cancer diagnosis). Associations between anxious preoccupation and response expectancies were revealed for all 20 chemotherapy-related toxicities ($r = .11$-$.34$), with 15 demonstrating a correlation greater than a small-to-moderate effect ($r > .20$). Moreover, there were no significant relationships between response expectancies and the opposite MAC coping style, *fighting spirit* – defined as ignoring or rejecting negative information about one's cancer diagnosis and treatment. This suggests that anxious preoccupation might be a more useful covariate of response expectancies than anxiety to consider in cancer patient groups. Potentially, patients with this coping style are more motivated than the average patient to research impending treatment and attend to information presented to them (i.e., during informed consent sessions). This could contribute to increased knowledge about, and a focus on possible toxicities which might in turn enhance (or explain) their formation of side effect expectancies.

Despite that novel, and potentially important finding, coping style has yet to be controlled for in multivariate analyses of side effect expectancies and subsequent experience.

1.3.2.2 Previous history of side effects

Another variable that has been consistently related to response expectancies is an individual's previous history of the side effect being measured. This stems from the suggestion that response expectancies may not be directly self-confirming cognitive states, but instead either reflect patients' misattribution of pre-existing symptoms to treatment, or reveal patients' knowledge about their propensity for side effects, based on what they have previously experienced. As suggested by Colloca and Miller "the patient does not come to the clinical encounter as a blank slate" (2011, p. 1860).

Indeed many symptoms exist before cancer treatment (Hofman et al., 2004). More than half of 1,015 patients with cancer reported pre-surgery fatigue, pain, sleep problems, depression, or memory loss (David, Montgomery, & Bovbjerg, 2006) and 84% of 1,129 patients with mixed cancer diagnoses reported some symptoms pre-radiotherapy (Hickok, Morrow, Roscoe, Mustian, & Okunieff, 2005). Thus, it is likely patients would have expectancies of symptoms that they are already experiencing, which would strongly relate to their continued reporting of these experiences during treatment. Therefore, baseline (pre-existing) symptoms are important predictors that need to be controlled in analyses of response expectancies and subsequent experiences.

Furthermore, Montgomery and Bovbjerg (2003) suggested that if response expectancies were based on social learning, patients that were naïve to a treatment

should form response expectancies through any previous general history relevant to that toxicity. However, in a sample of 80 chemotherapy-naïve patients, they failed to find a relationship between patients' lifetime histories of nausea, and expectancies of nausea. Similarly, other studies found that nausea expectancies remained independent predictors of nausea experience even when history of morning sickness (Roscoe et al., 2004), motion sickness (Colagiuri et al., 2008), and a general history of nausea/ vomiting experiences (Molassiotis et al., 2014) were statistically controlled. Although one study found nausea expectancies were no longer significant in a model which included a generalised history of nausea/ vomiting among other covariates (Molassiotis et al., 2013), a meta-analytic review (Colagiuri & Zachariae, 2010) reported the relationships between expectancies of nausea and experience remained significant in seven studies that controlled for a previous history of nausea. Thus, it appeared that response expectancies, and their association with experience, were predominantly independent of an individual's previous relevant general history. However, because this research has been limited to nausea and vomiting, no wider conclusions can currently be drawn.

Previous identical experience (i.e. classical conditioning) with the same treatment (including response expectancies measured after some treatment experience) has revealed a different pattern. Montgomery and Bovbjerg (2003) found nausea from a previous treatment cycle was the strongest predictor of subsequent nausea expectancies (explaining between 48% and 68% of the variance in response expectancy formation for Cycles 2-4 of chemotherapy). Sohl et al. (2009) also found significantly higher associations between side effect expectancies and toxicities when a treatment had previously been experienced,

compared to when it was novel and Schnur et al. (2007) concluded that generalised previous experiences did not predict the formation of response expectancies, but identical previous experience did influence their formation.

Therefore, it appears that *similar* past experiences do not necessarily affect the formation of response expectancies, or their influence on subsequent toxicities, but *identical* experiences (i.e., conditioning) do. However, this does not explain patients' response expectancy formation during a novel treatment. Furthermore, previous experience of the same treatment does not always appear to completely account for the influence of expectancies of side effects. Response expectancies have been found to perfectly mediate the effect of previous identical experience on pain (Montgomery & Kirsch, 1997). Similarly, opposing verbal information has been shown to reverse the effect of conditioned responses on a pain stimulus (Montgomery & Kirsch, 1997), an effect subsequently repeated elsewhere (Benedetti et al., 2003). This implies that the formation of side effect expectancies, and their relation to toxicity experiences are not entirely determined by previous identical experience.

1.3.3 Response expectancy-based interventions to reduce or prevent side effect experience

Response expectancies may be useful for more than the prediction of toxicity severity; they may also provide an opportunity to reduce side effect severity and/or incidence. This is evidenced by research demonstrating that patients' treatment responses can align with their response expectancies to a greater extent than what would be predicted medically (Roscoe et al., 2006). In one trial, a reduction in dental pain was recorded in patients who *believed* they

were receiving acupuncture, regardless of whether they were receiving real or fake (sham) treatment, whereas if patients *believed* they were receiving sham acupuncture, no benefits were experienced irrespective of the treatment condition (Bausell, Lao, Bergman, Lee, & Berman, 2005). In another investigation, patients given hidden analgesics required up to 50% more pain relief than those who witnessed administration of their analgesic and thus expected the benefits (Amanzio, Pollo, Maggi, & Benedetti, 2001). Moreover, patients told they were receiving a strong pain killer needed 16.4% less medication than patients told they might receive either a placebo or pain killer, and 33.8% less than patients who were told nothing (Pollo et al., 2001). Likewise, patients who were given a relaxant (but told it was a stimulant) reported significantly more muscle tension than those informed it was a relaxant, or those provided with an inert relaxant in the guise of a stimulant (Flaten, Simonsen, & Olsen, 1999). Thus, it appears that many intervention outcomes align with individuals' expectancies of future reactions, suggesting side effects could potentially be influenced by altering response expectancies. This is discussed in more detail below.

1.3.3.1 The placebo effect

Perhaps the most well-known manifestations of response expectancies are *placebo effects*; positive responses induced or intensified by an inert treatment or substance (i.e., a pill, injection, or acupressure band), that creates positive expectancies of improvement. Contrary to popular belief, placebos do not need to be 'given' to elicit placebo effects, they can also be shaped through the psychosocial context of a healthcare interaction (e.g., a verbal suggestion, the clinic layout, the practitioner attitude), leading some to suggest it may be more

accurate to call them 'meaning responses' rather than 'placebo effects' (Moerman, 2002a, 2002b). Response expectancies are one mechanism that appear to underlie placebo effects, alongside previous direct experience (classical conditioning) and desire (Finniss, Kaptchuk, Miller, & Benedetti, 2010; Frisaldi, Piedimonte, & Benedetti, 2015; Milling, 2009; Milling, Shores, Coursen, Menario, & Farris, 2007). Response expectancies have been shown to partially mediate and moderate the relationships between placebos and outcomes (Freeman et al., 2015; Stewart-Williams & Podd, 2004), and in some cases the strength of an individual's response to placebos corresponds to the strength of their response expectancies (Lidstone & Stoessl, 2007; Pollo et al., 2001).

Despite their evidenced utility for producing more positive outcomes, there are barriers to the use of placebos in a clinical environment, often due to a misunderstanding of what a placebo is. Some physicians consider placebos inherently deceptive (Moerman, 2002a), and have reported believing that their use signifies a failure on their part (Linde, Fässler, & Meissner, 2011). Moreover, placebos do not align with current understandings of informed consent. It is not currently ethical to prescribe treatment without any *specific* medicinal benefit, regardless of the benefit the placebo itself can provide (Miller & Colloca, 2011; Moerman, 2002a), nor to use deception in clinical encounters (Finniss et al., 2010). Thus, the use of placebos in clinical practice is promising, but not without problems to overcome.

However, novel research has indicated that patients can be informed that they are receiving a placebo and still experience treatment benefits (Berna et al., 2017; Carvalho et al., 2016; Colloca & Miller, 2011c; Kelley, Kaptchuk, Cusin, Lipkin, & Fava, 2012; Sandler, Glesne, & Bodfish, 2010), known as *open-label*

placebo treatment. A sample of 37 patients with irritable bowel syndrome (IBS) given a placebo, of which the participants were aware, showed significant overall improvements in IBS ($d = 0.53$) compared to 43 controls (Kaptchuk et al., 2010). Furthermore, 83 adults experiencing back pain were randomised into a control condition (treatment as usual) or an open-label placebo condition. The participants receiving the placebo, aware it was a placebo, still experienced a significant reduction in back pain (revealing moderate-to-large effect sizes; Carvalho et al., 2016). Indicating placebos do not need to be deceptive to be effective. This is a promising area of research still in its infancy.

1.3.3.2 Hypnosis

Another well-known area in which response expectancies play an important role is hypnosis (Kirsch, 1999b; Milling, 2009; Montgomery et al., 2010a). *Hypnosis* is generally defined as the induction of a dissociative state in an individual, and this altered consciousness in collaboration with suggestive directions (usually verbal) are utilised to elicit a response. Response expectancies have been shown to be a consistent correlate of hypnotisability (suggestibility), and changes to response expectancies correspond to changes in hypnotic responding (Kirsch, 1999b). Furthermore, response expectancies play a mediating role (perfect and partial) of hypnotic effects (Kirsch, 1999b; Milling, 2009).

Hypnosis was being utilised to reduce cancer treatment-related side effects before the conceptualization of response expectancies as a separate form of expectancy (Zeltzer, Kellerman, Ellenberg, & Dash, 1983), and has been shown to reduce a range of cancer-related toxicities, including nausea, vomiting, and hot flashes, across many patient groups (Richardson et al., 2007; Roscoe et al., 2006).

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In a study of 20 female patients undergoing biopsy for possible breast cancer, Montgomery, Weltz, Seltz, and Bovbjerg (2002) reported those who had received hypnosis, with toxicity focused positive suggestions, experienced significantly less pain and distress compared to a control group undergoing the same surgical procedure. They also found that expectancies of pain partially mediated the relationship between hypnosis and pain reduction, and expectancies of distress fully mediated the relationship between hypnosis and subsequent distress. Later, a larger study was undertaken (Montgomery et al., 2010a), with 200 women scheduled for surgery for breast cancer. The authors found that expectancies of pain and fatigue partially mediated their reduction following hypnosis, but this did not occur for expectancies of nausea. They suggested this latter finding may be because nausea does not always relate to its response expectancies until later in treatment.

Thus, hypnosis is another promising intervention, but again there are limitations to its potential utility. There are issues with the accessibility of hypnosis within hospitals, and external referrals are not commonly utilised by patients (Kessler, 2005). Furthermore, stigma and misunderstandings attached to hypnosis prevent its uptake by some health-care providers (Whorwell, 2012) and patients (Coe, 1993; Yu, 2004). Lynn, Vanderhoff, Shindler, and Stafford (2002) found that when hypnosis was characterised as a trance state, individuals were less responsive than when it was described as cooperation between the individual and responder, proposing this resulted from a common reluctance to be in a different state of consciousness.

However, this latter finding also raises a potential benefit of hypnosis, supported by sociocognitive theories which posit that dissociation is not

necessary to achieve the responses to suggestion during hypnosis (Kirsch, 1999b).

When hypnosis was described to participants as a non-deceptive placebo, there

was no reduction in responsiveness than when a standard rational was used

(Accardi, Cleere, Lynn, & Kirsch, 2013). Moreover, although the relaxation

process (creating a dissociative state) has been found to moderately enhance

responses to suggestion, it is not necessary for hypnotic effects (Braffman &

Kirsch, 1999; Kirsch, 1999b; Lynn, Laurence, & Kirsch, 2015; Milling, Kirsch,

Allen, & Reutenauer, 2005), and in some cases it can reduce the effects of

suggestion (Braffman & Kirsch, 1999; Lynn et al., 2002). Furthermore, responses

to non-hypnotic suggestion have been shown to be the strongest predictor of

hypnotic responding, followed by response expectancies (Braffman & Kirsch,

1999). Thus, non-hypnotic suggestion appears to be beneficial in reducing

toxicity outcomes through changes to side effect expectancies.

1.3.3.3 Non-deceptive suggestion as a response expectancy-based intervention

Taken together, placebos (by means of deceit) and hypnosis do not appear

to be essential for the responses they produce, and verbal and non-verbal

suggestion alone appear adequate to alter participants' subsequent outcomes (e.g.,

nausea, blood loss, bowel movements, and neural activity; Benedetti et al., 2007;

Roscoe et al., 2006), through changes in response expectancies (Braffman &

Kirsch, 1999). Suggestion entails what is said to patients, as well as the context of

a clinical encounter, the specific treatment (i.e., a pill, injection, or cream), the

colour and shape of a tablet, the attitude of a practitioner, and so on. Therefore,

this might provide a simple, ethical, and cost-effective way to reduce toxicity

experience through reduction in expectancies of side effects. Unintentional suggestions are already common in healthcare settings (Michael, Garry, & Kirsch, 2012); however, intentional and direct suggestion (Kirsch, 1999b) may intensify side effect reduction.

Colloca and Miller (2011c) highlighted that the way information is presented to patients, through necessary informed consent, might influence the experience of side effects. For example, framing statistically equivalent information in different ways has been shown to influence the incidence of experienced side effects (O'Connor et al., 1996). In a sample of 292 cardiac patients, the researchers specifically used *valence framing*; presenting the same statistical information in a positive (e.g., "40% of patients get a sore arm") or negative (e.g., "a side effect of the vaccination is a sore arm; however, 60% of people do not experience this side effect") frame (Levin, Schneider, & Gaeth, 1998). Although the main aim of the study was to determine the impact of valence framing on patients' decision-making (a common use of framing), the authors found, in a side investigation, that patients in the positive framing group had fewer toxicities (subjectively reported) and sick days (objective) in the subsequent three days (O'Connor et al., 1996). Thus, framing appears to be one way through which expectancies of side effects and subsequent reduction might occur through small changes to suggestion.

1.4 The research literature: limitations and future directions

Based on this review of the literature, a number of limitations and promising research endeavours have been identified. In this section I summarize these limitations and ideas, to present the central aims and research questions

within this thesis, and provide rationales for the four study designs reported in the remaining chapters.

1.4.1 Summary of gaps in the literature to date and the specific chapter aims

1.4.1.1 Methodological and measurement differences

Perhaps the greatest limitation within the current research on expectancies of cancer treatment-related side effects is its similarity of investigations (with regard to toxicities, samples, and treatment modalities). Few toxicities have been comprehensively investigated. Although a previous meta-analysis (Sohl et al., 2009) worked to address this problem by locating and synthesising existing research, the evidence remains conflicting. A number of studies within this review (see Section 1.3) found response expectancies were significantly related to the experience of some toxicities, but not others, even across similar samples and treatments. Furthermore, there is evidence that different placebo and nocebo effects (which response expectancies have been found to underpin) work through different mechanisms (Benedetti et al., 2011; Finniss et al., 2010). Thus, it is far from clear whether there is a general influence of response expectancies on cancer treatment-related toxicities, or whether this effect is different across individual side effects. This also highlights uncertainty about whether expectancies of more abstract or ambiguous side effects (e.g., nausea versus the more 'objective' toxicity of vomiting) have stronger predictive effects, as theorised (Kirsch, 1985). Although this idea has a conceptual basis (the role of response expectancies in schema activation), and has been supported by some studies (e.g., Roscoe et al., 2000a), research including more objective toxicities (i.e., vomiting) have also

demonstrated significant relationships between their response expectancies and experience (Cobeanu, 2013; Zachariae et al., 2007b). Therefore, this proposed distinction requires further clarification.

Chapter 2 of the thesis systematically addresses the current state of knowledge, by reporting a meta-analysis, designed to investigate the effect of response expectances on side effect experiences across a number of studies. This was deemed necessary given the length of time since the previous meta-analyses (Colagiuri & Zachariae, 2010) and the greater number of studies since Sohl et al. (2009) considered specific side effects. This allowed exploration of differences between the effect sizes of individual side effect response expectancies, and a comparison of objective and subjective side effects. The aim of the meta-analysis was to inform future potential intervention programs whether expectancies of all toxicities can be generally targeted, or whether individual side effects (or groups of side effects) are independent. If the latter was the case, another aim was to discover which toxicities showed stronger associations with their response expectancies. In addition to the major aims, the influence of methodological aspects on pooled effect sizes was explored, including the impact of the use of different measures for both response expectancies and side effect experiences; measurement contexts for both response expectancies and side effects, including measurement occurring in the clinic, at home (through patient report diaries); and the number and timing of response expectancy and follow-up experience measurements. It was considered important to determine whether and how different methodology affects the reported strength of side effect expectancy and experience relationships, to assist with future research.

Next, *Chapter 3* presents a psychometric study, which specifically explored whether differences in administration of the most commonly used measure, the 5-point SEEQ was related to different responding. This was analysed through a psychometric exploration of the SEEQ, and direct comparison of responses on this scale with another commonly used scale; visual analogue scale (VAS), in a clinical sample.

1.4.1.2 Patient groups and treatment modalities

Another limitation, based on the homogeneity of current research base, is the lack of available information for diverse groups of patients. Accordingly, firm conclusions can currently only be made about the influence of expectancies of cancer treatment-related side effects on experience for middle aged female patients undergoing chemotherapy. Based on this literature review (Section 1.3), studies including patient samples with mixed diagnoses have often reported non-significant results. Whether this outcome reflects measurement of expectancies of toxicities across pooled diseases, with symptomatic differences, or whether this is evidence that response expectancies are not influential beyond patients treated with chemotherapy for breast cancer, is not known. Moreover, although men report fewer response expectancies (Hofman et al., 2004), they have also been found to demonstrate stronger nocebo responses (Klosterhalfen et al., 2009). Therefore, evidence concerning response expectancies in men is needed. Similarly, although older patients (>65 years of age), report fewer response expectancies (Hofman et al., 2004), they are at higher risk of medication interactions (Butkiewicz, Restrepo, Haines, & Crawford, 2016), and most likely have a higher degree of comorbid illnesses (Edwards et al., 2014). Thus, they may

potentially have the most to gain from development of toxicity reduction interventions that do not involve additional medications. However, there has been minimal research investigating the influence of cancer treatment-related side effect response expectancies in older cohorts, so additional research in geriatric groups is a valuable first step. Furthermore, the majority of cancer treatments investigated in this field of research appear to be for expectancies of chemotherapy-related side effects and their impact on experience. Studies investigating surgery-related toxicities are available but limited (Montgomery & Bovbjerg, 2004; Montgomery et al., 2007; Montgomery et al., 2010b; Montgomery et al., 2002; Schnur et al., 2007), and to my current knowledge, there are no published studies specifically directly investigating the impact of expectancies of radiotherapy toxicities in isolation. Only investigations of response expectancy formation, pre-intervention trials, or adjuvant chemotherapy and radiotherapy have been identified. The most common radiotherapy, *external beam radiation therapy* (EBRT), involves short (approximately 15 minute), repetitive interventions at localised tumour sites, every weekday (i.e. 5 days per week). This localised, external treatment is therefore very different to therapies such as chemotherapy; where treatment is systematic, breaks between cycles occur, and common knowledge of the procedure and its effects on the body are more commonly known. It also differs greatly from the usually isolated and acute provision of surgery (Poirier, 2013). It follows that response expectancies could potentially play an important role within radiotherapy, particularly given research evidence that previous identical treatment can play a strong role in response expectancy formation (Montgomery & Bovbjerg, 2003).

Chapter 4 therefore reports a clinical, prospective longitudinal study that investigated the influence of expectancies of toxicities on subsequent experience in a group of older men who were treated with a similar dose of EBRT for prostate cancer. This investigation was designed to determine whether the previously demonstrated influence of response expectancies could be replicated in a novel sample (in terms of gender, age, and treatment modality), yet to be studied. Thus, indicating whether response expectancies are influential across a greater variety of treatment and patient groups. In multivariate analyses investigating side effect response expectancies, and subsequent experience, relevant covariates, outlined in Section 1.3.2 (e.g., anxiety, coping style, baseline levels of toxicities), were controlled.

1.4.1.3 The influence of framing on response expectancy formation and side effect experience

Finally, understanding alternative methods through which toxicity expectancies can be harnessed in order to better manage or reduce subsequent side effects is a necessary future research direction. Although hypnosis and deceptive placebos are promising interventions (Kirsch, 1999b), their translation into clinical practice can raise ethical and practical problems, as detailed in Section 1.3.3. However, there is evidence that suggestion alone, without either deceit or hypnotic induction, may influence patients' response expectancies and thus subsequent side effect experiences (Braffman & Kirsch, 1999; Roscoe et al., 2006). For example, if healthcare information could be presented (i.e., framed) in such a way that toxicity expectancies and subsequent experience were reduced, this could provide simple, cost-effective, and universal reduction strategies.

Framing has been found to influence side effect experience (O'Connor, Pennie, & Dales, 1996); however, whether the underlying mechanism is a reduction in response expectancies has not been established.

Knowledge about the influence of information presentation methods is not only beneficial for the potential to reduce expectancies of toxicities and experience, but it is also essential to determine the impact that current informed consent practices are having on patients' experiences in healthcare systems. Informed consent mandates that all potential toxicities be explained to patients before they begin a new medication or other treatment, and further checked that individuals understand the information provided (Faden & Beauchamp, 1986). This disclosure can be enough to produce the negative toxicities discussed with a patient (Miller & Colloca, 2011; Wells & Kaptchuk, 2012). Thus, understanding the impact of such discussions, as well as whether small changes to the presentation of this information, might be protective, is an important step in this area of research given the lack of simple, universal interventions.

Chapter 5 therefore reports a randomized controlled experimental trail investigating the potential ability of a cognitive technique, valence framing*,* to influence response expectancy formation and in turn, subsequent experiences. Because this study was novel, it was undertaken in a healthy sample, using a safe pain induction technique - the cold pressor test (CPT) - a highly structured, controlled experimental technique commonly utilised as an analogue medical treatment. Participants were randomly divided into two groups, and presented with statistically equivalent information, in either a positive or negative frame for comparison. Based on successful techniques previously utilised in similar contexts (Heisig, Shedden-Mora, Hidalgo, & Nestoriuc, 2015; O'Connor et al.,

1996), the impact of this intervention on the subsequent formation of expectancies of CPT reactions, and the post-intervention experience of these reactions were assessed. Again, important correlates identified in Section 1.3.2 were incorporated in multivariate analyses.

1.4.2. Thesis aim and research questions

The research presented in this thesis was designed to investigate research to-date, and to further address research limitations by exploring the scope and utility of response expectancies in cancer treatment for predicting, and potentially reducing side effect experiences. This overarching aim led to the development of three specific research questions:

1. Could methodological differences in research regarding expectancies of cancer treatment-related toxicities (and subsequent experience) explain variability in individual study outcomes, and can results obtained from different measurement methods be discussed interchangeably?

2. Does the influence of response expectancies on toxicity experience extend to alternative side effects, and novel groups of patients and treatment regimens?

3. Can the modified presentation of information, incorporating non-deceptive, and non-hypnotic suggestion, influence individuals' expectancies of side effects and in turn, reduce toxicity severity?

1.5 Conclusions

Despite the possible benefits of investigating response expectancies for predicting and potentially reducing cancer treatment side effects, gaps and contradictions in our current knowledge are evident. Expectancies of toxicities

may present an opportunity to better understand patients' risk profiles However, even more valuable, they may inform tailored interventions that could be as simple and cost-effective as updating informed consent procedures across the entire healthcare system (and for all patients), potentially negating the need for individualised, complex interventions. The goal of this thesis is to inform clinical practice, and reignite research on response expectancies specifically in the area of cancer treatment-related toxicities, through a new literature review and empirical studies.

Chapter 2: Meta-analysis

Cancer Treatment Side Effects: A Meta-Analysis of the Relationship between Response Expectancies and Experience

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Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis

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Preamble

There is a considerable body of research indicating that expectancies of cancer treatment side effect influence patients' experience of subsequent toxicities. However, based on the preceding chapter, it is apparent that there are inconsistencies in the literature. Two meta-analyses (Colagiuri & Zachariae, 2010; Sohl et al., 2009) have compiled research on expectancies of nausea, pain, vomiting, and fatigue, finding small to moderate associations with subsequent experiences.

The most recent review ceased data collection in June 2009 (Colagiuri & Zachariae, 2010), and since then there has been new research published, with a wider variety of toxicities measured, and methodologies (including measurement tools) utilised. Thus, this study was designed to explore the influence of response expectancies across a range of side effects, and contrasting methodological differences, to determine (1) whether the relationship between response expectancies and experiences of side effects remained, (2) whether expectancies of different side effects showed different associations with their subsequent experience, and (2) whether methodological and measurement differences altered this association.

Manuscript

Abstract

Context. Although previous research has, overall, suggested a moderate relationship between response expectancies (REs) and cancer treatment-related side effects, empirical results have been mixed.

Objectives. We aimed to further explore these relationships, hypothesizing that REs would predict subsequent toxicities with the inclusion of more recent studies, across a broader range of side effects, while incorporating the impact of potential moderators including patients' experience with treatment and measurement methods. We further investigated the impact of REs across individual toxicities.

Methods. A systematic search and analysis were conducted across four databases (PsychInfo, PubMed, CINAHL, Embase) and reference lists, from 1985 to February 2016. This provided 27 eligible studies with 4474 participants, through which the main analysis, moderator analyses, and individual side-effect analyses were explored.

Results. REs were moderately related to side effects overall ($r = .26$), and effect sizes were significantly influenced by sample diagnostic homogeneity, whereas differences between type and timing of measurement showed trends. Of the 16 toxicities examined, 15 demonstrated significant relationships between REs and side-effect experience, with hair loss ($r = .48$) the strongest. No clear difference emerged between objective and subjective side effects; however, significant differences across individual toxicities were revealed.

Conclusion. Findings support a relationship between REs and a wide range of subsequent side effects, yet differences between individual RE-toxicity associations emerged. These findings provide direction for the measurement of side effects and REs, and support REs as potential targets for intervention during the informed consent process.

Keywords: Medical oncology, informed consent, chemotherapy, toxicity, placebo response

With advancements in cancer detection and treatment and better survival rates, management and reduction of treatment associated side effects (toxicities) are increasingly important in maintaining patients' quality-of-life and optimizing outcomes. Pharmacologic attempts to reduce side-effect severity are often costly (Hassett, O'Malley, Pakes, Newhouse, & Earle, 2006), toxicity specific (Roscoe, Morrow, Hickok, & Stern, 2000b), and can produce drug interactions (Zhang, Wang, Wang, & Xu, 2008) and additional side effects (Navari, 2013; Zhang et al., 2008). Consequently, nonpharmacological predictors of toxicities, such as response expectancies (REs), are important to consider as potential methods of reducing side-effect severity.

REs (Kirsch, 1985) refer to individuals' anticipations of their own nonvolitional (automatic) reactions to stimuli or behaviour, e.g., the expectancy of becoming nauseated after chemotherapy. Research has established that REs can account for side-effect severity beyond what is explicable pharmacologically (e.g., pain relief resulting from ingestion of an inert substance; Kirsch & Lynn, 1999), because of their theorized direct link with subsequent experience (Kirsch, 1997; Kirsch & Lynn, 1999). Currently, a number of potential predictors of REs (Miller & Colloca, 2011; Montgomery & Bovbjerg, 2003; Montgomery et al., 2007; Montgomery et al., 2010a; Redd, Montgomery, & DuHamel, 2001; Roscoe et al., 2006; Roscoe et al., 2003) are being investigated as possible methods of reducing REs; thus, better understanding of how REs influence side-effect severity, and under which circumstances, may assist the development of pre-treatment strategies to minimize and manage toxicities. Research into the RE-toxicity relationship to date has demonstrated mixed results.

Although early investigations into the relationship between REs and side-effect experience (Cassileth et al., 1985) did not predominantly identify significant relationships, subsequent empirical results have varied. Some studies reported no significant relationships (Andrykowski & Gregg, 1992; Higgins et al., 2007; Ryan et al., 2007) nor independent predicative ability of REs (Molassiotis et al., 2013). Other investigations concluded that REs predicted some toxicities, but not all (Olver et al., 2005; Rhodes et al., 1995; Whitford & Olver, 2012) found significant links overall between REs and a range of toxicities (Colagiuri & Zachariae, 2010; Sohl et al., 2009), and/or found REs were stronger predictors of side effects than a range of other established predictor variables (Booth et al., 2007; Haut et al., 1991; Roscoe et al., 2000a).

The body of research on RE-toxicity associations has previously been synthesized in two separate meta-analyses. In 2009, Sohl et al. (2009) compiled 14 studies, totalling 1445 participants (before June 2008) treated with chemotherapy ($n = 12$) and surgery ($n = 2$). They identified significant relationships between REs and pain ($r = .58$), fatigue ($r = .46$), nausea ($r = .32$), and vomiting ($r = .19$) and an overall moderate and significant relationship between REs and all side effects combined ($r = .36$). Differences in patients' treatment histories and the timing of side-effect measurement demonstrated significantly different pooled effect sizes, whereas the use of different measurement scales did not. Although this meta-analysis provided support for the impact of REs on subsequent side effects, and some explanations for divergent findings among previous studies, at that time very few published studies had described side effects other than nausea or utilised differing assessment scales for both REs and side effects. Thus, the generalizability of these findings across

multiple side effects, and the conditions under which REs are reliable predictors, could not be examined in depth.

Subsequently, in 2010, Colagiuri and Zachariae reviewed 17 studies published up to June 2009 with 2400 participants being treated with chemotherapy. Examining the relationship between REs and nausea in more detail, they found a small effect of REs on subsequent nausea ($r = .18$), which was influenced by whether studies had statistically controlled for other predictor variables but not gender or cancer type. Unlike in the previous meta-analysis by Sohl et al. (2009), Colagiuri and Zachariae (2010) found no association between effect sizes and either measurement timing or previous history of nausea. Although these reviews had different aims, both studies mainly investigated the impact of REs and nausea; therefore, the difference between the study results is surprising.

Sample and methodological differences between studies may help explain the varying results. When only considering nausea (Colagiuri et al., 2013), no significant differences were found between samples with homogeneous diagnoses (i.e., only breast cancer) and studies including patients with heterogeneous (different) diagnoses. Nevertheless, when observing the literature of REs and all side effects, most studies reporting nonsignificant relationships for some, or all, side effects analysed heterogeneous samples (Andrykowski & Gregg, 1992; Olver et al., 2005; Rhodes et al., 1995; Ryan et al., 2007; Whitford & Olver, 2012), whereas studies with homogenous samples tended to report consistently significant effects (Booth et al., 2007; Montgomery & Bovbjerg, 2000, 2004; Montgomery et al., 1998; Roscoe et al., 2000a; Watson et al., 1998). This pattern

may indicate the potential of specific investigation into whether effects may be moderated by diagnostic heterogeneity.

Empirical investigations of the influence of patients' prior experience (specifically treatment naivety) have also reported inconsistent results. Kirsch theorized (Kirsch, 1985; Kirsch & Lynn, 1999)(5, 6) that if REs resulted in increased side effects, subsequent expectancies of this side effect would become stronger. Consequently, studies that measure the RE-side-effect relationship in patients with previous experience should obtain stronger effects. This has been observed in some (Montgomery & Bovbjerg, 2000; Sohl et al., 2009) but not all studies (Colagiuri & Zachariae, 2010).

Additionally, researchers have used different tools to measure REs, including categorical scales, Likert scales, and 10-point Visual Analogue Scales (VAS). Although Sohl et al. (2009) concluded that the RE scale distinction did not influence outcomes, research using a wider range of scales has subsequently become available, permitting more comprehensive investigation of measurement types. Differential measurement, including take-home diaries or in-clinic assessments, and number of follow-ups remains to be explored.

Finally, as first investigated by Sohl et al. (2009), it is important to understand how REs predict multiple side effects and whether different patterns emerge for specific individual toxicities; now additional studies and side effects are reported in the literature. This can provide information about whether REs can be treated as general indicators of future side-effect experience or whether they are only informative for specific side effects. Kirsch (1985) theorized more ambiguous stimuli are associated with greater expectancy effects. Based on the mind-body identity assumption (Kirsch, 1985), REs and subjective side effects

are directly linked (unmediated; Kirsch, 1997; Kirsch & Lynn, 1999), whereas physical responses are indirectly linked to REs through corresponding subjective expereince. For example, pain cannot be separated from its perception; thus, anticipation of its occurrence is directly related to its experience. Alternatively, an objective side effect, such as vomiting, is indirectly linked to its expectancy through a subjective experience (i.e. nausea). This distinction has been empirically supported, with nausea more commonly related to its RE than vomiting (Olver et al., 2005; Whitford & Olver, 2012). Yet significant relationships between some objective side-effect REs and experience have been reported (Rhodes et al., 1995; Roscoe et al., 2004; Whitford & Olver, 2012; Zachariae et al., 2007b). Thus, it remains to be determined whether more subjective, ambiguous toxicities (e.g., nausea) have stronger links to their REs than toxicities with a physiological correlate (e.g., vomiting).

In summary, we aimed to update and extend previous research by meta-analysing the relationship between REs and experience for a wider range of side effects than previously reported, in a larger number of studies using more diverse measurement methods. We hypothesized a positive relationship between REs of side effects and subsequent experience in general. We further hypothesized that these relationships would be affected by sample heterogeneity, whether patients were naïve to the treatment (i.e., had no previous experience with the cancer therapy), and differences in the method and timing of measurement (of both REs and side effects). Finally, we aimed to explore the strength of effects between REs of individual side effects and their subsequent experience, to determine whether different patterns emerged for subjective vs. objective toxicities, given previous equivocal findings.

Methods

Literature Search

In accordance with previous reviews (Colagiuri & Zachariae, 2010; Sohl et al., 2009), the PubMed, PsychInfo, and CINAHL online databases were searched electronically. Additionally, a biomedical database, EMBASE was searched. The aim was to identify studies investigating the relationships between pre-treatment REs of side effects and subsequent post-treatment commencement experience, in patients being treated for cancer. Searches were conducted between August 2015 to February 2016 and were limited to studies published during or after 1985. This was when REs were first conceptualised (Kirsch, 1985), and a check of the literature (through reference list and database searching) before this date showed no prior relevant studies, which had not used the specific term "response expectancies". Broad search terms, singular and plural terms, and spelling variations were used (see Supplementary Table 1 available from jpsmjournal.com), to ensure substituted terminology was detected. Reference and publication lists of key authors and journals were also searched manually.

Inclusion Criteria

Eligible studies were required to report findings for adult cancer patients (>18 years), undergoing cancer-related surgery, radiotherapy, or chemotherapy (Sohl et al., 2009), with a curative intent. Studies reporting excisional lumpectomy or biopsies were included because investigational and interventional surgical procedures do not differ in the context of potential side effects (Montgomery & Bovbjerg, 2004; Montgomery et al., 2010b). Studies were

required to be published in English in a peer-reviewed journal and provide adequate statistical information to calculate an effect size. Although language was restricted to English (to ensure studies could be coded precisely), no cultural restrictions were placed on eligible studies during the search. Instead, country of origin was coded and culture was considered in the analyses. Eligible studies measured treatment-related RE, then subsequent experience of the same side effect(s) either during or following treatment, or before subsequent treatment in a prospective design. These criteria permitted investigation and comparison of a range of side effects including anticipatory effects, such as nausea, a commonly investigated side effect in previous RE research (Hickok et al., 2001; Hofman et al., 2004; Montgomery & Bovbjerg, 2001; Montgomery et al., 1998; Watson et al., 1998).

Study Selection

Studies were reviewed and coded by the primary author (E. D.). A subset of studies (25%) were also independently reviewed by a co-author (H. W.) and showed a high level of consistency; therefore, the remainder were coded by E. D. (Bown & Sutton, 2010). Ambiguities were discussed by the full panel of authors until a consensus was reached. Following PRISMA and MARS meta-analysis reporting guidelines (American Psychological Association, 2009; Moher, Liberati, Tetzlaff, Altman, & Group, 2009), specific study characteristics (e.g., measurement timing, and type, sample characteristics, side effects, etc.) and report characteristics (e.g., language, year published, etc.) were extracted using a study-specific coding form. Studies did not undergo critical appraisal because the inclusion criteria required a specific sample and study design; thus,

methodological differences were not present (CASP, 2014). Similar multiple scores for the same outcome variable (e.g., at multiple time points) or very similar outcome variables (e.g., nausea severity and unpleasantness) that were provided in a study, were averaged into one effect size statistic (e.g., nausea; Higgins & Green, 2008). If data from the same sample were presented in separate studies, the study with the largest sample size was selected. In one instance, two sample sizes ($n = 77$ and $n = 55$) were comparable, so the study examining more than one side effect was selected, in line with the aims of the meta-analysis. If published data were insufficient to determine an effect size, authors were contacted to request additional information. If data were not available, the effect size was, where possible, extracted from multivariate analyses using formulae published by Peterson and Brown (2005) in following substantial evidence Beta values and ESrs are highly related ($r = .75$), in an attempt to reduce sampling error (Peterson & Brown, 2005). If these analyses were not possible, studies were excluded. Sensitivity analyses, which involve re-running an analysis without an imputation, were run to ensure results did not change based on this decision (Higgins & Green, 2008; Rosenthal, 1979).

Moderators

In addition to the main analysis, we assessed the influence of moderators on pooled effect sizes. To ensure analyses were informative, moderators were only investigated if they were reported in three or more independent studies. Finally, each side effect was analysed separately, to explore any differences in magnitude and whether they related to objectively and subjectively perceived side effects.

Several variables did not meet criteria for inclusion in moderator analyses. Patient gender had too similar groupings to homogeneity distinctions to produce informative results, there were not adequate numbers of surgery and radiotherapy to investigate treatment type, and only two studies reported measurement of RE on multiple occasions.

Publication Bias

The file drawer problem (Rosenthal, 1979), a bias towards publication of studies finding statistically significant results, can potentially reduce the validity of meta-analytic findings (Borenstein, Hedges, Higgins, & Rothstein, 2009b; Lipsey & Wilson, 2001; Rosenthal, 1979). Accordingly, an investigation of potential publication bias, and an estimated correction for this, was undertaken (Borenstein, Hedges, Higgins, & Rothstein, 2009a). Funnel plots were inspected to examine whether publication bias might be present (evidenced by asymmetry; a pattern between sample size and results). Rosenthal's failsafe number (1979) was calculated and compared with a criterion value ($N_{fs} > 5*K+10$) to estimate the number of unpublished studies with an effect size of zero that would have to be missed to reduce the observed effect size to a nonsignificant result. Additionally, Orwin's failsafe number (1983) was calculated (Lipsey & Wilson, 2001) to estimate how many studies would need to be missed to reduce the effect size to a number that is no longer meaningful, determined in this case by a small correlation coefficient ($r \leq .10$; Cohen, 1988). The criterion for a robust effect is a greater failsafe number than the number of studies ($N_{fs} > N_{studies}$). The trim and fill analysis by Duval and Tweedie (2000), which corrects for asymmetry of the funnel plot, was then run for any studies that were found to be unreliable in the

previous analyses. Results of this analysis are presented in the text alongside observed effects.

Data Analysis

Analysis of data was performed using Meta-analysis with Interactive eXplanations (MIX) 2.0 software (Bax, Yu, Ikeda, Tsuruta, & Moons, 2006). Subgroup and trim and fill analyses were tested with Comprehensive Meta-analysis Version 3 (Borenstein, Hedges, Higgins, & Rothstein, 2005). Orwin's Failsafe analyses were calculated by hand (Lipsey & Wilson, 2001). Effect sizes were amalgamated to ensure only one effect size was contributed by each study to the main analysis, so the independence assumption was not violated. Empirical studies with an intervention included the control group or pre-intervention effect sizes only, to avoid including any REs and side-effect experience post-measures affected by an intervention.

The primary effect size index selected was a Pearson's correlation (ESr), a measure of the magnitude of the relationship between two continuous variables. In some studies, ESrs were directly available as univariate correlations: in others, they could be extracted. Specifically, estimation formulas (Lipsey & Wilson, 2001) were used for studies presenting results as means and SDs, odds ratios, or Chi-square tests of side effects for groups. One study had ESr imputed from Beta scores using formula by Peterson and Brown (2005). Confidence ratings (a ranking of confidence in the accuracy of the calculated ESr; Lipsey & Wilson, 2001) were recorded alongside ESrs to test their relationship with effects through correlation analyses. Artificially dichotomized RE measures were not corrected because not all studies provided adequate information to make corrections, and

numbers above and below the dichotomization differed between side effects; therefore, accuracy and consistency across produced ESrs could not be ensured (Cohen, 1988).

ESrs were transformed to Fisher's Z scores (a standardized normal metric) and weighted by their inverse variance, assigning more weight to studies with larger samples. Weighted scores were averaged, before being transformed back into ESrs for ease of interpretation and reporting. Confidence intervals, z-scores and p-values were also calculated in the pooled analysis. Homogeneity statistics were calculated using Cochrane's Q statistic, and the I^2 statistic. A significant Q statistic indicates that the variance associated with the ESr is significantly greater than sampling error alone (Borenstein et al., 2009a), supporting the use of the random-effects model and indicating that there may be methodological variance to explore. The I^2 statistic provided the proportion of variance potentially measurable (not random; Borenstein et al., 2009a). Interpretation of ESrs followed thresholds set by Cohen (1988) for a Pearson's correlation, suggesting a small effect is .10, a medium effect is .30, and a large effect is .50.

To explore the impact of potential moderators, subgroups were synthesized and then group differences were analysed using metaANOVAs (Lipsey & Wilson, 2001). Independent side effects were compared by observation of their 95% confidence intervals (CIs); cross-over of confidence intervals indicated that the side effects were considered not statistically significant (Higgins & Green, 2008).

Results

Study Selection

See Figure 1 for the inclusion and exclusion flow diagram. The database search produced 10,094 records (within date and language limits): 7749 from PubMed, 1085 from PsychInfo, 834 from CINAHL, and 426 from Embase. Reference list screening retrieved an additional 88 records. After removing duplicates, the remaining records were screened. Most were not relevant or were not a prospective study design. Full-text articles were then screened, excluding any that did not measure both REs of side effects and subsequent experience or were not the correct study designs. The remaining studies were assessed in greater depth, with most not meeting methodological criteria or insufficient information to calculate an ES*r*. This process eventuated in the inclusion of 27 studies in the final analysis and review.

Demographics

There were 4573 participants across the 27 studies, with an average sample size of 169.4 ($SD = 185.1$). The mean age of participants across studies was 53.5 years ($SD = 5.1$). Most studies ($n = 15$, 55.5%) did not indicate the location where participation occurred, but of those that did, 10 (83.3%) studies were located in (mostly) Western locations (e.g., United States, Australia, Europe), and two (20.0%) were located in (mostly) Eastern locations (e.g. Hong Kong, China). Similarly, 18 (66.6%) did not report whether the participants were inpatients or outpatients, but of those that did, eight (88.9%) were outpatients, no groups were exclusively inpatients, and one (11.1%) study had both inpatients and

outpatients in the sample. Twelve studies (44.4%) reported that patients were

taking antiemetic medication (preventing vomiting and nausea), ranging from a

standard dosage to as-required, and 15 (55.5%) did not provide this information.
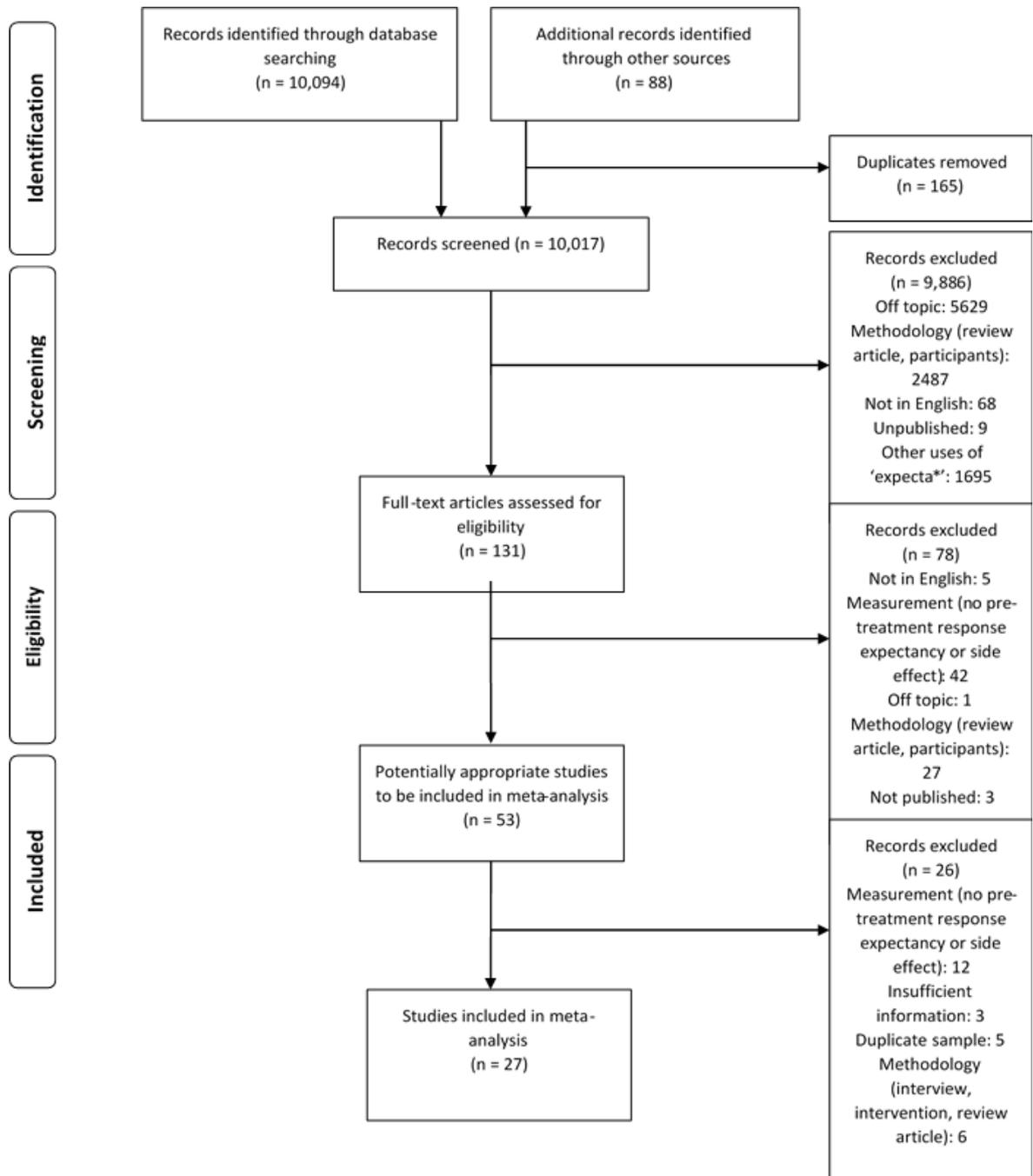
Figure 1. PRISMA flow diagram of study inclusion and exclusion process

Demographics and moderator information are available in Table 1. There was a similar number of studies with only women ($k = 14$, 33.9%) and mixed gender samples ($k = 13$, 48.1%), the latter with an average of 62.0% female participants. Slightly more studies recruited samples with a range of cancers ($k = 15$, 55.5%) than only breast cancer ($k = 11$, 40.7%), and one (4.0%) investigated only gynaecological cancer. Thus, 15 (55.6%) included studies had diagnostically heterogeneous cohorts and 12 (44.4%) had homogenous samples. Most patients were only having chemotherapy treatment ($k = 23$, 85.2%), but in two studies (7.0%), patients had surgery, in one (4.0%) they had radiotherapy, and one (4.0%) either chemotherapy or radiotherapy. Most patients were treatment naïve ($k = 18$, 66.6%). This was not a defined criterion in four studies (14.8%), and not reported in five (18.5%). Various scales were utilised to measure REs, including different versions of the same scales (e.g., 3-point vs. 10-point Likert scales). REs were generally only measured once, pre-treatment ($k = 25$, 92.6%), but two studies (7%) measured them again during treatment. Follow-ups of side- effects occurred once in 59.3% ($k = 16$) of studies, and multiple times in 40.7% ($k = 11$), and were recorded in a diary in 37.0% ($k = 10$) of studies.

Table 1

Study characteristics and moderators

			Demographics					Moderators			
Study	n	Gender	Type of Cancer	Type of Treatment	No. Times REs Measured	Sample Homogeneity	Patients Naïve?	Diary	RE Scale Used	No. of Followups	Side Effects[i]
1. Cassileth et al. (15)	42[d]	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	No	SEEQ[e]	1	Multiple[j]
2. Haut et al. (25)	36	Mixed	Multiple	Chemotherapy	1	Heterogeneous	No[f]	No	Likert (5 pt)	Multiple	NV
3. Andrykowski et al. (16)	65	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Not stated	No	Likert (7 pt)	Multiple	PTN
4. Rhodes et al. (22)	299	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	No	SEEQ[e]	1	PTN, V
5. Montgomery et al. (28)	59	Female	Breast Cancer	Chemotherapy	Mixed	Homogenous	Yes	No	SEEQ (3 pt)	Multiple	PTN, AN
6. Watson et al.[d] (29)	87	Female	Breast Cancer	Chemotherapy	Mixed	Homogenous	Not stated	No	SEEQ (3 pt)[g]	Multiple	PTN, AN
7. Montgomery et al. (30)	52	Female	Breast Cancer	Chemotherapy	1	Homogenous	Yes	No	SEEQ (3 pt)[g]	Multiple	PTN
8. Roscoe et al. (26)	29	Female	Gynecologic	Chemotherapy	1	Homogenous	Yes	Yes	SEEQ[e]	1	PTN
9. Montgomery et al. (35)	60	Female	Breast Cancer	Chemotherapy	1	Homogenous	Yes	No	VAS	Multiple	AN
10. Hickok et al. (36)	63	Female	Multiple	Chemotherapy	1	Heterogeneous	Not stated	No	SEEQ[e]	1	PTN, AN
11. Molassiotis et al.[h] (53)	71	Female	Breast Cancer	Chemotherapy	1	Homogenous	Yes	Yes	Likert (10 pt)	Multiple	PTN, V

54

	N	Gender	Cancer type	Treatment		Homogeneity			Measure		Symptoms
12. Montgomery et al. (31)	63	Female	Breast Cancer	Surgery	1	Homogenous	No	No	VAS	1	PTN, F, P, discomfort
13. Roscoe et al. (32)	194	Female	Breast Cancer	Chemotherapy	1	Homogenous	Yes	Yes	Likert (5 pt)	1	PTN and V
14. Olver et al.[a] (20)	87[d]	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	No	VAS	1	Multiple[j]
15. Booth et al. (27)	143	Female	Breast Cancer	Chemotherapy	1	Homogenous	No	Yes	Likert (3 pt)	Multiple	NV
16. Higgins et al. (17)	56	Female	Breast Cancer	Chemotherapy	1	Homogenous	Yes	Yes	SEEQ (3 pt)[g]	1	PTN
17. Ryan et al. (18)	407	Mixed	Multiple	Mixed	1	Heterogeneous	No	No	SEEQ	1	Skin problems
18. Zachariae et al. (61)	125	Female	Breast Cancer	Chemotherapy	1	Homogenous	Yes	Yes	VAS	Multiple	PTN, V, F
19. Shelke et al.[b] (64)	163	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	Yes	SEEQ[e]	1	PTN
20. Colagiuri et al.[a] (65)	671	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	No	Multiple	1	PTN
21. Roscoe et al. (66)	88	Mixed	Multiple	Radiotherapy	1	Heterogeneous	No	Yes	SEEQ	1	PTN
22. Montgomery et al. (34)	101	Female	Breast cancer	Surgery	1	Homogenous	Not stated	No	VAS	1	PTN, F, and P
23. Whitford et al.[a] (21)	59	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	No	VAS	1	Multiple[j]
24. Molassiotis et al.[a] (19)	285	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	No	VAS	Multiple	NV
25. Colagiuri et al.[a] (67)	91	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	No	Likert (10 pt)	1	PTN, F, AC, and Dep

26. Chan et al.[a] (68)	648	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	Yes	Likert (10 pt)	1	PTN
27. Molassiotis et al. (69)	529[d]	Mixed	Multiple	Chemotherapy	1	Heterogeneous	Yes	Yes	VAS	Multiple	PTN

[a]Authors provided additional information to calculate effect size; [b]Control group only included; [c]Esr taken from 2-day pre-intervention period; [d]N is less than the total number of study participants; [e]Scale dichotomized; [f]One patient in the study was not chemotherapy-naïve; [g]Analysed as a dichotomous variable; [h]Non-significant result set to zero; [I]NV = nausea and vomiting combined; PTN = post-treatment nausea; V = vomiting; AN = anticipatory nausea; F = fatigue; P = pain; AC = appetite change; Dep = depression; [J] = more than 10 side effects.

Main Effect

The relationship between confidence ratings and study ESrs was not significant (r = .20, p = .33), nor was the location (Eastern or Western) of studies (r = -.19, p = .53); therefore, all 27 studies were pooled (Fig. 2) for subsequent analyses. There was a significant, medium effect for REs of side effects on subsequent experience (Table 2; r = .26), using a random-effects model. Although Egger's test displayed some asymmetry, Duval's trim and fill analyses did not change the ESr or CIs. Furthermore, Rosenthal's and Orwin's failsafe numbers were both above the criteria, indicating a robust effect. A homogeneity analysis reached statistical significance, with an I^2 value suggesting a moderate-to-large amount of the variance is measurable. This provided support for further investigation of how theoretically established moderators impact on this relationship. Sensitivity analyses confirmed the inclusion of one study (Molassiotis et al., 2002), which required imputation of ESr (from beta values), made no change to the ESr or confidence intervals, and so it was retained in the analysis.
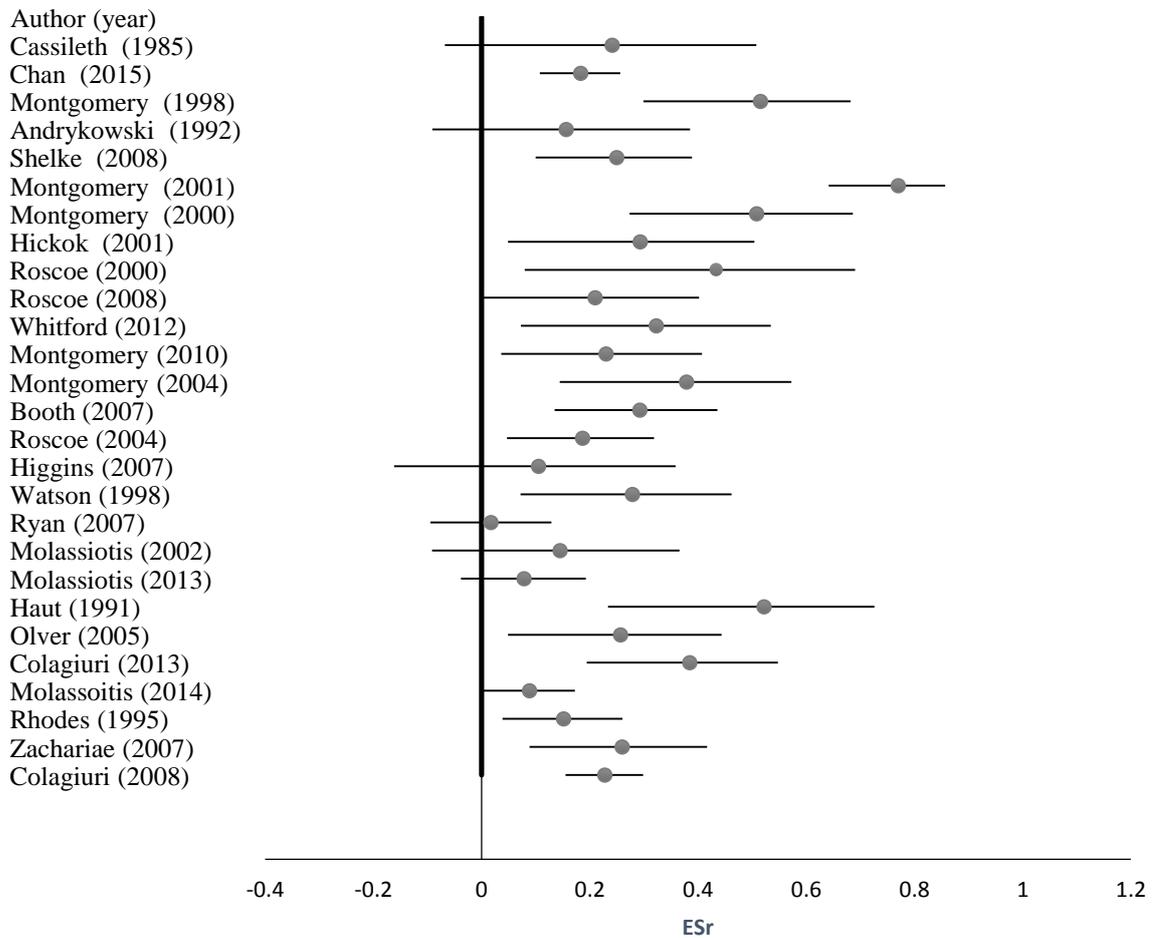
Figure 2. Expectancy-experience relationships by study: effect sizes and confidence intervals

Sample Homogeneity

ES*r*s of studies with samples including either homogenous or heterogeneous diagnoses were pooled, and the results were then compared (Table 2). Twelve studies with homogenous samples yielded an ES*r* (*r* = .35) significantly greater than 15 studies with heterogeneous samples (*r* = .19). Orwin's failsafe number indicated that the homogenous group ESr was reliable, whereas the heterogeneous groups' was slightly below the criterion, indicating susceptibility to publication bias. However, following the trim and fill method, the ES*r* for this group remained the same.

Table 2

Meta-analysis results of the main effect of RE on side effects and moderators

| | | | Pooled Effect Sizes | | | | [a]Rosenthal | [b]Orwin | Test of Homogeneity | | | | | | |
| | | | | | | | | | Within Groups | | | | Between Groups | | |
		k	r	CI	z	P	N_{fs}	N_{fs}	I^2 (%)	Q	df	P	Q	df	P
Overall effect		27	.26	.20, .32	8.40	<.001	1506	45	72.1	93.19	26	<.001			
Sample homogeneity	Heterogeneous	15	.19	.13, .24	5.58	<.001	389	14[c]	54.79	30.97	1	.01			
	Homogenous	12	.35	.23, .46	6.61	<.001	352	32	75.11	44.18	1	<.001	5.84	1	.02
Naive	Yes	16	.29	.21, .38	6.22	<.001	600	35	78.98	16.54	1	.35			
	No	4	.24	.06, .38	2.64	.01	18[d]	6	79.97	3.01	1	.39	2.46	1	.12
RE Scale	SEEQ 5-pt	7	.18	.10, .28	4.06	<.001	56	7[d]	41.43	11.95	3	.10			
	SEEQ 3-pt	4	.36	.16, .53	3.48	.001	31	11	63.93	8.32	3	.04			
	VAS	8	.31	.15, .45	3.71	<.001	146	18	86.87	53.32	3	<.001			
	Likert	7	.21	.15, .27	6.70	<.001	114	7	34.49	7.63	3	.18	3.72	3	.29
Side-effect follow-up	Once	17	.21	.16, .25	8.51	<.001	483	19	30.22	22.92	1	.16			
	Multiple	10	.35	.21, .48	4.50	<.001	273	27	87.11	69.80	1	<.001	3.46	1	.06
Side-effects recorded in diary	Yes	10	.20	.15, .24	8.08	<.001	228	10	25.22	12.03	1	.21			
	No	15	.31	.20, .42	5.33	<.001	442	33	79.04	66.78	1	<.001	3.63	1	.06

[a]Rosenthal's failsafe number; [b]Orwin's failsafe number; [c]Rosenthal's failsafe number is below the criterion ($N_{fs}>5*K+10$); [d]Orwins failsafe number is below the criterion ($N_{fs}>N_{studies}$).

We also investigated whether studies requiring patients' naïvety to the treatment produced higher ESrs than those that did not. Studies (n = 16) requiring naïve patients demonstrated a higher pooled ESr ($r = .29$) than the four that did not have this requirement ($r = .24$); however, this difference was not statistically significant. Rosenthal's failsafe number was below criterion for the studies not requiring treatment naïvety, and trim and fill analysis led to a reduction of the ESr ($r = .17$, 95% *CI* [-.03 to .36]), which was no longer significant.

Measurement of Response Expectancy

We additionally examined whether the use of different scales corresponded with different pooled ESrs. The five-point Side Effect Expectancy Questionnaire (SEEQ) and VAS were the most commonly used scales (Table 1), with seven and eight studies, respectively. The three-point SEEQ ($k = 4$) had the highest pooled ESr ($r = .36$), followed by VAS scales ($r = .31$), Likert ($k = 6$; $r = .21$), and the five-point SEEQ ($r = .18$). No significant differences resulted from the use of different scales, but the five-point SEEQ demonstrated a slightly lower Orwin's failsafe number than criterion. Trim and fill analyses subsequently reduced the effect size ($r = .13$, 95% *CI* [.04 to .21]) and, hence, widened the gap between this scale and others.

Measurement of Side Effects

Differences in the measurement of side effects were also investigated (Table 2). First, whether side effects were measured at one time, or two or more times was considered. Results indicated that a single measurement of side effects was associated with a lower pooled ESr ($r = .21$) than when side effects were

measured more than once ($r = .35$). This difference was not statistically significant, but did show trends and was robust. Second, trends were found between ES*r*s of studies with side effects recorded in a diary ($r = .20$), which were robust.

Individual Side Effects

Ten of the side effects included in the pooled overall analysis were excluded from individual side-effect analysis because they were not directly measured in at least three independent studies. These were anticipatory nausea, weight gain, skin problems, discomfort, nail changes, depression, mood changes, sore mouth, bleeding, and concentration. For the remaining 16 toxicities, no pattern differentiating between perceived "objective" side effects (e.g., vomiting), and "subjective" side effects (e.g., nausea) was apparent. REs of side effects and all subsequent experience were significantly related (see Figure 3), apart from "chills" ($r = .12$). Hair loss was measured in three studies and demonstrated the highest ES*r* ($r = .48$). As indicated by confidence intervals, this magnitude was significantly higher than those for weakness, nausea, vomiting, nausea and vomiting combined, and chills. Nausea ($k = 22$) and vomiting ($k = 7$) demonstrated significantly lower ES*r*s than diarrhoea, sleep problems, fatigue, appetite changes, and pain.
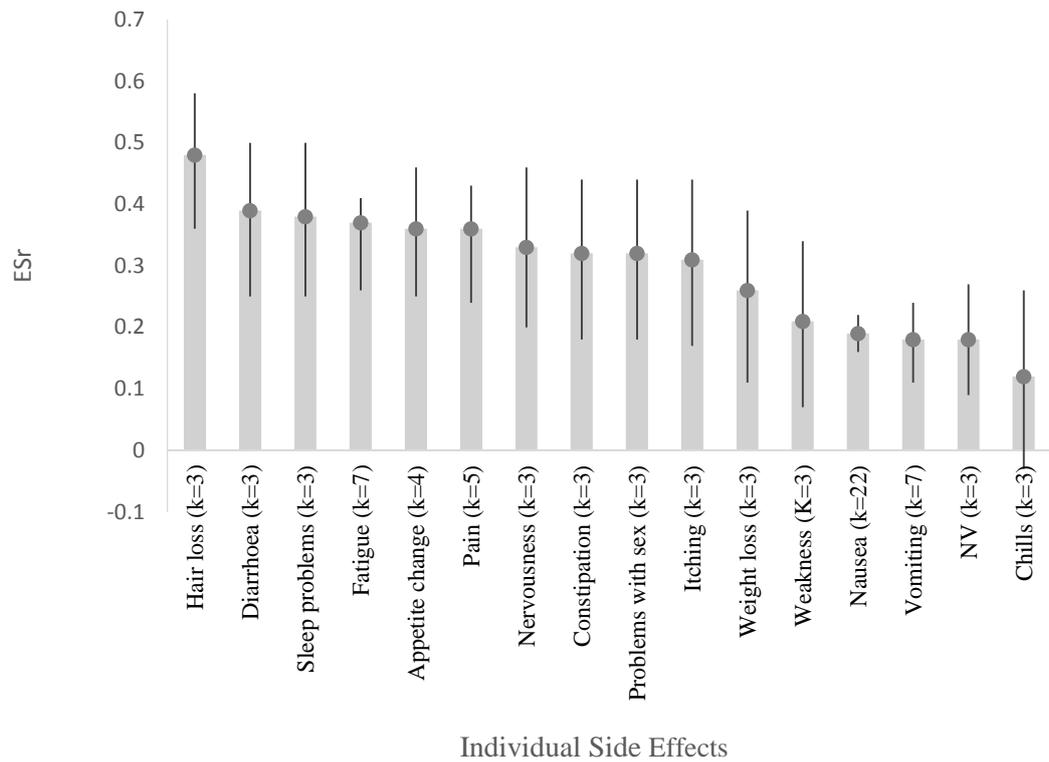
Figure 3. Expectancy-experience relationship for individual side-effects: effect sizes and confidence intervals

Discussion

We examined the influence of REs of cancer treatment side effects on the subsequent experience of these same toxicities, across pooled studies. We further examined the impact of potential moderators on this relationship, and patterns of individual side effects. Results indicated, as predicted, that there was a significant, moderate effect of REs on side effects (ESr = .26). This corresponds with an odds ratio of 2.66, signifying that the expectancy of a side effect increases the likelihood of experiencing it about two and a half times. Further investigation indicated that this effect was robust, and the relationship had a high degree of measurable variance, which supported moderator analysis (Borenstein et al., 2009a).

REs showed generalised prediction when cancer-related side effects were combined and significantly predicted subsequent experience for 15 of 16 individual side effects. Consequently, consideration of how REs may be addressed to reduce side-effect experience is warranted. This information is particularly salient during the provision of informed consent, during clinical interactions, with research suggesting that REs are sensitive to the information provided by healthcare workers. Simply presenting treatment toxicities and their risks to patients can facilitate their subsequent experience (Benedetti et al., 2007; Colloca & Miller, 2011c; Garg, 2011), and different modes of RE information provision shown to create different REs (Benedetti et al., 2007). Although some promising intervention and reduction methods have been proposed (Miller & Colloca, 2011; Montgomery & Bovbjerg, 2003; Montgomery et al., 2007; Montgomery et al., 2010a; Redd et al., 2001; Roscoe et al., 2006; Roscoe et al., 2003), they can be costly, difficult to administer, side effect specific, or in breach of informed consent guidelines. Alternatively, ethical methods of modifying the information provided to patients while still adhering to informed consent protocols, such as framing (the presentation of pretreatment side-effect information in different formats; Colloca & Miller, 2011c) and suggestion without deceit (Benedetti et al., 2007; Pollo et al., 2001; Stewart-Williams & Podd, 2004) may assist with reducing REs and the resulting side effects.

Methodological distinctions uncovered between studies reporting different outcomes may help direct future research and aid in the contextual understanding of the influence of REs on side effects. Studies including samples with homogenous diagnoses yielded significantly higher effect sizes than those including heterogeneous samples. Previously not thought to influence research

outcomes (Colagiuri & Zachariae, 2010), this potentially explains many nonsignificant findings in the literature to date. Homogenous studies may involve more specific measurement of REs and side effects, tailored to a specific treatment, thus being more sensitive. This result may also reveal inherent differences in REs for different diagnoses (i.e., resulting from different information provided from healthcare workers) and, thus, differential predictive ability for individual side effects. While other possible factors, such as gender or treatment regimen, could have confounded this outcome, this seems unlikely due to the majority of studies having no, or few, male participants and because surgery and radiotherapy were evenly divided between the homogenous and heterogeneous categories.

Although initially no significant differences were found between studies requiring patients' treatment naivety or not, when adjusted for publication bias, REs failed to significantly predict side effects for the pooled studies in the group without the requirement. Our results were similar to the most recent meta-analysis (Colagiuri & Zachariae, 2010), which also considered history of nausea (i.e., motion or morning sickness). However, when "non-naivety" was classified as recent experience of treatment (i.e., studies measuring REs after the treatment began, such as before the third infusion), significant differences between study ESrs emerged (Sohl et al., 2009). Therefore, REs appear to strengthen with recent experience but not necessarily experiences (identical or similar) in the past.

Nonsignificant trends were found between measurement methods, including the use of patient diaries and number of side-effect measurements, consistent with previous research (Sohl et al., 2009). This highlights the need for caution during interpretation and comparisons of study results stemming from

different methodology. Furthermore, a reduced effect was found for studies utilizing one of the most commonly used measures, the SEEQ five-point scale, and when potential publication bias was corrected, the effect was reduced substantially. The modified three-point version of the SEEQ, requiring a forced choice of expect, unsure, or do not expect demonstrated the strongest pooled effect. Thus, some RE scales seem to better predict subsequent side-effect experience better than others. To date, scales and measurement methods have often been discussed interchangeably, warranting further investigations of the use of these scale, and how often side effects are measured.

No clear differences emerged between ESrs and side effects with (objective) or without (subjective) physical correlates, and the ESrs for nausea and vomiting (and nausea and vomiting combined) were similar, contrary to previous findings and theories (Olver et al., 2005; Roscoe et al., 2006; Sohl et al., 2009; Whitford & Olver, 2012). Although we distinguish between subjective and objective side effects, all were measured subjectively (via self-report) in the included studies; therefore, definitive conclusions cannot be drawn from these results. Olver et al. (2005) also reported some of the strongest associations between REs for seemingly objectively perceived side effects, such as hair loss, diarrhoea, and bleeding and their experiences. They suggested that some side-effect reports may reflect heightened awareness (i.e., the perception of hair loss by noticing hair in a hairbrush), rather than evidence of a measurable change. However, REs have been shown to relate to objectively measured responses (Kirsch & Lynn, 1999), including analgesic responses in neuroimaging scans, which correlate to subjective reporting of pain relief (Benedetti et al., 2011).

Thus, investigating objectively measured side effects would be beneficial for an increased understanding of the importance of REs prior to cancer treatment.

Significant differences were found between nausea and the five strongest side effects. Thus, although REs appear to have consistent predictive ability, they do so to significantly different degrees, balancing the effects of each other out in pooled analyses. This supports research suggesting that there are different mechanisms and physical systems for responses to different REs (Benedetti et al., 2011).

Hair loss revealed the highest ESr in this review, significantly higher than nausea and vomiting, and chills (associated with fever) was the only side effect that demonstrated a nonsignificant relationship with REs. Fewer studies investigated the influence of REs for hair loss than nausea and vomiting. Each study that measured hair loss also measured multiple side effects; hence, publication bias is not suspected for this individual side effect. However, it would be more prone to outliers and, thus, less reliable. Given hair loss reflects one of the most common side effects depicted in mass media, this provides potential support for the media as an influence on RE formation, through stereotype threat, where the activation of stereotypical information (i.e. chemotherapy causes hair loss) is associated with strengthened experience of a side effect (Schagen, Das, & Vermeulen, 2012). In addition, nausea and vomiting may be lower due to better treatment, with 12 studies reporting patients received anti-emetic medication.

Our results are consistent with general patterns in previous research finding, pain and fatigue have the strongest effects, with nausea and vomiting showing somewhat lower effects (Montgomery & Bovbjerg, 2004; Sohl et al., 2009). Because of the focus on nausea and vomiting in the literature to date, the

relationship between REs and side effects may be stronger than it often appears. The lack of significance for the side-effect "chills" could reflect its abstract nature, which may be misinterpreted as other more commonly expected side effects, such as fatigue or weakness.

Limitations

Although our results support the influence of REs on side effects for female patients being treated for breast cancer with chemotherapy, our conclusions cannot extend beyond the available empirical research. We found few studies of the impact of REs in surgery and radiotherapy and no studies with homogeneous male samples. Male patients, > 60 years, with less education, and undergoing radiotherapy, have been found to form significantly fewer REs (Hofman et al., 2004). Accordingly, investigation of whether REs remain influential in more diverse patient, diagnostic, and treatment groups is indicated.

Additionally, because of the novel investigation of many side effects, in both a pooled and individual capacity, more thorough investigation into differences between the individual side effects was not possible. For example, the influence of the moderator variables investigated may influence individual side effects differently. Thus, investigation of these less commonly measured side effects is suggested for future empirical research.

Other limitations involved the potential exclusion of relevant studies. Studies not published in English were excluded for practical reasons; however, some potentially relevant studies may have been missed as a result. Similarly, potential duplicates were removed to ensure independence of studies. This strategy was conservatively applied in studies where this information was not

clearly stated, potentially excluding some studies without individual patient crossover.

Furthermore, a critical appraisal of studies was not undertaken in the meta-analysis. Because of the similarly in design of studies, as per the stringent inclusion criteria, studies were not able to be rated based on their design, potentially introducing bias into the results. Studies not published in peer-reviewed journals were excluded from the review to maintain quality, but this method is often criticized (Lipsey & Wilson, 2001), for potentially increasing the risk of publication bias and lacking precision. However, the addition of confidence ratings (which did not significantly relate to effect size), moderator analyses, searching of a range of sources, and investigation of publication bias, minimized this potential problem.

Subgroup analyses, because of their observational nature, can potentially create Type I (false positives) and Type II (false negative) errors (Higgins & Green, 2008). It is recognized that these risks are increased with each additional subgroup analysis; thus, the results were interpreted with this possibility in mind. On the other hand, combining ESrs may not have produced reliable or meaningful indicators. For example, incidence, frequency, severity, duration, acute, and delayed nausea were combined to produce a single effect size for "nausea". Although we specified that side effects must appear in three or more studies to be included, 12 of the included side-effects were described in only three or four studies; therefore, the results may reflect individual study variations.

Finally, it should be acknowledged that as is often the case with meta-analytic research, that other factors possibly affecting the RE/ side-effect relationship were not controlled because of the univariate design of the studies

included in the review. It is, thus, possible that REs are not directly related to their subsequent side effects as theorized (Kirsch, 1997), but both REs and side-effects are related to other variables, for example, patients' knowledge of their susceptibility to side effects, or their increased body monitoring for side effects. However, evidence has dispelled many of these alternate explanations (Colagiuri et al., 2013; Kirsch & Lynn, 1999; Zachariae et al., 2007a), and a meta-analysis considering multivariate analyses still found a significant effect (Colagiuri & Zachariae, 2010); therefore, theory and empirical research are in line with the current meta-analysis.

Conclusions

In summary, our findings reflect previous reviews, demonstrating a moderate relationship between REs of side effects and related experience, indicating that this overall consistency remains across a wide range of cancer treatment-related toxicities. However, despite this moderate combined effect, when individual side effects were considered separately, significant differences emerged, indicating that although REs consistently predict subsequent side effects in cancer treatment, they do so to varying degrees. Accordingly, it is suggested that future studies investigate toxicities other than the most commonly considered nausea and vomiting, which tended to show lower effects, potentially underestimating the impact of REs in the literature.

Additional directions for future research have been suggested, based on evidenced differences for studies accruing samples with the same or different diagnoses and trends depending on the method of side-effect measurement. The way REs and side effects are measured and the impact of patients' previous

treatment history remain inconclusive. The novel finding of stronger effects for RE of hair loss and perceived experience of this toxicity highlight a need for further investigation of whether this is a robust effect, and potential reasons as to why (i.e., stereotype threat in the media). Taken together, despite REs being researched for > 30 years, there is still much to learn about their impact during cancer treatment.

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Chapter 3: Psychometric study

'Beyond measure': A psychometric study exploring the ability of 5-point scales and visual analogue scales to detect response expectancies of cancer side effects

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Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis

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Preamble

In the afore mentioned meta-analysis, it became apparent that the most commonly used measure for expectancies of cancer treatment side effects; the 5-point scale, demonstrated reduced associations with related toxicities than the other, less common measurement tools. Thus, the aim of this next study was to explore potential reasons for this difference.

Manuscript

Abstract

Objective. Response expectancies of cancer treatment side effects are often, but not always associated with subsequent experience. The use of different tools to measure response expectancies reveal different effects, potentially explaining inconsistent research findings. In a clinical sample, we investigated psychometric properties of the most common response expectancy measure, the 5-point scale, and directly compared it with another commonly used instrument: the visual analogue scale.

Methods. Four-weeks prior to commencing radiotherapy for prostate cancer, forty-five men (mean age 71 years) completed two types of self-report measure (5-point and visual analogue scales) for 19 toxicities, presented in random order. The 5-point scales had descriptors at every point, including an 'unsure' midpoint. The visual analogue scales had descriptors anchoring each extreme end.

Results. Across all side effects, 'unsure' – an option unavailable on visual analogue scales – was selected on the 5-point scale by 17-62% of participants. Notably, on 5-point scales no response expectancies were reported for either 'blood in stools' or 'rectal urgency', yet on visual analogue scales more than half of the patients indicated expectancies of both toxicities. As measures of expectancies of the same side effects the two scales showed only small to moderate associations (ϕ=.20-.56).

Conclusion. Visual analogue scales and 5-point scales should be considered independent measures of response expectancy and not used or

described interchangeably. This novel investigation also demonstrated that when the 'unsure' option is provided, it will often be selected, potentially reducing the sensitivity of the 5-point scale.

Response expectancies are individuals' anticipations of how they will non-volitionally (automatically) respond to stimuli or behaviour (Kirsch, 1985); for example, expecting to become alert after drinking coffee or to become fearful when seeing a snake. Numerous studies have investigated the impact of response expectancies on related experiences, including cancer treatment side effects. Although most studies report moderate relationships between response expectancies and related side effects (Colagiuri & Zachariae, 2010; Sohl et al., 2009), other studies have failed to find significant associations (Andrykowski & Gregg, 1992; Higgins et al., 2007; Molassiotis et al., 2013; Ryan et al., 2007).

A recent meta-analytic review of 27 studies and 4,474 patients (mostly women treated with chemotherapy), indicated measurement differences may contribute to inconsistencies in the literature (Devlin, Denson, & Whitford). The most common measure of response expectancies, a 5-point scale often referred to as the Side Effect Expectancy Questionnaire (SEEQ), produced weaker associations with related toxicities than other measures: Visual Analogue Scales (VAS), dichotomous scales (yes/no), and Likert scales (3-point, 10-point, etc; Devlin et al.). Although this difference did not reach significance, correction for potential publication bias further reduced the effect size produced by studies utilising the SEEQ, indicating that these differences require additional investigation.

This weaker evidenced relationship between expectancies of side effects and experience, when measured with the SEEQ, may reflect inconsistent inclusion of a midpoint option, representing that a patient is 'unsure' whether or not they will experience a toxicity. Studies including the SEEQ often omit information about whether or not each point is labelled during patient assessment

(Andrykowski et al., 1988; Haut et al., 1991; Jacobsen et al., 1988a; Roscoe et al., 2009; Roscoe et al., 2004; Roscoe et al., 2000a; Ryan et al., 2007; Shelke et al., 2008), only reporting the anchor labels at each end (Cassileth et al., 1985). Those authors who have clearly specified the labelling have differed in their interpretation (Andrykowski & Gregg, 1992; Hickok et al., 2001). Despite this, the scales are generally categorised into three groups for analysis; 'expect not to have the side effect' (selection of points 1 or 2), 'unsure' (selection of the midpoint 3), and 'expect to have the side effect' (selection of points 4 or 5).

The inclusion of a midpoint may also be intrinsically problematic for the measurement of response expectancies. When expectancies of post-treatment nausea in 52 patients undergoing chemotherapy for breast cancer, Montgomery and Bovbjerg (2000) were informed by patients that the inclusion of an 'I don't know' option to the existing forced dichotomous yes/no response format, was desirable. The authors thus provided this option in their scale, but later removed it because it was rarely selected. This suggests that an option representing not knowing what side effects would occur was reassuring for patients, but it did not reflect their response expectancies. Similarly, when investigating expectancies of chemotherapy-related side effects in 59 patients with breast cancer, Montgomery et al. (1998) found no difference in anticipatory nausea between patients either reporting no expectancies of anticipatory nausea or reporting that they did not know if they would experience it, implying that not knowing was not statistically different than not expecting anticipatory nausea. Whether this evidence for an 'I don't know' option on a 3-point scale extends to an 'unsure' option, on a 5-point scale (such as the SEEQ) requires investigation, ideally incorporating more diverse cancer diagnoses, treatments and patients.

Furthermore, different instruments may reveal patients' side effect expectancies with different degrees of sensitivity. For example, VAS can assess both incidence and severity of response expectancies. Typically, VAS scales range from 0 to 100, with anchors defined at both ends and no descriptors between, only numerical points (Streiner & Norman, 2008). Respondents circle (or mark) the point on a line which corresponds with the strength of their expectancies of a given side effect. Thus, zero versus any other score can be interpreted as a measure of the incidence of a response expectancy. Because differences between the VAS and SEEQ were recently identified following meta-analytic corrections for potential publication bias (Devlin et al.), empirical investigation into whether the measurement of incidence is the same across both measurement formats is important, to determine whether outcomes measured in these different ways are comparable.

In the current study, we explored potential reasons for the weaker relationships between expectancies of side effects and subsequent experiences, measured with the commonly used SEEQ, recruiting a sample of prostate cancer patients prior to radiotherapy. We specifically investigated the incidence of selecting the 'unsure' midpoint for 19 common toxicities, predicting (based on previous research) that this would rarely be selected (Montgomery & Bovbjerg, 2000). The 5-point SEEQ and 0-100 VAS were then compared to determine the consistency, or lack thereof, between these measures in discovering the incidence of expectancies of all toxicities (given the SEEQ can only assess incidence). Based on previous results indicating differences between these scales (Devlin et al.), we hypothesised that the VAS and SEEQ would not be strongly associated for the measurement of response expectancy incidence.

Method

Participants and procedure

Participants in the current study were part of a larger project investigating the impact of response expectancies on subsequent side-effects (*Study 3, Chapter 4*). Men who were due to commence radiotherapy for prostate cancer were recruited between March 2014 and July 2015, when they were booked into pre-treatment scans at the Royal Adelaide Hospital (RAH), a public teaching hospital in Adelaide, South Australia. Eligibility criteria were: male patients older than 18 years of age, able to read and understand English, naïve to cancer treatment, and receiving treatment with curative intent. Patients remained eligible if they had androgen deprivation therapy (hormone therapy) or were scheduled for adjuvant brachytherapy. Exclusion criteria were: psychiatric disease or cognitive impairment, having other adjuvant cancer treatment, and participation in other studies.

Following informed consent, 48 men agreed to participate. Three failed to complete either the VAS or SEEQ and were excluded, yielding a retention rate of 94%. Following their pre-treatment planning scan sessions, participants completed questionnaire packs with demographic information and recorded their expectancies of 19 toxicities. Data collection is described in detail in Study 3 (*Chapter 4*). A study-specific demographic questionnaire with 26 questions recorded patients' demographic details, baseline health, and perception of radiotherapy and resulting side effects. Emotional state and coping style were also documented using the Depression, Anxiety and Stress Scale 21 (Henry & Crawford, 2005), and Mental Adjustment to Cancer Scale (Watson et al., 1988) in the larger project, but not included in this analysis.

Patients completed VAS and SEEQ in random order. Our list of 19 side effects, identical in both scales, included 18 common acute toxicities based on the literature (Mayo Cinic Staff, 2017) and compiled for this study in consultation with radiation oncologists and a radiotherapy nurse at the hospital site. Each measure also contained an extraneous 19th toxicity: hair loss (on head), not considered a radiotherapy side effect for this treatment, as a quality control marker for careless responding. Two follow-up sessions recording patients' subsequent side effect experiences, 2- and 7-weeks into treatment, were conducted for the larger study (*Study 3, Chapter 4*), but not analysed in the current study.

Ethical approval was obtained through the Royal Adelaide Hospital Ethics Committee and Site Specific Governance Board (Approval #130929) in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Measures

Response Expectancies: 5-point SEEQ

Participants were instructed to circle the number that best described their response expectancies for each side effect within the first 2-weeks of treatment: "Please circle the number that best describes your expectations for having each side effect in the first two weeks of your Radiotherapy treatment. Answer each question based on what you THINK will happen, not what you HOPE will happen" (Hofman et al., 2004). Descriptors corresponded with each number as follows (1) 'I am certain I will not have this side effect', (2) 'I am reasonably certain I will not have this side effect', (3) 'I am unsure whether or not I will have

this side effect', (4) 'I am reasonably certain I will have this side effect', and (5) 'I am certain I will have this side effect'.

Response Expectancies: 100-point VAS

Participants were instructed to circle a point along each line to rate how severely they expected to experience the listed side-effect for the first 2-weeks of radiotherapy: "Please circle the point along each line to rate how severe you expect to experience the listed side effect for the first two weeks of your Radiotherapy treatment". They did so on a horizontal 100mm line, marked at 10mm increments in multiples of ten (i.e., 0, 10… 100), with descriptors only anchored at (0) 'do not expect the side-effect at all' and (100) 'expect the worst possible severity of the side-effect'.

Statistical analysis

Descriptive statistics characterized the sample, and frequency counts ascertained the number of men selecting 'unsure' on the SEEQ. To compare the incidence of anticipated side effects across the two scale types, SEEQs were trichotomized and the 'unsure' categories were removed, to permit dichotomous comparison of participants being certain or reasonably certain they would experience the side effect in question versus being certain or reasonably certain they would not. Dichotomization of VAS scales was achieved by splitting each between '0' (not anticipating the side effect) versus all other scores 1-100 (expectancy of that toxicity). Exact *p*-values were reported, with the alpha set at .05. Effect sizes were reported alongside *p*-values. Specifically, phi coefficients (ϕ) are represented as .10 for small, .30 for moderate, and .50 for large effects (Cohen, 1988).

<center>**Results**</center>

Demographics

Table 1 shows demographic and health characteristics for the sample, prior to treatment commencement. The average age of the male participants was 70 years old. Most were not currently working, could maintain a normal activity level, reported English as their first language, and identified with Western culture. Half had completed secondary education (12 years of high school). Just over half had been treated with androgen deprivation (hormone) therapy pre-treatment, and were receiving radiotherapy in isolation, and almost half felt they knew little or nothing about radiotherapy side-effects.

Use of the midpoint in the SEEQ

Frequency analyses revealed that the 'unsure' midpoint of the SEEQ was selected by between 36% and 62% of participants across most (16) side-effects (Table 2). For the other 3 toxicities (the sexual side effects) there was a lower frequency of midpoint selection, with approximately 20% of participants selecting 'unsure' for each. The midpoint was selected more often than the other groupings (i.e., 1 and 2 combined or 4 and 5 combined) for fatigue, skin irritation, discomfort when urinating, slow urine stream and blood in stools.

Table 1

Patients' demographic and treatment information (N = 45)

	Mean	SD
Age in Years (range 52-81)	70.6	7.5
	n (yes)	% (yes)
English first language	41	91.1%
Married	28	70.5%
Currently working	4	9.0%
Normal activity level	30	66.7%
Hormone therapy	25	55.6%
Culture		
Western	38	88.4%
Eastern	1	2.3%
Both	4	9.3%
Highest level of education		
Primary	7	16.3%
Secondary	22	51.2%
Tertiary	14	32.5%
Perceived knowledge of radiotherapy side-effects		
A lot or a fair amount	13	28.9%
A little	13	28.9%
Not much or nothing	19	42.2%
Radiotherapy in isolation		
Yes	14	43.8%
Additional brachytherapy	11	34.4%
Unsure	7	21.9%

Table 2 also shows that for three side-effects, hair loss (head), rectal urgency, and blood in stools, no patients reported response expectancies (i.e., no selection of points 4 or 5) on the SEEQs. Because hair loss was an extraneous item, this was expected and demonstrated that participants were not responding carelessly. Based on this clear result, we subsequently investigated the frequency of reporting response expectancies on VAS for the other two side effects that had not been selected on the SEEQs (rectal urgency and blood in stools), as a comparison. More than half (64.3%; n = 27) of the sample reported expectancies of rectal urgency on VAS, with three participants reporting expectancies of this side effect at a severity 50 or above. Similarly, 54.8% (n = 23) of participants reported expectancies of blood in stools on VAS, with four reporting expectancies of this side effect at a severity of 50 or above.

Comparison of SEEQ and VAS

Direct comparison of the SEEQ and VAS measures of response expectancies was conducted after dichotomization, to determine whether responses were comparable. Hair loss (head), rectal urgency, and blood in stools were excluded because, as mentioned above, there were no endorsements of 4 or 5 on the SEEQ; thus, chi-square statistics could not be calculated. Seven of the 16 toxicities analysed (43.8%) showed significant relationships in incidence reporting (Table 3). However, strong associations between scale responses were reported for only four toxicities; slow urine stream and the three sexual side-effects. All remaining associations were small to moderate.

Table 2

Frequency of selection of points on the SEEQ (N = 45)

Side effect	1-2	3	4-5	% of 3
Fatigue	14	20[a]	9	46.5%
Nausea	22	16	3	39.0%
Abdominal cramps	21	20	1	47.6%
Skin Irritation	13	27[a]	3	62.8%
Hair loss (head)[b]	31	13	0[c]	29.5%
Frequent urination	18	16	9	37.2%
Hair loss (pelvic region)	21	21	1	48.8%
Pain, burning or discomfort when urinating	17	21[a]	5	48.8%
Slow urine stream	16	19[a]	8	44.2%
Blood in urine	25	18	1	40.9%
Urgent urination	18	15	8	36.6%
Incontinence	20	18	4	42.9%
Rectal urgency	26	17	0[c]	39.5%
Painful bowel movements	26	16	1	37.2%
Bowel leakage	23	18	1	42.9%
Blood in stools	19	23[a]	0[c]	54.8%
Reduced sexual desire	18	8	15	17.8%
Inability to reach orgasm	18	7	15	17.5%
Inability to have or maintain erection	17	9	14	22.5%

[a] Selection of the midpoint (3) was more frequent than other scale groupings (1 and 2, or 3 and 4);
[b] This was a distractor item used to determine any careless responding; [c] No response expectancies were recorded for this side-effect.

Table 3

Comparison of measurement of response expectancies between the SEEQ and VAS scales

Toxicity	n	X^2	p	ϕ [a]
Fatigue	23	2.22	.14	.31
Nausea	24	2.06	.15	.29
Abdominal cramps	22	1.05	.31	.22
Skin Irritation	16	1.68	.20	.32
Frequent urination	26	4.13	.04	.40
Hair loss (pelvic region)	22	1.26	.26	.24
Pain, burning or discomfort when urinating	22	3.70	.05	.41
Slow urine stream	24	6.00	.01	.50
Blood in urine	25	1.56	.21	.25
Urgent urination	25	4.28	.03	.43
Incontinence	24	3.43	.06	.38
Painful bowel movements	27	1.11	.29	.20
Bowel leakage	23	1.36	.24	.24
Reduced sexual desire	32	9.41	.002	.54
Inability to reach orgasm	31	8.88	.003	.54
Inability to have or maintain erection	30	9.55	.002	.56

[a] For Cramer's V a small effect is .10, medium is .30, and large is .50.
Note: Hair-loss (head), rectal urgency and blood in stools were excluded as they were not expected by any participants on the SEEQ.

Discussion

We investigated whether differences between commonly used response expectancy measurement tools could explain discrepancies between studies in the relationships between side effect response expectancies and experiences. We explored how commonly the 'unsure' midpoint of the 5-point SEEQ was selected, and compared this measure with another commonly utilised scale: 0-100 VAS.

Contrary to prediction, and previous research which included an 'I don't know' midpoint (18, 19), in the current study the midpoint of the 5-point SEEQ representing 'unsure' was commonly selected. Across most side effects between one-third and half of patients selected it, and for five side effects it was selected by most participants. This may reflect expectancies of male patients undergoing radiotherapy, compared with previous research involving female patients treated with chemotherapy for breast cancer (Montgomery & Bovbjerg, 2000). Research suggests that women show increased health reporting behaviour (Caroli & Weber-Baghdiguian, 2016), and have higher rates of response expectancies (Hofman et al., 2004). Consequentially, females may be more likely to report expecting each side effect and thus, less likely to select 'unsure'.

The inclusion of an 'unsure' midpoint in scales is debated (Krosnick, 1991; Krosnick & Fabrigar, 1997; Sturgis, Roberts, & Smith, 2014). Provision of this option has been thought to facilitate *satisficing* (Krosnick, 1991), whereby participants can minimise cognitive demand while completing measures, in this instance by selecting a midpoint despite truly leaning in one direction. Thus, the ability of a scale with this option to detect underlying constructs may be reduced. However the alternative for researchers, offering no midpoint (such as in the VAS), implies *forced directional responding* (Sturgis et al., 2014): respondents

must select an option, even if they do not feel this applies to them. If participants are genuinely unsure, the result is invalid. This is an important consideration when measuring response expectancies; are some patients truly unsure about their expectancies of particular side effects?

In addition, inconsistencies surrounding the interpretation of the midpoint could introduce further variation in reported responses to the SEEQ. In Cassileth and colleagues' (1985) original investigation of side effect expectancies in 56 chemotherapy-naïve patients treated for a range of cancers, it was unclear whether the midpoint was labelled or not. Since then different research groups have continued research based on this seminal publication; however, because of the stated ambiguities, measurement practices have diverged. Many authors continue to not specify whether or not descriptor labels were used with the intermediate numbers (Andrykowski et al., 1988; Haut et al., 1991; Jacobsen et al., 1988a; Roscoe et al., 2009; Roscoe et al., 2004; Roscoe et al., 2000a; Ryan et al., 2007; Shelke et al., 2008), making it difficult to know how comparable studies are. However, two studies referencing the scale designed by Cassileth and colleagues (1985) clearly stated the measurement method they used. In a sample of 65 chemotherapy patients, Andrykowski and Gregg (1992) reported using 5-point scales with the midpoint labelled 'unsure'. Conversely, Hickok et al. (2001) measured anticipatory nausea in 63 chemotherapy-naïve patients using 5-point scales, specifying there were no written descriptors between the two anchors of 1 and 5. Thus, research based on this seminal response expectancy study have used unclear and varying measurement methods in producing the 5-point scale, based on different assumptions. Taken together, this could influence the reduced effect in pooled studies using the SEEQ.

Our results also suggest that SEEQs were less sensitive than VAS for this sample. Unexpectedly, although two side effect expectancies on the SEEQs were not endorsed by any patients (rectal urgency and blood in stools) we observed positive responding on VAS for those same two toxicities. Expectancies of each toxicity were reported in VAS by more than half of participants, some above the halfway point of the severity scales (<50). This suggests that VAS may be sensitive to detecting response expectancies when SEEQs with a midpoint are not. The strength of some recorded response expectancies on the VAS – that would have gone undetected using SEEQs – implies this is unlikely to be an artefact of forced responding in VAS, and suggests 'unsure' is likely represents satisficing in at least some instances. An alternative explanation, supported by the low numbers of patients indicating response expectancies at a level 4 or 5 on the SEEQ, is that the wording on this scale may be too strong. Patients are asked whether they are 'certain' or 'reasonably certain' they will experience a toxicity. Potentially, this language is stronger than patients' perceived level of response expectancies; thus, explaining the high number of participants selecting 'unsure'.

When comparing expectancies of side effect incidence, measured with the SEEQ and VAS, matches between the two scales were not uniformly significant, and most demonstrated small or moderate effects (except for sexual side effects and slow urine stream). This indicates that measurement indicating expectancies of toxicity experience is dependent on the scale used. Thus, these measures should be considered independent and not be used or discussed interchangeably. This supports findings in a recent meta-analysis, that there are differences between the 5-point SEEQ and 100-point VAS scales (Devlin et al.). Although no differences between the VAS and other measures (e.g., the dichotomous scale, 3-

or 10-point Likert scales) were revealed in the meta-analysis, comparisons of those scales would assist in more consistent research and reporting in future empirical studies.

Although this exploratory study was conducted in a small sample, with potential power issues, effect sizes were calculated throughout, and hypotheses were theoretically-based. Moreover, the homogeneity of the sample strengthened reliability. However, replication is required in other samples (e.g., chemotherapy regimens, other diagnostic groups, mixed and female cohorts) to determine the most appropriate response expectancy measurement for each.

In the current study, patients tended to select the 'unsure' midpoint if it was available. Comparisons with VAS responses suggested that at least sometimes this phenomenon reflected satisficing. We also found that VAS and SEEQs are not similar enough to be used interchangeably; thus, they should be considered independent when used in analyses. In summary, response expectancies are sensitive to measurement methods, hence caution is required when reporting, comparing, pooling, and meta-analysing empirical results.

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Chapter 4: Prospective clinical study

Response expectancies of radiotherapy side effects as predictors of toxicities in men with prostate cancer

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Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Preamble

Based on the results of the meta-analysis (*Chapter 2*), it was apparent that there are large gaps in the literature on expectancies of cancer treatment-related toxicities. For example, no study had yet considered the association between response expectancies and radiotherapy-related side effects. Similarly, no investigation has included a homogenous male sample, and the average age of participants was 53 years.

Research by Hofman et al. (2004) indicated that male patients, patients over the age of 65, and patients scheduled to receive radiotherapy reported fewer expectancies of treatment-relate toxicities than their counterparts. Additional research has indicated that women are more responsive to nocebo effects than men (Vambheim & Flaten, 2017). Consequently, investigating whether response expectancies could still predict side effects in a novel sample could (1) inform whether expectancy reducing interventions might still be useful in this group of patients, and (2) provide some insight into the scope of the influence response expectancies can have across many patient groups and treatment modalities.

Manuscript

Abstract

Objective. Previous research, largely based on females undergoing chemotherapy, has indicated pre-treatment response expectancies of side effects often predict toxicity experience. We tested whether this association also occurred in a novel cohort; men with prostate cancer undergoing radiotherapy, controlling known and novel variables.

Methods. Men diagnosed with prostate cancer ($N = 35$, mean age 71 years) completed baseline measures of side effect expectancies, baseline health, hormonal treatment, emotional state, and coping style. Expectancies of radiotherapy toxicities were also measured 2-weeks into treatment. Toxicity experiences were assessed 2- and 7-weeks into treatment (before and after side effects were medically predicted to have commenced).

Results. Baseline response expectancies showed independent predictive value for six toxicities by Week 2, contributing 12-30% of explained variance ($\beta = .39$-$.59$). Response expectancies at Week 2 uniquely predicted seven toxicities by Week 7, explaining 17-50% of the variance ($\beta = .49$-$.91$). Sexual side effect expectancies revealed the strongest associations with their experience ($\beta = .46$-$.91$) through treatment.

Conclusions. In this older male sample, side effect expectancies predicted experiences throughout treatment, including the period before side effects were medically expected. Expectancies of sexual side effects were robust, independent predictors of subsequent toxicities across treatment; therefore requiring a substantial focus in practice and future research.

Cancer treatment side effects (toxicities) can have adverse physical, psychological, social, and economic outcomes for patients and survivors, that often continue to affect individuals post-treatment (Carelle et al., 2002; Curt et al., 2000; Hsiao, Loescher, & Moore, 2007). Consequently, it is important to identify the impact of non-pharmacological predictors of toxicities, in order to better understand how to predict and thus, potentially reduce side effect experience.

Response expectancies are individuals' anticipations for how they will non-volitionally (automatically) respond to treatments, medications, and other stimuli (Kirsch, 1985). The impact of response expectancies on subsequent cancer treatment-related side effects has been extensively investigated, with small to moderate relationships generally reported (Colagiuri & Zachariae, 2010; Devlin et al.; Sohl et al., 2009). Therefore, utilizing response expectancies to screen patients requiring additional assistance when providing pre-treatment toxicity information may be beneficial, especially for toxicities highly affected by response expectancies (Colloca & Miller, 2011c).

An investigation of the formation of response expectancies across different patient groups revealed the highest number were formed by females, and patients younger than 65 years of age (Hofman et al., 2004). This reflects the profile of most research of cancer treatment-related response expectancies to-date, which has focused on female patients with breast cancer, mainly treated with chemotherapy, and with an average age of 53.4 (SD = 5.81; Sohl et al., 2009). Consequently, explicit research considering the impact of side effect expectancies on other homogenous samples is required to determine whether they continue to be influential in other groups of patients.

Individuals scheduled for chemotherapy have also been found to form significantly more response expectancies than those anticipating radiotherapy (Hofman et al., 2004). The impact of side effect expectancies during radiotherapy has not been directly measured (Sohl et al., 2009); however, during a two day pre-intervention measurement, expectancies of nausea were related to nausea experience in patients treated with radiotherapy (Roscoe et al., 2009). Furthermore, no differences in the formation of toxicity expectancies were reported in patients undergoing chemotherapy in isolation and patients having adjuvant chemotherapy and radiotherapy (Zachariae et al., 2007b).

Thus, specific investigation of the impact of side effect expectancies during radiotherapy is needed, particularly given inherent treatment differences. Unlike chemotherapy, a pharmacotherapy that systemically targets all cancer cells within the body, radiotherapy is a localised therapy that targets specific body regions. Thus, radiotherapy most commonly causes isolated side effects in the area treated (e.g., skin irritation, organ disruption). Nevertheless, side effects are often severe enough to require reduction in treatment intensity (Bentzen et al., 2003), or premature discontinuation of a planned treatment (Lebwohl et al., 2010), potentially impacting tumour control. Furthermore, like chemotherapy, radiotherapy can also induce ambiguous or subjective toxicities, most prominently fatigue.

Another difference between treatment modalities is the treatment regularity. Chemotherapy is typically administered in cycles with a recovery period (of up to 4-weeks) between each dose, whereas radiotherapy is often continuous, every weekday, over approximately 7.5-weeks, until treatment is complete. Consequently, patients are exposed to radiotherapy on a near-daily

basis. Repeated experience with a treatment has been theorized (Kirsch, 1997) and shown (Montgomery & Bovbjerg, 2000) to strengthen future relationships between response expectancies and side effects that have occurred. Therefore, radiotherapy protocols may induce increasingly strong expectancies of side effects throughout treatment, and increase the likelihood of late effects that can occur weeks to years following treatment (Hsiao et al., 2007). It is also often observed (clinically) that patients experience non-specific side effects in the early weeks of radiotherapy, which are not medically expected and are sometimes reduced by reassurance alone (Garg, 2011). This suggests response expectancies may be prevalent and influential early in treatment. Investigation of the influence of side effect expectancies on toxicity experiences across the course of radiotherapy would reveal which side effects are influenced during treatment and how early this occurs.

Other pre-treatment variables are known to influence the association between response expectancies and side effects. Many relevant symptoms are present prior to treatment (Hofman et al., 2004), with 84% of 1,129 patients with mixed cancer diagnoses reporting some symptoms pre-radiotherapy (Hickok et al., 2005). Patients may misattribute pre-existing symptoms to treatments; thus, measurement of baseline symptoms should be measured and controlled (Roscoe et al., 2006). Research has also suggested that 30-50% of patients with prostate cancer experience psychological issues: 20-60% have reported suffering from anxiety during treatment (Bisson et al., 2002; Hsiao et al., 2007), and depression has been directly linked to the side effects of fatigue and pain in this population (Kunkel, Bakker, Myers, Oyesanmi, & Gomella, 2000). Coping style also appears relevant, with one study in chemotherapy finding 15 of 20 toxicity expectancies

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showed associations with an anxiously preoccupied coping style (Whitford &

Olver, 2012). Based on these reported relationships, it is important to ensure

response expectancies are uniquely predicting side effect experience.

We therefore investigated associations between expectancies of side

effects and subsequent toxicity experience in a diagnostically homogenous older

male sample, undergoing radiotherapy for prostate cancer. Based on response

expectancy research in chemotherapy, we hypothesized that response

expectancies would independently predict side effects at two follow-ups - after

controlling for baseline demographic, health, and psychological variables known

to impact the formation of response expectancies.

Methods

Patients and procedures

Consecutive male outpatients scheduled to be treated for stage I-III

prostate cancer with external beam radiotherapy (EBRT) between 74 and 78 Gray

(Gy), between March 2014 and July 2015, were identified. Eligible patients were

aged over 18 years; fluent in English; able to consent; naïve to chemotherapy and

radiotherapy; and had not had surgery for their diagnosis, but could have

undergone neoadjuvant and/or concurrent androgen deprivation (hormone)

therapy, and were due to receive treatment (with curative intent) at either the

Royal Adelaide Hospital or the Lyell McEwin Hospital, two public teaching

hospitals in the Australian state of South Australia. Patients were excluded if they

had a psychiatric disease or cognitive impairment, of if they were participating in

another study. Eligibility was determined in conjunction with each patient's

treating Radiation Oncologist based on the above criteria. This study was

approved by the RAH Human Research Ethics Committee (HREC), in accordance with the Declaration of Helsinki and The National Statement on Ethical Conduct in Human Research (Approval #130929).

Due to slower than anticipated accrual, the inclusion criteria were expanded in June 2014 to include patients having EBRT at 46-50 Gy, combined with high dose rate brachytherapy boost, after a Radiation Oncologist verified such treatment regimens were identical throughout the first 5-weeks of EBRT. Thus, the initial two assessments could be obtained from these patients. Forty-eight patients enrolled in the study at baseline (Figure. 1) after providing written informed consent. However, 13 did not continue to their specified final follow-up, leaving 35 participants (a 73% retention rate).

After being scheduled for pre-treatment planning computed tomography (CT) scans at the Royal Adelaide Hospital, eligible patients were identified and invited to participate by a clinical nurse through mail. Baseline self-report questionnaires were completed immediately after the planning scans at the RAH, or could be taken home to complete within a 48-hour time-frame, if requested (to increase accrual).

The first follow-up assessments occurred during Week 2 and Week 7 seventh week of EBRT (approximately 6- and 11-weeks after baseline), in waiting rooms prior to patients' appointments with their treating Radiation Oncologist. In rare ($n = 3$) instances patients could not complete the questionnaire on the day of their appointment: they completed it when visiting the hospital within the same treatment week.
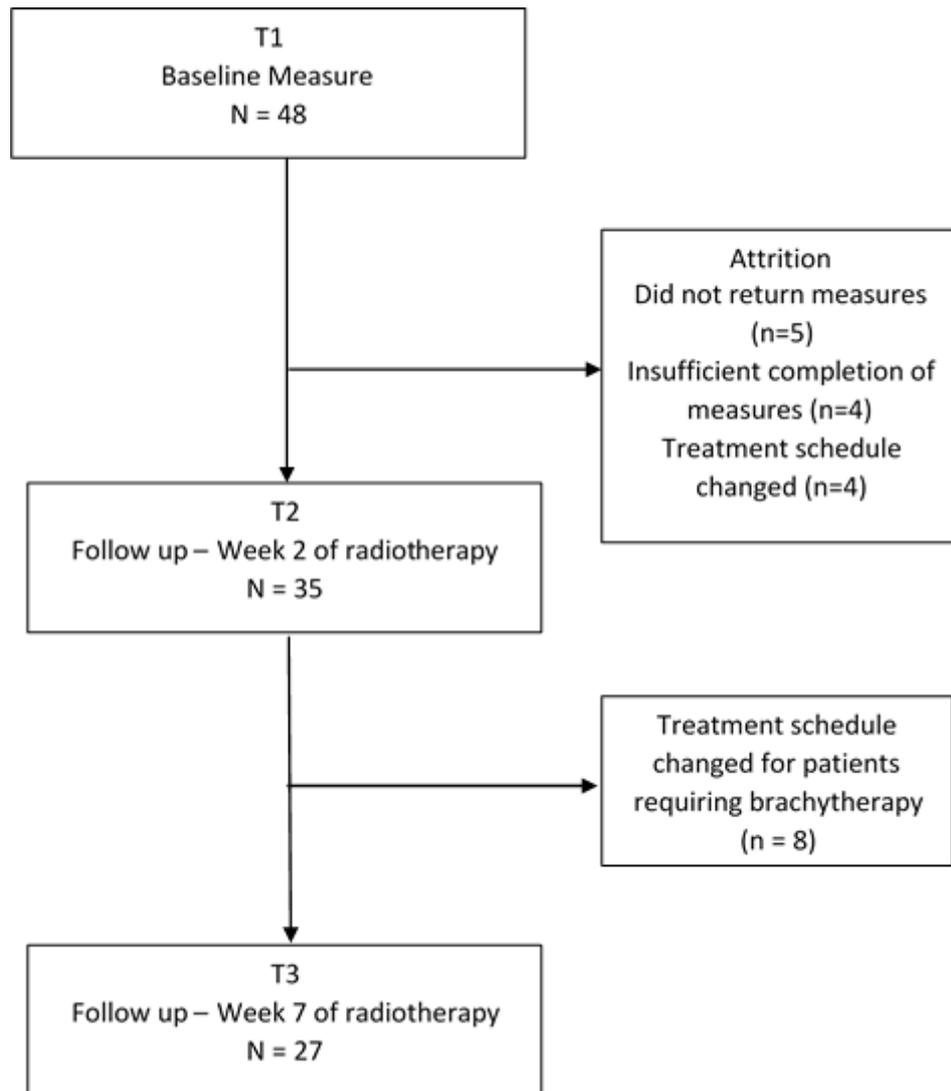
Figure 1. Participant flowchart throughout the study

Measures

Patients completed self-report questionnaires on up to three separate
occasions. The first, pre-treatment baseline measurement (T1) included
standardized emotional state and cancer coping style measures, and study-specific
measures of demographic information and expectancies of side effects anticipated
during the first 2-weeks of treatment. The second follow-up occurred 2-weeks
into EBRT (T2). Patients reported their experience of side effects, and again

reported their toxicity expectancies, anticipated during the next 5-weeks of treatment (for EBRT only patients). The patents scheduled for brachytherapy reported their side effect expectancies for the next 3-weeks of treatment because their treatment changed at this stage, thus their participation ceased at T2. The final follow-up during the seventh week of treatment (T3) was similar to T2 assessment, except that response expectancy assessments were excluded because EBRT treatment was nearing completion at this time.

A study-specific, demographic and health questionnaire comprised 26 questions: basic demographic, health, and lifestyle questions; perceived knowledge and understanding of treatment; and baseline incidence of the symptoms to be assessed in the response expectancy and experience scales.

The Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987) was calculated for each patient, using medical records, to assess the incidence of comorbid conditions.

The Depression, Anxiety and Stress Scale 21 (DASS21; Lovibond & Lovibond, 1995) measures an individual's level of depressive, anxious and stress symptomology, as separate constructs, over the preceding week. Twenty one-items produce separate scores for each of the constructs (7-items per scale). The 21-item shortened version of the DASS has been shown to have good reliability (Henry & Crawford, 2005b), replicated in the current study for stress and depression, but not anxiety (Cronbach's α = 0.86, 0.87, and 0.62 respectively).

The Mental Adjustment to Cancer (MAC) Scale measures cognitive and behavioural coping responses to a cancer diagnosis. Patients are asked to self-rate how 40 statements apply to them at the present moment. The MAC has five subscales; Fighting Spirit, Fatalistic, Helpless/Hopeless, Anxious Preoccupation,

and Avoidance and has been shown to have adequate reliability and validity, and be acceptable to patients (Watson et al., 1988). The currently study found similar reliability to original research; however the fatalistic scale's reliability was lower (Fatalistic scale, Cronbach's $\alpha = .43$; all others $\alpha = .70-.90$).

Patients rated their expectancies of 19 treatment-related side effects on Visual Analogue Scales (VAS); a horizontal 100mm line, marked at 10mm increments, in multiples of ten (i.e. 0, 10… 100). They were asked to rate how severely they believed they would experience the side effect in question at each specific time (Colagiuri & Zachariae, 2010), anchored at (0) 'do not expect the side effect at all' and (100) 'expect the worst possible severity of the side effect'. The times for each assessment were (1) the first 2-weeks of treatment, (2) the next 3-weeks of treatment (for brachytherapy patients), or the next 5-weeks of treatment (for EBRT patients). The list of side effects comprised common known acute toxicities compiled in conjunction with radiation oncologists and a radiotherapy information nurse at the RAH. Each scale had an additional implausible side effect (loss of head hair) included as a quality control test to detect any careless responding (Meade & Craig, 2012).

Participants recorded the severity of any side effect experience on near-identical VAS scales, with the same toxicities listed, but anchored by (0) 'did not experience the side effect at all' and (100) 'experienced the worst possible severity of the side effect'. The timing of the experience assessments were (1) at Week 2 covering the first 2-weeks of treatment, and (2) at Week 7 covering the third to seventh week of treatment (for patients treated with only EBRT).

A second set of response expectancy and experience questionnaires assessing the same 19 side effects based on 5-point scales (another common

response expectancy measurement method) was also administered, and have been reported elsewhere as part of a separate psychometric study (*Study 2, Chapter 3*).

Statistical methods

Data were analysed using the IBM SPSS Statistics program, version 22. Frequencies and descriptive statistics were used to characterize the sample and Pearson's correlations were used to inform the most appropriate covariates for inclusion in subsequent multivariate analyses. Hierarchical multiple linear regressions were used to determine the association between expectancies of side effects and subsequent experiences, above and beyond known and novel predictors. Unique covariate combinations (or single variables) were simultaneously added to Step 1 of models given no known theoretical reasons for temporal relationships, and patient response expectancies were added at Step 2 to determine their unique variance.

The prediction of response expectancies on experiences was split into two series for individual side effects (T1 to T2, then T2 to T3) to take advantage of sample size changes. The first model analysed T1 expectancies of side effects and their ability to predict experiences at T2, above and beyond covariates that correlated with response expectancies or experience for each side effect at $r \geq .35$ (i.e., significant relationships). The second model regressed T2 expectancies of side effects onto T3 experiences, and included covariates that were associated at least $r \geq .40$ (a higher association was utilized in line with statistical significance and to increase power due to the reduced sample size; Cohen, 1988).

A priori power analysis indicated that 39 participants were required to achieve 80% power with an alpha level of .05, to observe moderate effects of $r \geq$

= .30 in a within group design of three repeated measures (Cohen, 1988). Because

we were slightly under this number, and the group receiving brachytherapy only

participated on two occasions, effect sizes were reported and discussed, alongside

exact *p*-values (Tabchnick & Fidell, 2006). Correlation coefficients (*r*), phi

coefficients (ϕ), and standardized Beta coefficients (β) of .10, .30, and .50

represent small, moderate, and large effects, respectively (Cohen, 1988). Due to

the limited number of participants, and the empirical basis of hypotheses,

Bonferroni adjustments were not used to avoid inflating Type II error which was

of greater concern (Perneger, 1998).

<div align="center">

Re**sults**

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Data screening

Missing data were screened and 4 cases were removed from analysis

(Figure 1). The assumptions of no multicollinearity and homoscedacity were met

throughout analyses. Twelve (of 36) models had one outlier, with a *z*-score above

3.29 (range = 3.55-5.70; Tabachnick & Fidel, 2013). Outliers were removed and

models re-run, however this did not improve the normality of the error residuals,

and because the scores were considered true representations of patients' data, they

were eventually retained. All error residuals were normally distributed at T3,

however at T2 eight were normally distributed, and 10 were not. Transformations

were attempted for skewed data, but this reduced the sample size considerably

and did not improve score distributions. Ordinal logistic regression was

considered; however, the assumption of parallel lines was not met and there

would not have been sufficient power for covariate analyses (Tabachnick & Fidel,

2013). Therefore, we proceeded with raw data, conducting two sets of

hierarchical regression analysis. This was deemed preferable, because (1) this analysis is in line with similar studies of response expectancies in chemotherapy (Olver et al., 2005; Whitford & Olver, 2012), and (2) the violation of normality is not considered to invalidate regression outcomes (Tabchnick & Fidell, 2006).

Attrition analysis

No significant differences were found between men who did or did not continue to their specified final follow-up (T2 for brachytherapy patients and T3 for EBRT patients), for any demographic or emotional state data. However, those who did not continue reported significantly higher levels of the coping style Helpless/Hopeless on the MAC scale (see Appendix B). They were also significantly less likely to have urinary urgency before treatment began, but had higher T1 expectancies of urinary urgency, urinary frequency, hair loss in the pelvic region, and bowel leakage.

Descriptive statistics

Most patients were born in Australia, and identified with a Western culture, were married, and not working (Table 1). The majority of the sample ($n = 26$, 76.5%) were above 65 years of age, thus considered geriatric (Sieber, 2007), and the most common education level was completion of secondary education (high school). On average, the men reported a normal level of daily activity, and rated their knowledge of radiotherapy as moderate. Most were not receiving psychological assistance during treatment, and felt the level of side effect-related information received at the time of their baseline scans was adequate.

Despite an average age of 71 years, the patients had low levels of comorbid illness according to the Charlson Index, (Charlson et al., 1987). Just over a quarter ($n = 12$, 27.3%) of patients had one comorbid condition and 6.7% ($n = 2$) of patients had two. A separate investigation of comorbid conditions in a similar sample of 3,095 men diagnosed with prostate cancer found 76% had at least one comorbid condition (Klabunde, Reeve, Harlan, Davis, & Potosky, 2005); substantially different from the current sample.

The average time between diagnosis and participation in the study was 12 months (ranging from 2 months to 4.3 years). Just over half the patients had received androgen deprivation (hormone therapy; $n = 19$, 54.3%) and most were treated at the RAH ($n = 25$, 71.4%), with 10 (28.6%) treated at the LMH. Most patients ($n = 27$, 77.1%) were treated with EBRT in isolation, but eight (22.9%) had additional brachytherapy following participation at T2.

Baseline levels of side effects

Pre-treatment levels of side effects were measured to ensure experienced toxicities were not long-standing. Most baseline symptom levels were low, affecting between one and five patients (2.9-14.3%). However, 12 patients (34.3%) reported urgent urination, 14 (45.7%) an inability to reach orgasm, 16 (45.7%) a reduced desire for sex, and 17 (48.6%) an inability to have or maintain

Table 1

Participant characteristics

		Mean (*SD*)	Sample range
	Age	71.1 (7.5)	52.1 - 81.8
	Comorbidity	0.4 (0.6)	0 – 2
	Activity	1.3 (0.6)	0 – 3
	Radiotherapy Side effect Knowledge	3.1 (1.0)	1 – 5
		n (%)	
Country of birth	Australia	27 (77.1%)	
	Other	8 (22.9%)	
Culture	Western	29 (82.8%)	
	Both Eastern and Western	3 (8.6%)	
	Eastern	1 (2.9%)	
Marital status	Married or defacto	23 (65.7%)	
	Separated or divorced	6 (17.2%)	
	Never married or single	3 (8.6%)	
	Widowed	2 (5.7%)	
Education	Secondary	17 (48.6%)	
	Tertiary	9 (25.7%)	
	Primary	7 (20.0%)	
Work status	Not working	32 (91.4%)	
	Working	2 (5.8%)	
Psychological Assistance	No	33 (94.3%)	
	Yes	2 (5.7%)	
Perception of amount of information received	Right amount	27 (77.1%)	
	Not enough	7 (20.0%)	

erection. Baseline symptoms significantly associated with the relevant side effect expectancies or experiences were controlled in the regression models outlined below.

The unique prediction by expectancies of side effects on subsequent experiences

Hierarchical linear multiple regressions were used to determine the unique contribution of side effect expectancies on subsequent experience the same toxicities. For each model, covariates significantly associated with either the response expectancy or toxicity were entered into each model at Step 1 to control their influence (see Appendix C for correlations) and expectancies of each toxicity were entered at Step 2 to test their unique prediction.

Table 2 shows the first series of regressions for the prediction of T1 response expectancies on experiences perceived at T2 (pre-treatment baseline to 2-weeks into radiotherapy). Results revealed the full models (covariates and response expectancies) significantly predicted 13 of 18 T2 side effect experiences, explaining between 3-44% of the variance, according to adjusted R^2 outcomes. T1 response expectancies uniquely and significantly predicted six T2 toxicity experiences according to R^2 change values independently contributing 12-39% to the variance explained. These included inability to reach orgasm, blood in urine, bowel leakage, and reduced sexual desire (all large effects), erectile inability, and incontinence (moderate effects),

Table 2

The unique contributions of baseline expectancies of toxicities (T1) on subsequent experience (T2)

Toxicity	n	Covariates	Full model			Unique contribution of response expectancies			
			Adjusted R^2	F	P	R2 change	F change	p	β
Fatigue	33	a	-.06	0.31	.82	.02	0.54	.47	.16
Nausea	33	a, b, c, d, e, f	.50	4.93	.002	.06	0.05	.82	.04
Abdominal Cramps	34	a, b, d, e, f, g	.16	1.84	.13	.03	1.18	.29	.26
Skin Irritation	34	d	.01	1.20	.32	.06	1.82	.19	.26
Urinary Frequency	33	h, i, j	.45	7.31	<.001	.02	0.95	.34	.15
Hair Loss (Pelvis)	32	d	.06	2.53	.10	.06	1.98	.17	.27
Pain, Burning or Discomfort when Urinating	34	a, c, d, i, j, k	.36	3.42	.01	.01	0.42	.52	.13
Poor Urinary Stream	34	e, h, i, j, l	.40	4.70	.003	.04	2.18	.15	.26
Blood in Urine	34	b, d, e, j	.22	2.76	.04	.22	9.02	.01	.63
Urinary Urgency	33	d, e, i, j	.24	3.57	.01	.07	2.95	.10	.42
Urinary Incontinence	34	a, d, j	.27	5.28	.003	.12	5.31	.03	.39
Rectal Urgency	33	a, d, e, n, o	.39	4.07	.01	.03	1.48	.24	.21
Painful Bowel Movement	34	a, b, d, e, m	.31	3.07	.02	.01	0.58	.45	.16
Bowel Leakage	34	a, d, m, p	.32	3.76	.01	.20	8.80	.01	.50
Blood in Stools	33	a, b, d, e, p	.06	1.31	.29	.04	1.26	.27	.26
Reduced Desire for Sex	32	c, i, p	.61	12.99	<.001	.29	22.90	<.001	.57
Inability to Reach Orgasm	30	i, j	.38	6.92	.001	.30	14.19	.001	.59
Inability to Have or Maintain Erection	29	c, h, i, j	.41	8.30	<.001	.15	9.67	.01	.46

Note: Covariates required to have a significant (r ≥0.35) univariate association with response expectancies or outcomes for inclusion in the model; covariates include: [a]stage of disease; [b]age; [c]number of comorbidities; [d]highest level of education; [e]helpless/hopeless coping style; [f]stress; [g]anxious preoccupied coping style; [h]culture identification; [i]baseline level of that toxicity; [j]treatment; [k]day-to-day activity level; [l]avoidant coping style; [m]English as a first language; [n]marital status; [o]time since diagnosis; [p]hormone therapy.

Table 3 shows the next series of regressions for T2 response expectancies on experiences reported at T3 (response expectancies 2-weeks into treatment to predict experiences 5-weeks into radiotherapy). Models could not be fit for blood in stools at T3 because no men reported experience of this side effect. No covariates correlated with expectancies or experiences of blood in urine above the $r \geq .40$ cut-off, therefore a simple regression was used, revealing no significant prediction. $F(1,23) = 0.57$, $p = .46$), and a small adjusted R^2 value of -0.02. For the remaining 16 toxicities, full models significantly predicted 11 side effects. According to adjusted R^2 outcomes for each model, between 19 and 100% of variance was explained in the significant models. For all other toxicities, models explained between 4-13% of variance. Response expectancies uniquely contributed significant variance to 7 of the 18 models, explaining between 15-60% of the variance (R^2 change) in side effect experience. All other models explained between 0-8% of the variance in toxicities. The unique prediction of toxicities by response expectancies was considered large for inability to reach orgasm; inability to have or maintain erection; reduced sexual desire; pain, burning, or discomfort when urinating; poor urinary stream; and painful bowel movements, and moderate for bowel leakage; nausea; and fatigue; nausea.

Table 3

The unique contributions of Week 2 expectancies of toxicities (T2) on subsequent experiences at Week 7 (T3)

Toxicity	n	Covariates	Full Model			Unique contribution of response expectancies			
			Adjusted R^2	F	p	R2 change	F change	p	β
Fatigue	25	a, b, c	.06	1.83	.19	.15	3.65	.07	.44
Nausea	27	a, d,	.07	1.61	.22	.16	4.20	.05	.46
Abdominal Cramps	27	b, e, f, g	.40	4.00	.01	.00	0.03	.86	.03
Skin Irritation	27	f	.19	4.00	.03	.00	0.001	.97	.01
Urinary Frequency	27	h, i, j	.32	3.98	.02	.03	1.03	.32	.21
Hair Loss in Pelvic Region	27	g, h, k	.04	1.26	.32	.02	0.54	.47	.18
Pain, Burning or Discomfort when Urinating	27	i, j, l	.62	10.64	<.001	.17	10.71	.004	.52
Poor Urinary Stream	27	i, j	.55	11.30	<.001	.35	19.57	<.001	.77
Urinary Urgency	27	h, i, j	.32	3.99	.02	.04	1.61	.22	.28
Urinary Incontinence	26	h, i	.52	9.58	<.001	.03	1.24	.28	.17
Rectal Urgency	27	h, k	.13	2.18	.12	.002	0.06	.82	.05
Painful Bowel Movement	27	i, m	.46	7.98	.001	.23	10.56	.004	.51
Bowel Leakage	26	k	.44	10.92	<.001	.24	10.76	.003	.49
Reduced Desire for Sex	24	e, i, n	.96	142.62	<.001	.40	235.59	<.001	.70
Inability to Reach Orgasm	22	e, l, o	1.00	-	-	.50	-	-	.91
Inability to Have or Maintain Erection	23	e, o	.77	25.98	<.001	.37	36.09	<.001	.75

Note: Covariates required to have a significant (r ≥0.40) univariate association with REs or outcomes for inclusion in the model; covariates include: [a]age; [b]stage of disease; [c]avoidant coping style; [d]helpless/ hopeless coping style; [e]number of comorbidities; [f]anxiety; [g]highest level of education; [h]depression; [i]marital status; [j]treatment; [k]stress; [l]culture identification; [m]English as a first language; [n]hormone therapy; [o]baseline level of that toxicity.

Discussion

We extended previous research on the influence of side effect expectancies on subsequent experience to male patients with cancer being treated with EBRT. We investigated these associations across treatment and above and beyond known and novel covariates.

By the second week of radiotherapy, response expectancies independently explained a significant amount of moderate-to-large variance in six side effects. This is an interesting result, given toxicities are not medically expected to begin occurring at this early stage of treatment (Garg, 2011). Accordingly, these side effects may have a psychological basis making them susceptible to patients' side effect expectancies before treatment begins. This suggests such toxicities may benefit from interventions aimed at reducing response expectancies.

Many of the toxicities predicted at T2 (i.e., blood in urine and stool, bowel leakage, inability to have or maintain erection) were somewhat objective side effects (i.e., they can be objectively measured). These findings are supported by a recent meta-analysis (Devlin, Denson, & Whitford, 2017), that also found the strongest association between expectancies of a partly objective toxicity, perceived head hair loss, and subsequent experience, compared to expectancies of 15 other toxicities. However, because all toxicities were measured through self-report scales they were ultimately patients' subjective perceptions of side effects (Whitford & Olver, 2012); thus, investigation into the prediction of expectancies of side effects, measured objectively, is needed before conclusions can be drawn.

By the seventh week of radiotherapy (near completion), response expectancies uniquely predicted seven side effects (measured 2-weeks into treatment). This aligns with previous research and theory (Kirsch, 1985;

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Montgomery & Bovbjerg, 2000; Sohl et al., 2009). However this was not the case for all side effects; thus, utilizing response expectancies to investigate or employ preventative measures, or to categorize patients most at risk would be more effective if they are specific to individual side effect expectancies (or symptom clusters, such as sexual side effects), rather than targeting toxicities in general.

Expectancies of sexual side effects predicted subsequent experience of these toxicities consistently and a moderate to large degree throughout treatment. For inability to reach orgasm, the full model (including response expectancies, baseline levels of the side effect, culture, and patient comorbidity) entirely predicted the mens' experience of this toxicity by the end of treatment; therefore this may be highly sensitive to intervention. Kirsch (1997) highlighted male sexual dysfunction as a gap in response expectancy literature, however, since then minimal investigation has been conducted in this area. Male patients advised about potential erectile dysfunction when taking beta-blockers experienced this side effect more than those who were not told (Silvestri et al., 2003), and significant relationships between response expectancies and reported 'problems with sex' has been reported (Cassileth et al., 1985; Olver et al., 2005) in male and female patients scheduled for chemotherapy. Despite this, a study of 150 male patients treated with chemotherapy for a range of cancers revealed approximately 80% of the men reported receiving no information about sexual side effects from their doctor, and of those who did, 24% had directly requested it (Lorusso et al., 2016). Thus, it appears expectancies of sexual side effects have important implications clinically, for understanding how such information can be most effectively discussed with patients without heightening response expectancies (and hence, potentially increasing the risk of their occurrence).

Contrary to some previous research (Hofman et al., 2004), pre-existing levels of symptoms and comorbid conditions were low in the current sample, and did not often account for the ability of response expectancies to predict toxicities. As suggested by Hofman et al. (2004), response expectancies are 'not simply a case of [patients] expecting more of the same" (p. 856). Thus, while baseline symptom levels are important to control in analyses, it does not appear that patients are attributing side effect experience to treatment when it was already occurring.

Attrition analysis revealed that participants who withdrew from the study before completion reported significantly higher helpless/ hopeless styles of coping, and increased expectancies of two side effects, indicating potential selection bias of a more healthy and optimistic sample.

Study Limitations

Sample homogeneity was a strength of this investigation. This patient group was selected based on (1) the homogeneity of their treatment; thus, the treatment regime, including the dosage and schedule; and participant demographics were all similar across participants; allowing for greater control of confounds, and (2) the high incidence of treatment – in an attempt to maximize potential accrual (Torre et al., 2015). A previous review reported significant differences between the outcomes of studies including patients undergoing different treatment regimens (Devlin et al.), thus, we felt it important to remove potential sources of confusion during a novel investigation of toxicity expectancies.

However, this also made data collection of an adequate sample size difficult. The reduced sample size may have resulted in some statistical analyses being underpowered, risking Type II error. We mitigated this risk by having theoretically driven hypotheses, ensuring only variables significantly related to expectancies of side effects were included in the full models, and reporting effect sizes, alongside p-values. We also took steps to increase the sample size by broadening the inclusion criteria to include patients having EBRT for the initial 5-weeks. While successful, this also resulted in fewer participants being able recorded their experience at T3 because treatment schedules diverged by this point. Therefore, this difference in sample sized prevented the use of repeated measures analyses.

Moreover, some side effects did not demonstrate normally distributed error residues at T2, thus the model may have been less suited to capturing the full picture of the associations that would be captured by linear relationships (Tabchnick & Fidell, 2006). However regression analysis are often robust to this assumption (Tabchnick & Fidell, 2006). Based on the magnitude of many of the associations, and the homogeneity of the current sample, the influence of expectancies of radiotherapy side effect on subsequent experiences is apparent in this novel investigation, and further research is warranted.

Clinical Implications

Response expectancies appear to predict patients' experience of some toxicities, but differs between individual side effects are evident, so interventions should target those toxicities more strongly predicted by their expectancies. Response expectancies are influential from early in EBRT and may partly explain

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the experience of non-specific side effects. Sexual side effects appear to be strongly predicted by pre-treatment response expectancies of them; thus, caution during pre-treatment discussion between patients and healthcare workers is indicated.

Conclusion

Taken together, the relationship between expectancies of side effects and experiences were replicated in this novel sample and treatment regime, although not universally, and many toxicities were predicted by response expectancies before they were medically expected. The unique prediction of expectancies of sexual side effects became stronger over time and demonstrated large effects throughout. If, as Hofman and Colleagues (Hofman et al., 2004) reported, males over 60 years of age were the least likely to form response expectancies, the current study suggests that response expectancies may be predictors of side effects across a wide range of patients undergoing different treatment modalities.

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Chapter 5: Randomised controlled experiment

The impact of side effect information presentation on response expectancies and experience: a randomized controlled experimental trial of positively- versus negatively-framed information

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Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Preamble

The preceding chapters have presented research designed to better understand the scope of expectancies of cancer treatment-related side effects, and their ability to predict the severity of subsequent experience. The results indicated that response expectancies predict a wide range of toxicities (albeit to differing degrees) across patients with different ages, sex, diagnoses, and treatment.

It follows that there is a need to investigate whether response expectancies can be harnessed to reduce the severity of non-specific treatment side effects. Progress is being made through the use of verbal suggestion without deceit or a hypnotic state (Kirsch, Wickless, & Moffitt, 1999) and research has shown that different information presented in a clinical context can produce different responses (Colloca & Finniss, 2012). Research has also indicated that simply changing the presentation of the statistically same side effect risk (framing) may be able to influence response expectancies (Heisig et al., 2015) in healthy samples, and side effects (O'Connor et al., 1996) in clinical samples. Despite this, no research had considered whether there is a link between the presentation differences and both response expectancy formation and the severity of side effects experienced.

To shed light on the impact of the presentation of side effect information, valence framing (i.e. presenting the side effect information in a positive or negative format) was selected for the final study. Through framing, the statistical properties of the information are preserved. Thus, this conforms to informed consent and wider ethical standards, potentially enabling quick uptake by healthcare workers.

Manuscript

Abstract

Background. Pre-treatment response expectancies of side effects (toxicities) influence subsequent experience; however, clear reduction strategies are currently lacking. One potential intervention requiring detailed investigation is the influence of presenting statistically equivalent, but differently framed toxicity information on both the severity of response expectancies and experience of related side effects.

Purpose. Investigating the impact of differential framing of toxicity information on the severity of response expectancies and resulting experiences, and the associations between response expectancies and related experiences (after controlling covariates) can inform potential intervention strategies aimed at reducing toxicity severity.

Methods. Groups of university students (N=134) were randomly allocated to receive positively- or negatively-framed cold pressor information before completing measures of 12 response expectancies (for cold pressor-related reactions), emotional state, and coping style. During and immediately after the cold pressor, objective and self-report cold pressor experiences were assessed.

Results. Differential framing did not significantly impact response expectancies or experiences, but increased pain threshold (p=.08, ϕ=.16) showed a trend in the positive-frame condition. Hierarchical multiple regressions revealed all but one (itching) response expectancies uniquely predicted 6-23% of the variance in subsequent experience. Students participating after a popular, parallel

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charity event (the Ice Bucket Challenge) showed significantly less average pain (p=.05, ɸ=.24) and increased pain threshold (p=.003, ɸ=.63).

Conclusions. Although the influence of response expectancies on intervention experiences was replicated across reactions, the impact of framing on the severity of response expectancies or experience was not established. Importantly however, social influences on side effect experience were demonstrated, indicating future psychosocial research directions

Keywords: adverse reaction, toxicities, side effect, expect, valence framing, informed consent

Patients' treatment-related side effects (toxicities) often vary in ways that cannot be medically explained, termed *non-specific* responses (Shepherd, 1993). These adverse reactions are associated with patient distress, treatment non-adherence, and additional hospital costs, among others (Barsky et al., 2002). Predicting individual risk for non-specific side effect incidence and severity, and understanding application of this knowledge, may assist healthcare providers to reduce toxicities.

Individuals' pre-treatment beliefs about how they will automatically react to stimuli, including treatments and medications, are labelled *response expectancies*. Response expectancies are recognized predictors of non-specific toxicity variability (Kirsch, 1985), and are the main mechanism underlying placebo, nocebo, and hypnotic responses (Kirsch, 1999b, 2013). The strength of a patient's initial expectancy of a toxicity often predicts severity of that same side effect during treatment (Colagiuri & Zachariae, 2010; Roscoe et al., 2006; Sohl et al., 2009), suggesting side effects could be reduced by lowering response expectancies. A cognitive technique– valence framing – may have the potential to influence side effect response expectancies (and thus experience) while being simple and cost-effective to implement.

Framing is the presentation of statistically equivalent information in different formats. Specifically, *valence framing* (Levin et al., 1998) refers to presenting statistically equivalent information in a negative-frame (e.g., you have a 20% chance of experiencing fatigue) or a positive-frame (e.g., you may experience fatigue, but there is an 80% chance that you will not). These small differences in presentation have been shown to influence many healthcare-related variables, including decision-making (Edwards, Elwyn, Covey, Matthews, & Pill,

2001; Payne, Sagara, Shu, Appelt, & Johnson, 2013; Wilson, Purdon, & Wallston, 1988) and health promotion messages (Gallagher & Updegraff, 2012; Gerend & Shepherd, 2016), but their impact on response expectancies is not clearly established. Colloca and Miller (2011c) recommended framing as a potential toxicity reduction technique. Yet, despite the simplicity of framing modifications, we only identified two published studies investigating the impact of framing on response expectancies or experience (Heisig, Shedden-Mora, Hidalgo, & Nestoriuc, 2015; O'Connor et al., 1996).

O'Connor et al. (1996) utilised a randomized controlled trial to test alternate pre-treatment framing of influenza vaccine side effect information in 292 cardiac patients. They then measured the proportion who acquired a toxicity (or did not) three days later. Patients in the negative-frame reported higher incidence of five side effects for which verbal information had been supplemented by a visual-aid poster (an effect not seen for 10 toxicities verbally but not visually depicted). Although patients in the positive-frame had significantly higher *general* expectancies (i.e., remaining free of influenza toxicities), it was not clear whether variations in side effect experience reflected changes to individual response expectancies.

Heisig et al. (2015) investigated whether framing influenced response expectancy formation in 124 healthy volunteers imagining hypothetical interventions (endocrine therapy or chemotherapy). The positive-frame group received detailed treatment benefit information, compared to standard information (negative-frame). Results indicated significantly fewer response expectancies were formed by patients for endocrine therapy (partial $\eta^2 = .08$), but no differences were found for chemotherapy. They theorized the well-known side

effects of chemotherapy (e.g., hair loss) had pre-existing response expectancies (based on observation of other individuals or the media), already too strong to be influenced by framing. Because the study was hypothetical, the impact of these differing response expectancies on actual side effect occurrence could not be determined, and specific valence framing was not utilised.

However, the combined findings of these two studies suggest that framing may impact response expectancies of side effects and subsequent experience. Hence, the influence of framing (Heisig et al., 2015) and the provision of statistical information in visual form (O'Connor et al., 1996) require further investigation.

Importantly, other known correlates of response expectancies and experience may share or reduce the predictive power of response expectancies. Therefore they need to be considered in analyses of response expectancies and subsequent experiences. Expectancies of novel experiences are thought to be based on similar previous experiences (e.g., motion sickness may influence expectancies of chemotherapy-induced nausea; Rotter, 1982; Schnur et al., 2007), but the evidence is mixed (Andrykowski et al., 1988; Montgomery & Bovbjerg, 2003; Morrow, 1989; Roscoe et al., 2010a). Also, the impact of state anxiety on response expectancy formation (Andrykowski & Gregg, 1992; Cassileth et al., 1985; Jacobsen et al., 1988) is unclear, with an anxiously preoccupied coping style demonstrating stronger associations with response expectancies (2012).

To test the effect of valence framing on response expectancies and experiences in the current study, we used a well-established pain-inducing experimental technique; the cold pressor test (CPT), a temperature-controlled ice-cold water solution in which participants place their hand. The CPT was used as

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an analogue for naturally occurring clinical induction of medical treatment side effects (i.e., pain, itching, headache). Based on extant research, we hypothesized (1) different framing of pre-CPT information would influence the severity of response expectancies, and related experiences, and (2) expectancies of CPT-related reactions would significantly predict subsequent experience, above and beyond known and novel variables (i.e., similar previous history, emotional state, coping style, and framing condition).

Method

Participants and procedure

University students in South Australia (N = 134) were accrued between April-October 2014, when an adequate sample size was reached. Participants were recruited through a psychology student research participation program (*n* = 93), email list (*n* = 21), and posters displayed on-campus (*n* = 20). Incentives of course credit (research participant pool), or entry into a draw to win one of four $50 vouchers (email or poster respondents), were provided to maximize response rates (Brueton et al., 2013). Eligible participants were aged 18 years or above, fluent in English, and naïve to the CPT. Exclusion criteria included reporting any physical (cold hypersensitivity, hand injury), medical (hypertension, fainting, seizures, frostbite, Reynaud's Phenomenon, cardiovascular or chronic disease), or psychological/psychiatric conditions. Participants must not have consumed alcohol or analgesics within 12 hours (Walsh, Schoenfeld, Ramamurthy, & Hoffman, 1989), or been vaccinated 48 hours prior to the experiment. After 23 (17.8%) participants completed the study, one became momentarily faint after the

CPT; thus, an additional criterion ensuring participants had eaten 2 hours prior to the experiment was imposed (von Baeyer, Piira, Chambers, Trapanotto, & Zeltzer, 2005).

Informed consent was obtained from all individual participants. A maximum of three participants entered a designated university room in each experimental session, maintained at 22±1 degrees Celsius. Participants confirmed they met eligibility criteria, and completed baseline questionnaires in their participation groups. They were briefed about the CPT procedure and invited to ask questions *before* being presented with standardized (scripted) CPT information. Participants were then directed into an adjacent room, separated by partitions so they were no longer visible to each other, and asked to remain silent; to minimize social influences. When the experimenter (E. D.) said "Go", participants began the CPT by placing their non-preferred hand (i.e., the hand they did not write with) in the ice-cold water. They were instructed to briefly raise their free hand when they first experienced discomfort ("pain threshold"), and to remove their immersed hand from the water when discomfort reached an intolerable level ("hand withdrawal"). Both times were recorded on stopwatches by the experimenter, but the times were blinded to participants. Hot water bottles, towels, and warm water were immediately supplied to rapidly warm participants' hands to room temperature as they were debriefed and completed measures of their experience. Conduct of the study was approved by The University of Adelaide Human Research Ethics Committee (approval H-2014-037), in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The Cold Pressor Test

The cold pressor was a 12 litre insulated cooler containing water (8 litres) maintained with ice between 0-3 degrees Celsius (Schulz, Lass-Hennemann, Sütterlin, Schächinger, & Vögele, 2013; Walsh et al., 1989), measured by a spirit-filled thermometer. No ice remained visible in the tank during the test. A pump circulated the water to maintain a consistent temperature and prevent localised warming of water surrounding the hand (Mitchell, MacDonald, & Brodie, 2004), reducing the likelihood of ceiling effects. Participants gradually placed their non-preferred hand into the water to their mid-forearm, with the hand open and still. A maximum immersion of 180 seconds was enforced, as specified to participants beforehand (Schwabe, Haddad, & Schachinger, 2008).

Condition

This was a between-within groups, single blinded, randomized controlled design. An online randomization calculator (Inc., 2016) allocated each group attending an experimental session to either "positive-frame" or "negative-frame" (Figure 1). At recruitment, participants were informed that experimental information would be presented in one of two ways but the variation was not specified, blinding them to conditions (O'Connor et al., 1996). However, the experimenter was aware of the participants' condition following group allocation. A power analysis indicated 128 participants (minimum) were required to detect moderate differences between two groups using two-tailed tests, to achieve 80% power, $\alpha=.05$ (Cohen, 1988). Following randomization, five participants were

excluded or withdrew prior to study completion, achieving a participation rate of

96.3% (*n* = 129; Figure 1).
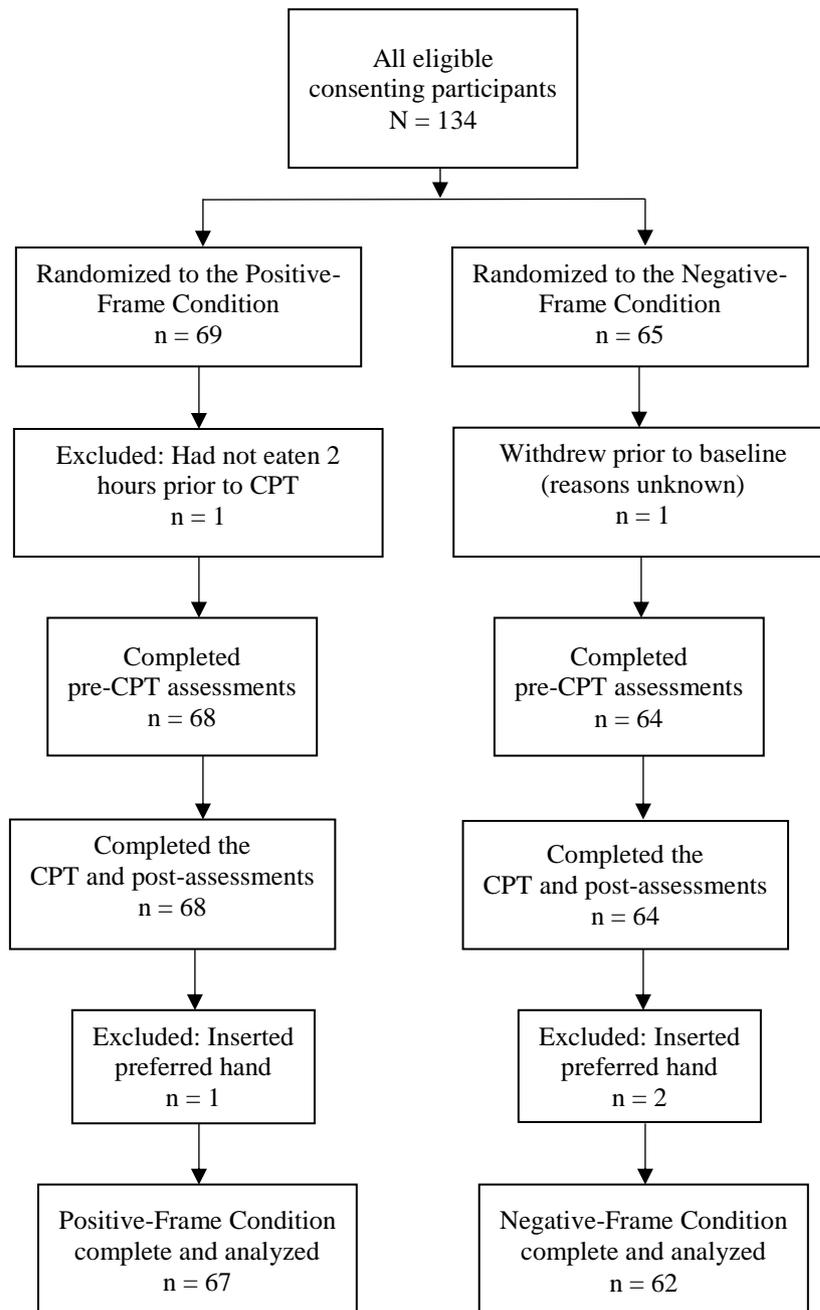
Figure 1. Participant flowchart for randomized CPT experiment

Intervention

Verbal information was supplemented by posters (O'Connor et al., 1996),

visually presenting the scripted wording statistics, to assist in information

retainability. The information format was based on O'Connor and collegues (1996) method but the text was study-specific. The experimenter informed patients of the duration for which a comparable sample of healthy students (Pud, Eisenberg, Sprecher, Rogowski, & Yarnitsky, 2004) were able to continue the CPT – expressed in either a positive- or negative-frame. Those in the positive condition were told "About 20% of people can leave their hand in the icy water for more than 80 seconds before their discomfort reaches an intolerable level, which means out of 100 people, 20 can leave their hand in longer than 80 seconds", and those in the negative condition were told "About 80% percent of people remove their hand from the icy water in less than 80 seconds as their discomfort is at an intolerable level, which means out of every 100 people, 80 are not able to leave their hand in for 80 seconds". Thus, the information was based on the single response "hand withdrawal", given its objective measurement, its centrality to the CPT, and because intolerable levels of any other reaction (i.e., pain or throbbing) would likely result in hand withdrawal. The word "discomfort" was selected over "pain", and the CPT was labelled a cold pressor t*ask* (not a "test") for participants, to prevent any unnecessary distress (von Baeyer et al., 2005). Positive and negative visual depictions used yellow and grey (colours not commonly associated with temperature), to avoid influencing individuals' perceptions.

Measures

Data were collected in a single session. Participants completed demographic questions, study-specific response expectancy measures, and standardized emotional state and coping scales immediately before the CPT. Cold

pressor-related reactions were recorded during (for objectively recorded time variables) and immediately after the CPT.

Demographic questionnaire: A study-specific questionnaire comprised demographic (age, gender, culture), health (current medication), history (previous injury to non-preferred hand, perceived sensitivity to cold), and study-related (study details, preferred hand, time of experiment) information.

The Miller Behavioural Style Scale: Monitoring and Blunting (MBSS): This coping style measure assesses the extent to which an individual attends to (Monitoring) or avoids (Blunting) information when faced with an uncontrollable, threatening situation (Miller, 1987). Responses are summated for each scale. This appeared comparable to "anxious preoccupation" – the cancer-specific coping style of greatest interest (Whitford & Olver, 2012) and was more appropriate for a healthy sample. Research has shown good internal consistency (Miller, 1987); however, reliability in this study was low for Monitoring ($\alpha = .52$) and Blunting ($\alpha = .54$).

The Depression, Anxiety and Stress Scale 21 (DASS21): This 21-item scale assesses symptoms of depression, anxiety, and stress as distinct constructs (Henry & Crawford, 2005b). Each of the 7-items per scale are summated and multiplied by two, to compare to normative data from the original 42-item version (Henry & Crawford, 2005b). Research shows good reliability for all scales (Henry & Crawford, 2005b), supporting the current study with Cronbach's α of .89, .81, and .84 for Depression, Anxiety, and Stress, respectively.

Response Expectancies Scales and Experiences Scales: Study-specific Visual Analogue Scales (VAS) measured both participant expectancies of CPT reactions and their subsequent experiences (severity of post-intervention

reactions). The response expectancy scales asked participants to indicate how severely they expected they would experience each of 10 potential CPT reactions (e.g., headache, discomfort, etc.), assessed on 11-point horizontal lines anchored at (0) 'Do not expect to feel any (response)' to (100) 'Expect to feel unimaginable (response)', increasing in increments of 1 centimetre, by multiples of 10. Using the same format, a second section asked participants to indicate their response expectancies for when they would first experience discomfort, known as "pain threshold", and when they believed they would remove their hand, "hand withdrawal", assessed on scales ranging from 0 to 180 seconds (the maximum hand immersion time), with 45, 90, and 135 seconds marked as guides.

The self-report section of The Experiences Scale mirrored the response expectancies measure, asking participants to rate if the same 10 CPT reactions were experienced but anchored at (0) 'I did not feel any (response)' to (100) 'I felt an unimaginable amount of (response)'. The second section, assessed objectively by the experimenter, timed "pain threshold" and "hand withdrawal". VAS have good test-retest reliability and are sensitive to pain measurement (Williamson & Hoggart, 2005).

Statistical analyses

Data were analysed using IBM SPSS Statistics, Version 22, with alphas set at .05. Frequencies and descriptive statistics characterized the sample. Chi-square tests and independent samples *t*-tests were used to compare demographics across framing conditions to determine whether randomization resulted in comparable groups. Independent samples *t*-tests and one-way Analyses of Variance (ANOVA) with Tukey HSD post-hoc tests were used to explore

influences of CPT reactions between subgroups, and any differences in response expectancies or subsequent experiences, because of framing. Univariate correlations identified covariates to be controlled in hierarchical multiple regressions (See Appendix D), utilised to determine the unique influence explained by expectancies of CPT reactions, on subsequent experience.

Effect sizes are reported alongside exact p values. Specifically, phi coefficients (ϕ), Cramer's V (V), and standardized regression coefficients (β) are represented as .10 for small, .30 for moderate, and .50 for large effects (Cohen, 1988) and partial eta squared (partial η^2) is equivalent to .01 for small, .06 for moderate, and .14 for large effects (Cohen, 1988).

Results

Data screening

Data were screened for missing values, outliers and normality, and to ensure assumptions were met for specific analyses (e.g., homogeneity of variances for ANOVAs, and multicollinearity, and homoscedasticity of residuals for regressions). One DASS21 item was omitted by four participants: each was substituted with individual means (Shrive, Stuart, Quan, & Ghali, 2006; Tabachnick & Fidel, 2013). As is often the case in non-clinical samples, DASS21 data were positively skewed. No substantial outliers were observed. Although one variable (experience of hand withdrawal) demonstrated a slight bi-modal distribution, it was not transformed because its error residuals were normally distributed (Tabachnick & Fidel, 2013).

Sample characteristics

No significant differences were observed across descriptive statistics between framing conditions, implying successful randomization (Table 1). The average age of participants was 22 years and just over half were female. The majority were born in Australia, spoke English as a first language, identified with Western culture, and preferred their right hand. Participants' hands remained immersed in water for an average of 92.8 seconds ($SD = 67.9$, range 6-180) with 43 (33.3%) participants persisting to the maximum time.

Table 2 shows participants had slightly lower levels of Monitoring, and much lower levels of Blunting coping styles compared with female student normative data for the MBSS (Muris, Van Zuuren, De Jong, De Beurs, & Hanewald, 1994); and similar levels of depression, anxiety, and particularly stress, compared to a sample of age-matched students (Larcombe et al., 2016).

Influences on CPT reactions

The number of participants within each experimental session varied. The final number in each group (after attrition) being 54 (49.1%) undertaking the CPT individually, 49 (38.0%) in groups of two, and 26 (20.2%) in groups of three. Significant, moderate differences were found between participants' pain thresholds and the number of participants in each session, $F(2, 125) = 4.05$, $p = .02$, partial $\eta^2 = .06$. Tukey HSD post-hoc comparisons demonstrated when two participants were present ($M = 56.8$, $SD = 24.7$), they were slower to indicate pain threshold than when there were three ($M = 41.7$ $SD = 22.8$, $p = .03$). However, no

Table 1

Comparison of descriptive statistics between framing conditions

	Condition				
	Positive-Frame n = 67 M (SD)	Negative-Frame n = 62 M (SD)	t	p	φ
Age (in years) Range, 18-45 years	21.6 (4.9)	21.4 (5.6)	0.19	.85	.02
Perceived Response to Cold	1.7 (0.6)	1.8 (0.6)	1.11	.57	.09
	Positive-Frame n = 67 n (%)	Negative-Frame n = 62 n (%)	χ^2	p	φ /V
Gender	38 (56.7%)	30 (51.6%)	0.16	.69	.05
Country of Birth					
Australia	47 (70.2%)	48 (77.4%)			
Asia	11 (16.4%)	8 (12.9%)			
America	3 (4.5%)	2 (3.2%)			
Other	5 (7.5%)	4 (6.5%)	2.64	.76	.14
English First Language	53 (80.3%)	50 (80.6%)	-0.05	.96	.004
Culture identification					
Western	44 (67.7%)	46 (74.2%)			
Both Eastern and Western	10 (15.4%)	7 (11.3%)			
Eastern	12 (16.9%)	9 (14.5%)	3.28	.51	.10
Preferred Hand (% right)	63 (94.0%)	53 (85.5%)	1.74	.19	.14
Currently Taking Medication (% yes)	12 (0.1%)	9 (0.1%)	0.56	.58	-.05
First Year of Study (% yes)	54 (42.2%)	53 (41.4%)	1.03	.31	.12
Previous Injury to Hand (% yes)	9 (13.4%)	5 (8.0%)	-0.98	.33	.09

Phi coefficient (φ) and Cramer's V (V); effect size where .10 is small, .30 is moderate, and .50 is a large effect (Cohen, 1988).

Table 2

Descriptive statistics and normative data for MBSS and DASS21 standardized

scales

N = 27	Current sample			Normative data[a]
	Possible range	Observed range	M (SD)	M (SD)
Monitoring	0-16	3-18	10.6 (2.7)	12.1 (2.0)
Blunting	0-16	0-10	3.6 (2.3)	7.3 (2.3)
Depression	0-42	0-42	8.1 (8.5)	10.2[b]
Anxiety	0-42	0-42	7.6 (7.5)	8.2[b]
Stress	0-42	0-42	13.3 (8.6)	13.7[b]

[a]Normative data for the Monitoring and Blunting scales of the MBSS, based on N = 70 female psychology students (Muris et al., 1994); [b]no standard deviation was available for this data; norms for the DASS (Depression, Anxiety, and Stress scales) based on 5061 undergraduate and postgraduate students in Australia (Larcombe et al., 2016)

significant differences between having one individual ($M = 46.4$, $SD = 24.3$) and either two ($p = .08$), or three ($p = .70$) present were found.

Significant differences were also associated with the timing of a social media *Ice Bucket Challenge* that unexpectedly emerged worldwide, midway through data collection (Florance, 2014). In this challenge, individuals had ice water poured over them (paralleling the current study). Participants completing the CPT before reported moderately higher average pain levels ($M = 6.8$, $SD = 2.0$) than those undertaking the CPT during or after the Ice Bucket Challenge ($M = 6.0$, $SD = 2.3$), $t(127) = 2.03$, $p = .05$, $\phi = .24$. Those participating before also displayed lower pain thresholds (experiencing discomfort sooner; $M = 16.9$, $SD = $

11.1) than those undertaking the CPT during and after the Ice Bucket Challenge

($M = 31.9$, $SD = 34.0$), $t(115) = -3.33$, $p = .003$, $\phi = .63$); indicating a large effect.

Positive- versus negative-frame conditions

To investigate the hypothesis that differential framing would predict the severity of response expectancies and subsequent experiences, independent samples *t*-tests were conducted. No significant differences between framing groups for any of the 12 CPT reactions were revealed, with negligible-to-small effects, suggesting framing had no meaningful influence (Table 3). For subsequent CPT reactions, no significant differences between framing conditions were found (Table 4). However, a higher pain threshold was trending toward significance (with a small effect) towards participants in the positive-frame condition. For multivariate analyses, we combined groups and proceeded to investigate the influence of response expectancies on subsequent experiences for the whole sample, to maximize power. Furthermore, given the lack of effect demonstrated by framing, condition was not entered as a predictor variable into subsequent multivariate models.

Table 3

Comparison of cold pressor-related response expectancies between framing

conditions

	Condition						
	Positive-Frame		Negative-Frame				
CPT reactions	n	M (SD)	n	M (SD)	t	p	Φ
Numbness	67	6.5 (1.5)	62	6.6 (1.6)	-0.43	.67	.04
Throbbing	67	5.1 (2.2)	62	4.6 (2.1)	1.40	.16	.12
Discomfort	66	6.5 (1.9)	62	6.9 (1.6)	-1.37	.17	.12
Crushing	67	3.7 (2.4)	60	3.3 (2.4)	0.89	.38	.08
Average Pain	67	5.2 (2.0)	62	4.9 (2.0)	0.92	.36	.08
Maximum Pain	67	5.9 (2.7)	62	5.7 (2.6)	0.57	.57	.05
Redness of Hand	67	6.5 (2.4)	62	6.6 (2.5)	-0.16	.87	.02
Headache	67	2.8 (2.1)	62	2.5 (2.5)	0.61	.54	.05
Heart Rate Increase	67	4.2 (2.3)	62	3.6 (2.6)	1.33	.19	.12
Itching	67	2.6 (2.2)	62	2.3 (2.2)	1.00	.32	.09
Pain Threshold	66	52.1 (24.5)	62	46.6 (24.9)	1.26	.21	.11
Hand Withdrawal	66	97.0 (36.8)	62	99.7 (41.0)	-0.39	.70	.04

φ = phi coefficient; effect size where .10 is small, .30 is moderate, and .50 is a large effect;
(Cohen, 1988) all response expectancies measured using Visual Analog Scales (VAS) ranging
from 0 −100, higher scores indicate greater anticipated severity; pain threshold and hand
withdrawal, ranging from 0-180 seconds, higher scores anticipating more time elapsed
(participants' hand immersion in the ice-water for cold pressor test)

Table 4

Comparison of cold pressor-related experiences between framing conditions

	Condition						
	Positive-Frame		Negative-Frame				
CPT reactions	n	M (SD)	n	M (SD)	t	p	Φ
Numbness[a]	67	6.8 (2.2)	62	6.7 (2.0)	0.43	.67	.04
Throbbing[a]	67	5.0 (2.9)	62	5.3 (3.0)	-0.45	.66	.04
Discomfort[a]	67	7.2 (2.4)	62	7.6 (2.1)	-0.82	.42	.07
Crushing[a]	67	4.4 (3.5)	62	4.2 (3.4)	0.32	.75	.03
Average Pain[a]	67	6.5 (2.3)	62	6.3 (2.1)	0.40	.70	.04
Maximum Pain[a]	67	6.9 (2.5)	62	6.9 (2.2)	-0.17	.87	.02
Redness of Hand[a]	67	7.0 (2.0)	62	7.5 (2.1)	-1.34	.18	.12
Headache[a]	67	0.9 (1.9)	62	0.7 (1.6)	0.67	.51	.06
Heart Rate Increase[a]	67	2.4 (2.5)	62	2.6 (2.7)	-0.42	.67	.04
Itching[a]	67	0.9 (1.8)	62	0.9 (2.0)	-0.17	.87	.02
Pain Threshold[b]	61[b]	29.2 (35.5)	56[c]	20.6 (15.0)	1.78	.08	.16
Hand Withdrawal[b]	67	86.2 (68.8)	62	100.0 (66.7)	-1.16	.25	.10

ϕ = phi coefficient; effect size where .10 is small, .30 is moderate, and .50 is a large effect;(Cohen, 1988) [a]measured using Visual Analog scales (VAS) ranging from 0 –100, higher scores indicate greater response expectancy severity; [b]objectively measured time variables, ranging from 0-180 seconds, higher scores indicating more time elapsed (participants' hand immersion in the ice-water for cold pressor test); [c]lower sample sizes reflect some participants forgetting to signal initial discomfort (Pain Threshold).

Response expectancies and experience of CPT reactions

A series of hierarchical multiple regressions investigated whether response expectancies predicted subsequent experience for each CPT reaction after controlling for associated covariates (Table 5). Covariates with univariate associations $r > .10$ with response expectancies or subsequent experiences were chosen for model inclusion (See Appendix D); thus covariates for each regression were unique, to maintain power. All covariates were added to Step 1 of regressions, given a lack of theoretical evidence for novel variables to warrant multiple steps.

Each model, including covariates and response expectancies (Step 2), significantly predicted all reactions (except average pain, $p = .06$), explaining between 6-38% of the variance (adjusted R^2). Response expectancies significantly contributed unique variance to the prediction of each reaction (except itching, $p = .05$). All other response expectancies uniquely contributed 6% (average pain) to 23% (crushing). For the significant models, the standardized regression coefficients (β) indicated response expectancy contributions were all moderate in size, except for crushing (a large effect).

Table 5

The unique contribution of response expectancies of CPT reactions on subsequent experience, controlling for covariates

CPT reactions	n	Covariates	Full model			Unique Contribution of response expectancies			
			Adjusted R^2	F	p	R^2 change	F change	p	β
Numbness	129	a, b, c, d, j, k, l	.20	5.01	<.001	.09	12.25	.001	.29
Throbbing	129	b, c, d, g, h, k, l	.21	5.14	<.001	.11	17.00	<.001	.34
Discomfort	128	a, d, e, g, h, j, k, l	.20	4.37	<.001	.13	21.00	<.001	.39
Crushing	127	a, d, e, h, j, k	.38	11.72	<.001	.23	54.42	<.001	.55
Average Pain	129	a, d, h, i, j, k, l	.06	1.94	.06	.06	7.79	.01	.25
Maximum Pain	129	a, c, d, g, h, j, k, l	.18	4.10	<.001	.13	19.43	<.001	.37
Redness of Hand	129	a, b, c, e, h, j	.15	4.29	<.001	.09	13.19	<.001	.32
Headache	129	d, f, g, h, k, l	.18	5.08	<.001	.17	26.82	<.001	.45
Heart Rate Increase	129	d, f, i, k	.18	6.71	<.001	.18	27.90	<.001	.44
Itching	129	b, c, d, f, h, i,	.07	2.41	.02	.03	3.89	.05	.18
Pain Threshold	128	c, d, e, g, k, l	.17	3.88	.001	.17	23.42	<.001	.44
Hand Withdrawal	115	b, c, d, g, k, l	.18	4.92	<.001	.15	20.92	<.001	.41

Covariates: [a]Age; [b]Gender; [c]Degree [d]English as a first language; [e]Culture identification; [f]Previous injury to non-preferred hand; [g]Perceived cold response; [h]Monitoring coping style; [i]Blunting coping style; [j]Depression; [k]Anxiety; [l]Stress; Adjusted R^2 = the amount of variance explained, adjusted for the amount of predictors in the model; R^2 change = the unique variance contributed to the model by REs of the specified response; β = standardized regression coefficient (beta), where 0.10 is a small effect, 0.30 is moderate, and 0.50 is large (Cohen, 1988); framing condition was not included in the model based on lack of effect found in the previous analyses.

Discussion

In this exploratory study, we aimed to ascertain whether framing information in positive or negative formats could limit response expectancies and thus, the severity of toxicity experience. We further sought to confirm the relationship between response expectancies and subsequent experience, controlling the impact of framing (which we were unable to analyses due to the lack of effects produced by the framing condition) and additional variables (covariates).

Although groups were successfully randomized, other contextual factors may have influenced outcomes. For instance, the Ice Bucket Challenge (Florance, 2014) demonstrated similarities to the current study. Participants who took part during or after the challenge became popular reported less average pain and increased pain threshold (i.e., they experienced initial pain later) compared to those who participated beforehand, signifying a positive influence of the media (and social media) on experience in a naturalistic setting. Interestingly, the Ice Bucket Challenge did not predict any change in expectancies of these reactions, suggesting this media influence had a direct impact on experience (Lorber, Mazzoni, & Kirsch, 2007). This analysis was based on the timing of participation (i.e., before or after the Ice Bucket Challenge was reported in the media), so it did not establish whether every participant in the 'after' condition had witnessed the Ice Bucket Challenge. However, due the pervasive nature of the challenge (Florance, 2014), it is likely most individuals had observed it. Furthermore, a failure for some participants in the 'after' condition to view this challenge would have led to an underestimation of group differences, which was of moderate-to-

large magnitude, suggesting the current results reflect the minimal difference between groups.

Social influences have been evidenced (Hofman et al., 2004) to produce relevant response expectancies, supporting suggestions by Heisig et al. (2015) that common media portrayals of interventions for cancer may explain different patterns between expectancies of chemotherapy toxicities, compared with expectancies of side effects for the less commonly known endocrine therapy. Pain, measured through self-report and objectively recorded, has been shown to be influenced by social influences, particularly socially instructed beliefs about others (Koban & Wager, 2016), like those provided in the current study. More specifically, pain threshold appears especially sensitive to social influences. Increased pain thresholds have been associated with viewing others experiencing less pain for the same task (Craig & Weiss, 1971), social laughter (Dunbar et al., 2012), and synchronized dancing (Tarr, Launay, Cohen, & Dunbar, 2015).

The current research builds upon this literature, and investigations of direct positive social influences (Colloca & Benedetti, 2009), by demonstrating that indirect influences; through media and social media representation, also impact individual expereinces, an area of inestigation still in its infancy (Hunter, Siess, & Colloca, 2014). Further investigation of the influence of media on side effect experiences is warranted, particularly because media reports can also lead to negative outcomes. For example, news reports of formula changes to a popular thyroid medication, thyroxine, were related to an increase in adverse effect reporting (of the toxicities specifically mentioned), despite no changes to the active ingredient (Faasse, Petrie, & Cundy, 2010).

The Ice Bucket Challenge may have also encouraged competitiveness between participants. Any perception of the CPT as an achievement task could have been further emphasized by watching others participate in the challenge. This competitive focus was reflected in one-third of participants continuing to the cut-off time, and might also explain the increase in pain threshold experienced when two individuals took part alone as opposed to with another participant (although silent and blocked from others' view). This may reflect the N-effect (Garcia & Tor, 2009a) whereby individuals oriented to social comparisons are more competitive when there are fewer competitors. Future research should be aware of this potential confound.

Unlike previous research (Heisig et al., 2015; O'Connor et al., 1996), no significant framing-related differences for response expectancy or subsequent experience severity were observed. However, participants who received positively-framed information showed trends toward reporting higher pain threshold in the expected direction. Furthermore, this particular analysis may have been underpowered because not all participants remembered to raise their hand when they first experienced discomfort, resulting in fewer responses. Thus, the findings in the current study indicated that pain threshold, an objectively recorded response, appeared sensitive to media influences, competitiveness, and framing. Further exploration of social influences specifically considering pain threshold is encouraged, to determine whether these can aid in directly increasing pain threshold in medical contexts.

Pre-intervention response expectancies predicted individuals' subsequent experiences, above and beyond mixes of previously tested (i.e., anxiety, coping style) and novel (i.e., depression, stress) covariates, for all but one CPT reaction.

This provides further evidence for the stability of these associations. Non-specific side effects can be costly to the healthcare system and often increase patients distress (Barsky et al., 2002), indicating the need to further consider methods of response expectancy reduction. For example, Barsky and colleagues (2002) suggest explaining the basis of toxicities to patients can help them understand why they are occurring, provide meaning, and reduce associated fear. Furthermore, Peerdeman, van Laarhoven, Bartels, Peters, and Evers (2017) have found imagining no or very little pain can reduce side effects (mediated by a reduction in response expectancies), to a greater extent than verbal suggestion.

Because this preliminary investigation considered a novel intervention, we selected the CPT as an acute pain induction method and recruited a young healthy sample, to inform the utility of this intervention in clinical settings. The task induced real responses, like pain, but provided a safe highly-controlled experimental situation. Experimentally-induced pain is considered a good model for clinical pain, however it is generally acknowledged that results may always not be transferrable (Peerdeman et al., 2016). Thus, its generalizability to clinical samples is limited based on different contexts and meaning; patients often experience greater distress, more ongoing communication with health care providers, and multiple chronic uncertain side effects (Moerman, 2002a). The current sample displayed low levels of response expectancies overall, indicating optimism. Indeed, recruitment for the CPT may be inherently biased toward individuals who are not avoidant or fearful of discomfort. Nevertheless, as in other tertiary student samples (Larcombe et al., 2016) participants' levels of depressed, anxious, and stressed mood were high.

The positive- and negative-framed pre-intervention information referred directly to one single CPT response; "hand withdrawal" (an objective measure of time). This was selected because the presentation of visual information about multiple side effect would be difficult to achieve, and hand withdrawal indirectly encompasses all other responses that occur as a consequence of an individual's hand being immersed in ice-cold water. Although the groups did not differ in their response expectancies or experience of "hand withdrawal", more explicit framing pertaining to specific reactions (e.g. "redness") may have produced different outcomes, as in the O'Connor et al. (1996) study. Thus further information of the impact of framing on response expectancies is warranted.

Methodologically, the response expectancies and experiences scales were almost identical, potentially inflating their statistical relationships. Furthermore, the MBSS displayed substantially lower internal consistency than recommended (Bland & Altman, 1997), potentially indicating overestimation of other effect sizes in multiple regression models because of an underestimation of the effect size of covariates (Osborne & Waters, 2002). Others have recommended a 5-point Likert scale version of the MBSS with better internal consistency, which is suggested for subsequent research (Muris et al., 1994).

In summary, framing CPT information did not substantially impact response expectancy severity or most experiences, contrasting with previous research. However, there was some indication of a beneficial effect on pain threshold, which also appeared to be influenced by competitiveness and social influences. Given this finding, previous research, and the potential to improve upon this study design, we feel future investigation into framing specifically targeted to pain threshold response expectances and experience. Because

informed consent mandates clinicians provide all possible side effect information (Faden & Beauchamp, 1986), it is imperative to understand not only whether information frames can be helpful, but also whether they can be harmful in current practice. Research investigating the impact of social influence on pain threshold is also recommended. All but one of the CPT reactions were predicted by their response expectancies in the full regression models demonstrating the consistency and reliability of these relationships in a novel context. The use of pre-treatment measurement of response expectancies for screening is recommended at minimum for prevention and/or management of side effects for at-risk patients in medical settings, while intervention strategies continue to be researched.

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Chapter 6: Discussion

'I expected as much': A general discussion of the research project

6. Overview

This research project explored different aspects of the relationship between expectancies of cancer treatment-related toxicities and subsequent experiences. The overall research aim, stemming from gaps identified in the literature review, was to explore the scope and utility of response expectancies for predicting and potentially reducing the incidence and severity of side effects experienced during cancer treatment.

To address this aim, a meta-analysis and three research studies were conducted including a psychometric study, a clinical study, and an experimental intervention. First, methodological differences were explored, especially measurement variations in expectancies of side effects, to determine whether individual study results can be interpreted interchangeably. Second, variations between individual side effects were explored, with comparisons between ambiguous and objective side effects investigated. Third, the scope of response expectancies for predicting subsequent side effects was investigated, across a novel sample of homogenous patients (men with prostate cancer), scheduled for radiotherapy (highly similar doses of an under-researched treatment modality). This prospective, longitudinal study, aimed to determine the robustness of associations evidenced to-date, over the course of radiotherapy. Forth, using a randomised controlled experiment, pre-intervention valence framing was tested to determine whether subtle alterations to the suggestions made to individuals could

reduce response expectancies and thus experiences, by utilising a simple, cost-effective intervention which could be easily implemented in healthcare practice.

The specific research questions in the introduction (Chapter 1), will be discussed in turn within this chapter. Each discussion will involve a detailed evaluation of the outcomes of the empirical investigations, how they compare to previous findings in the literature, and how they can inform resulting clinical applications. Additional themes, especially novel outcomes unveiled throughout the research project as a whole, will be presented in a subsequent section. A critical analysis of the limitations of each study and the overall contribution of the research to future directions will then be summarised, before the chapter concludes with final remarks.

6.1   Research question 1: Could methodological differences in research regarding expectancies of cancer treatment-related toxicities (and subsequent experience) explain variability in individual study outcomes, and can results obtained from different measurement methods be discussed interchangeably?

This research question was partly addressed by a meta-analytic investigation (*Study 1, Chapter 2*) of 27 quantitative studies. Analyses revealed studies utilising different inclusion criteria and measurement methods reported different effect-sizes. Specifically, homogenous samples demonstrated significantly higher effect sizes than heterogeneous samples. Trends and wider differences between effects sizes (following adjustment for potential publication bias) were also found for the use of patient diaries, and the number of follow-ups measurement occasions, patient's level of experience with treatment, and the use of different scales.

An additional unexpected finding was that expectancies of toxicities related more strongly to experience for patient samples who were naïve to treatment. This result contrasted with theory and an array of previous findings (Kirsch, 1985, 1997; Montgomery & Bovbjerg, 2000, 2004; Rescorla & Wagner, 1972), including two previous meta-analyses (Colagiuri & Zachariae, 2010; Sohl et al., 2009) that revealed higher effect sizes for studies measuring response expectancies following some treatment experience. Similarly, this result challenged the observations in the prospective clinical study (*Study 3, Chapter 4*), that found more side effects demonstrated unique, significant relationships with their response expectancies measured after 2-weeks of radiotherapy, than with pre-treatment (baseline) response expectancies. However, as this was not empirically tested in this study, this is not a conclusive outcome and should be viewed with caution. Potentially, the finding in *Study 1* reflects the small number of studies that had investigated response expectancies after treatment had commenced (k = 4), and thus, was potentially influenced by a single study (Ryan et al., 2007) with a substantial sample (n = 135), demonstrating a negligible effect size between expectancies of skin irritation and subsequent experience. This result, based on a novel toxicity also provides initial evidence that pooling the influence of response expectancies across side effects may be problematic (discussed in more detail in Section 6.2).

Furthermore, the meta-analysis analyses revealed differences between studies measuring response expectancies using alternate scales, particularly after correction for possible publication bias. The most commonly used measurement tool, the 5-point scale named the Side Effect Expectancy Questionnaire (SEEQ), demonstrated a lower effect size than studies utilising other measures. While

collecting data for the meta-analysis, it was observed that the SEEQ was used and interpreted differently by separate research groups, jeopardizing standardisation across studies. It was predicted that this might contribute to the lower effect size of the SEEQ revealed in *Study 1*. Thus, *Study 2 (Chapter 3)* was designed to explore potential reasons for the reduced effect of the association between response expectancies, and relevant toxicities, measured with the SEEQ. It was predicted this could be explained by the inclusion of a midpoint labelled '*unsure*' in the SEEQ, potentially because of satisficing (reducing cognitive effort), or misinterpretation of how to present the midpoint. Results revealed that when provided with a midpoint specifically labelled *'I am unsure whether or not I will have this side effect',* many patients selected it across all side effect expectancies measured. Furthermore, some participants within the current research sample reported response expectancies on Visual Analogue Scales (VAS) for two side effects that were not detected by the SEEQs, which may suggest that VAS are more sensitive measures of response expectancies. Direct investigation of the association between the SEEQ and the VAS revealed the measurement of 'incidence' did not produce strong relationships (Cohen, 1988), as would be expected if the scales were measuring the same underlying construct. This lack of consistency between the two scales, and within the SEEQ potentially explains many discrepancies in the literature to date; thus, caution is required when determining which response expectancy measure to use, and when combining or discussing results across studies interchangeably.

Qualitative research into why patients' select '*unsure*' should be considered, to determine whether patients are selecting the midpoint because they are truly unsure, or because this is a less cognitively demanding option

(satisficing), and thus whether this midpoint should remain in response expectancy measures. This knowledge will assist in a more consistent and detailed understanding of the impact expectancies for cancer treatment side effects have on subsequent toxicity experience.

Taken together, these results suggest that different methodologies may help to explain discrepancies between investigations of how strongly expectancies of side effects influence subsequent experiences. These evidenced differences include the whether the patient samples studied were homogenous or heterogeneous; the measurement methods, including the use of patient diaries, and the scale used to measure response expectancies; and the quantity and timing of response expectancy measurement, and follow-ups (measuring subsequent side effect experience). Consequently, careful consideration of methodology used in future research is important, both when designing studies and when integrating research findings into the literature (e.g., when conducting systematic reviews and meta-analyses).

6.2 **Research question 2:** Does the influence of response expectancies on toxicity experience extend to alternative side effects, and novel groups of patients and treatment regimens?

6.2.1 Alternative side effects

Study 1 revealed expectancies of cancer treatment-related toxicities demonstrated a moderate influence on subsequent experience, in line with previous meta-analyses of the area (Colagiuri & Zachariae, 2010; Sohl et al., 2009). However, when expectancies of individual side effects were compared, significant differences were found. Although this result mostly differs from

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previous meta-analytic findings (Sohl et al., 2009), it aligns with other specific response expectancy and placebo research (Benedetti et al., 2011; Kirsch, 2013), that indicate different underlying processes occur for different responses. As posited by Kirsch "Even the psychological construct of expectancy is likely to be too broad. Instead, we need to establish the physiological correlatives of specific expectancies, such as expectations of alterations in arousal, pain sensitivity, nausea, and so on" (1999b, p. 105). Therefore, determining which side effects are most strongly predicted by their response expectancies, and which are most problematic for patients, can focus and prioritise future research on understanding the mechanisms through with they occur and informing prevention strategies.

For example, in *Study 1* expectancies of hair loss revealed the strongest relationship with subsequent occurrence of hair loss, across pooled studies. Because hair loss is a specific medical effect of some treatments, such ascertain chemotherapies (Genre et al., 2002; Palmieri, Bird, & Simcock, 2013), the current findings may partially reflect patients' knowledge (and thus stronger expectancies) of this toxicity that match known experiences. However, many chemotherapy treatments do not cause all patients to experience hair loss, or at least not to the same degree (Fobair et al., 2006; Macquart-Moulin et al., 1997). The three studies combined in *Study 1* all analysed expectancies of hair loss in patient samples with mixed diagnoses (Cassileth et al., 1985; Olver et al., 2005; Whitford & Olver, 2012), indicating that individual differences also contributed to experiences of this toxicity. Despite this, patients consistently report feeling as though chemotherapy and hair loss are synonymous across treatments, and hair loss is one of the initial questions raised when patients are told about the necessity of chemotherapy (Frith, Harcourt, & Fussell, 2007), potentially because of a

strong emphasis on hair loss in the social arena (FernÁNdez-Morales, 2009). In a group of 319 women scheduled for chemotherapy, 83% reported shopping for wigs before they had experienced any hair loss (Marie Borsellino & Young, 2011), implying response expectancies may be particularly strong for this well-known side effect. Moreover, hair loss has been reported by patients as the third most commonly dreaded toxicity, after nausea and vomiting (Lorusso et al., 2016). Some patients choose less effective treatments to avoid this side effect (Hesketh et al., 2004), describing it as traumatic and distressing (Lemieux, Maunsell, & Provencher, 2008). When 34 breast cancer survivors were interviewed about their treatment experiences, most reported fear of hair loss; stating "…I was fearful of losing my hair", "…Chemo would make me sick and lose my hair", "…I knew my hair was going to fall out", despite not all subsequently experiencing this toxicity (Kreling, Figueiredo, Sheppard, & Mandelblatt, 2006). This knowledge, taken together with the current findings, indicates that expectancies of hair loss during chemotherapy are problematic and relevant intervention strategies may be highly beneficial for those treatments where this is not a certain outcome.

Similarly, *Study 3* provided further evidence of differences between expectancies of individual toxicities, with the toxicity cluster, 'sexual side effects' demonstrating different patterns of relationships to response expectancies than the other 15 measured radiotherapy toxicities for patients with prostate cancer. Expectancies of reduced desire, inability to have or maintain an erection, and inability to reach orgasm showed significant associations with their experience throughout treatment. By the end of treatment, response expectancies explained between three quarters and half of the variance in subsequent experience, even

after controlling for the pre-existence of these symptoms, androgen (hormone) therapies, and psychological variables. Sexual side effects are one of the most frequently reported areas of concern for prostate cancer survivors (Ream et al., 2008), and many patients feel they do not receive adequate information about them, particularly if they do not feel comfortable raising such questions or concerns themselves (Lorusso et al., 2016). The influence of expectancies of sexual dysfunction also occurs in other cancer treatments, with expectancies of 'problems with sex' and experience often reported in patients with a range of cancers undergoing chemotherapy (Cassileth et al., 1985; Olver et al., 2005), although not always (Whitford & Olver, 2012). Nocebo effects have been shown to be strong in the area of sexual dysfunction (Colloca & Miller, 2011a). Patients told of the risk of sexual side effects when receiving treatment for a benign prostatic hyperplasia were significantly more likely to experience them (43.6% versus 15.3%; Mondaini et al., 2007). Importantly, erectile dysfunction, has specifically been shown to be particularly sensitive to suggestion (Silvestri et al., 2003), indicating potential benefits from suggestion-based interventions. Thus, further research in this area is of notable clinical importance to inform whether and how expectancies of sexual side effects might be reduced to assist in reducing experienced severity. For example, when radiotherapy-related side effect information was paired with self-care strategies for two other toxicities, severe fatigue and sleeping problems, patients were less likely to report them (Kim, Roscoe, & Morrow, 2002); however, as established earlier in this section, this may not generalise to sexual side effects.

Despite significant variation between individual side effect expectancies, no clear differences between more subjective (abstract) and objective toxicities

were revealed, as previously theorised (Kirsch, 1985). Furthermore, nausea and vomiting demonstrated similar effect sizes, again differing from some previous reports (Roscoe et al., 2000a) but not others (Sohl et al., 2009). In *Study 3,* many of the side effects reported 2-weeks into treatment were also somewhat objective (e.g., blood in urine, bowel leakage, and inability to have or maintain erection). However, because all toxicities were measured through patient self-report, there was likely not a clear enough distinction between levels of abstractness to determine clear differences. For example, a potentially objective response, patients' reports of hair loss may reflect an individual's perception of more hair in their brush (Olver et al., 2005) or less hair when looking in the mirror, rather than an objectively or independently measured changes in hair density.

Although no differences between expectancies of objective and subjective side effects relationship with experience were apparent in *Studies 1 and 3*, any toxicity perceived by a patient, whether measurable or abstract, is clinically problematic. A multicentre study, involving 555 patients being treated for a heart condition revealed patients who received consent forms specifying the risk of gastrointestinal side effects showed no differences in objective toxicities (i.e., ulcers, bleeding, etc.) than patients not provided with this information. However, those patients given this information were six times more likely to stop treatment because of reported gastrointestinal side effects. Perceived and objective toxicities both contribute to the cost of hospital visits, the need for additional medical care or medication (Siefert, Blonquist, Berry, & Hong, 2015), reduced quality of life (Mazzotti et al., 2012), and days absent from work (O'Connor et al., 1996); thus, any perceived toxicity experience requires attention.

Studies 1 and 3 demonstrated that expectancies of individual side effects (or toxicity clusters) exhibit different relationships with their experiences, indicating that specific interventions for individual toxicity expectancies would be more beneficial than generalised expectancy reduction methods. Focusing on what side effects are most problematic to patients, and what toxicities are highly related to their response expectancies, can prioritise those toxicities best suited to intervention. Hair loss during chemotherapy (where there are non-specific reasons for this toxicity), and sexual side effects during radiotherapy (for the treatment of prostate cancer) both show clear links to their response expectancies and are also reported as challenging by patients.

6.2.2 Novel patient groups and treatment regimes

The prospective longitudinal clinical study *(Study 3)* was designed to ascertain whether expectancies of side effects relate to subsequent toxicities in a novel patient group, specifically a homogenous older (than usually accrued) cohort of male patients being treated with radiotherapy. This patient population was selected because according to previous research (Hofman et al., 2004; Vambheim & Flaten, 2017), they would be expected to form the fewest response expectancies (based on the combination of their sex, age, and treatment modality). Hence, if response expectancies influence side effects in this group, this provides some insight into the potential scope of expectancies of side effects across a broad range of cancer treatments and patients. Associations between half the measured response expectancies and experiences were significant at two follow-ups. When other variables (i.e., emotional state, coping style, baseline side effects, and comorbidities) were controlled in multivariate models, expectancies of six side

effects independently predicted their experience by the second week of treatment. This is an important finding, because although side effects have been clinically observed at this stage of treatment, but they are not medically explicable, in terms of the accrued dosage of radiotherapy a patient has received by that time (Garg, 2011). Thus, it appears reasonable to suggest that expectancies of side effects occurring at this stage of treatment may help explain their early presence. The multivariate models also showed that response expectancies measured following experience of radiotherapy (i.e., following 2-weeks of treatment) independently predicted seven side effects at the seventh week of treatment (near the completion of treatment), reflecting other results in different populations (woment being treated with chemotherapy; Montgomery & Bovbjerg, 2000). These findings have important implications for radiotherapy, a treatment which is given on a regular and frequent schedule. It appears important to intervene promptly, because response expectancies predict some toxicities early into radiotherapy, and it has previously been shown that this experience can then in turn reinforce response expectancies, making them stronger (Montgomery & Bovbjerg, 2000); potentially exacerbating late effects which can continue for years post-treatment (Curt et al., 2000). Thus, reducing or preventing these early and potentially psychological side effects through response expectancy reduction could have implications for patients throughout treatment and many years into survivorship.

To summarise, consistent with the current literature on response expectancies in chemotherapy, the impact of side effect response expectancies on experience was demonstrated in a previously unexamined cohort of older men undergoing radiotherapy. Some non-specific toxicities were related to experiences early in treatment, indicating the importance of early intervention.

6.3   Research question 3: Can the modified presentation of information, incorporating non-deceptive, and non-hypnotic suggestion, influence individuals' expectancies of side effects and in turn, reduce toxicity severity?

The final study (*Study 4, Chapter 5*) was a randomised controlled experimental trial utilising an experimental pain-induction technique (CPT), as an analogue for treatment toxicities. The aim of this study was to determine whether the method of presenting information to individuals about adverse events (positive or negative valence framing) altered the formation of response expectancies and subsequent responses. Within this healthy student volunteer sample, framing had no significant influence on either response expectancy formation or toxicity experience, differing from previous studies (Heisig et al., 2015; O'Connor et al., 1996). Comparing *Study 4* with a previous investigation of framing revealed some potential reasons for this difference. O'Connor et al. (1996) found that framing impacted both subjective and objective toxicities of an influenza vaccine in a sample of cardiac patients who would likely experience severe complications from contracting influenza, a highly different situation than the CPT, in terms of affect, meaning, and other contextual factors (Moerman, 2002a). In a healthy sample, such as in the current research, there is likely less distress and fewer other negative psychological processes or outcomes associated with a chronic condition, and there is a lack of real risk or benefit associated with the CPT. In addition, O'Connor et al. (1996) framed the risk of toxicities individually, whereas only 'time to hand withdrawal' was framed in *Study 4* (to encompass all toxicities associated with the pain experienced before hand withdrawal). In retrospect, based on the findings of the current research project

(i.e., *Studies 1 and 3*), which revealed implicit differences between individual responses, this decision potentially confounded the study outcomes.

More generally, the impact of information provided by doctors or other healthcare workers on patients' side effect expectancies is not currently well understood and the influence of suggestion-based interventions on side effects appears complex. Some studies have found only patients with high levels of response expectancies appear susceptible to targeted interventions (Quinn & Colagiuri, 2015; Roscoe et al., 2010b). Others have found that response expectancies measured before a patient has received information (when suggestions would be provided) are better predictors of experiences than those measured after. Roscoe et al. (2004) found that the strongest predictors of side effects were response expectancies measured *before* patients saw their doctor, rather than their response expectancies measured after the appointment. Shelke et al. (2008) provided 358 chemotherapy-naïve patients with either standard information about nausea during chemotherapy or information designed to reduce nausea expectancies. They found that although the intervention was effective at reducing patients' reported expectancies of nausea, their subsequent severity of nausea did not differ; it matched the patients' pre-intervention response expectancies. Thus, response expectancies measured after an intervention may be reduced momentarily; however, it appears initial response expectancies often retain their influence on subsequent experiences. This could be due to biases whereby schema congruent information is noticed and perceived, but information that does not match existing schemas is less salient so does not remain influential (Piaget, 1923). Therefore, although O'Connor et al. (1996) found differential framing was associated with different side effect experiences, this may not reflect

changes in response expectancies produced by the framing intervention. Instead it may represent pre-existing expectancies of the side effects produced by the influenza vaccine, another commonly discussed treatment in the media.

Although the randomised controlled experimental study did not find an impact of framing side effect information in a positive or negative way, on either response expectancies or experiences, further investigation of suggestion is still considered warranted. This will not just guide potential interventions, but also ensure that current practice (including the provision of informed consent) is not exacerbating patients' response expectancies (Miller & Colloca, 2011). Even subtle verbal suggestion during clinical interactions between doctors and patients have been shown to impact response expectancies, highlighting the power of the language used in clinical encounters (Blasi & Kleijnen, 2003; Moerman, 2002b). Patients told about the relationship between chemotherapy and cognitive impairment (Schagen et al., 2012) reported, and demonstrated higher levels of cognitive impairment. Also, patients informed of sexual side effects but told 'these are uncommon' still reported significantly more sexual side effects than patients not informed (Mondaini et al., 2007). Furthermore, the risk of toxicities was overestimated by patients when information about the probability of the occurrence of side effects was provided in numbers, as opposed to words (Büchter, Fechtelpeter, Knelangen, Ehrlich, & Waltering, 2014), and vague levels of information have been found to increase the formation of outcome expectancies, compared to specific information (Mishra, Shiv, & Nayakankuppam, 2008).

In summary, based on the current results valence framing does not appear to influence response expectancies, using this specific design with a young,

healthy sample. Taken together with previous research, even if this were the case, it is not assured that it would, in turn, affect side effect experiences. However, based on the possibility that communication of toxicity risk might be harmful (in certain instances) at present, and that modification of the current informed consent practice has the potential to assist in reducing the severity of toxicities, additional suggestion-based research appears warranted.

6.4 Additional findings

6.4.1 Covariates

Within the current project, additional related variables were measured and controlled in two empirical studies. In *Study 3,* the addition of covariates to multivariate models analysing side effect experience resulted in the significant prediction of more toxicities then when the independent contribution of response expectancies was considered alone. Thus, it is apparent these additional variables also contribute to some toxicity experiences.

The specific coping style, anxious preoccupation, measured in *Study 3* did not correlate with many toxicities in the group of patients included, unlike previous research with patients with a range of cancer diagnoses, and a mix of genders (Whitford & Olver, 2012). This may be based on the sample, given that the 'fighting spirit' coping style is more prevalent than anxious preoccupation in men being treated for prostate cancer (Bjorck, Hopp, & Jones, 1999). Interestingly, no variables were consistently associated with side effect response expectancies and experiences in this investigation. In fact, covariates differed greatly between individual toxicities, despite the homogeneity of the sample and treatment. This aligns with findings throughout the research project about the

different mechanisms producing individual toxicities and indicates the complexity of generating risk profiles of patients at danger of severe toxicity experiences, even within identical treatment modalities.

Conversely, *Study 4* revealed that expectancies of CPT reactions significantly, consistently, and independently predicted reported experiences. Psychological and coping style variables did not predict individuals' reactions in these analyses. This reflects differences in the samples and contexts between *Study 3 and 4*, discussed in Section 6.2, with clinical patients potentially having higher levels of relevant psychological variables (anxiety, depression, stress, and specific coping styles). It also highlights the difficulty of translating the results of experimental and analogue studies of response expectancies into clinical environments. Differences may also be due the different measures used to asses coping styles between these two studies. One study utilised a specific measure about adjusting to a cancer diagnosis (the MAC scale). The other measured coping style based on an imagined threat given the cancer-specific measure was not appropriate in a healthy sample (the MBSS), because the two coping styles were the most similar found in the literature to compare to the two major styles of interest in previous cancer studies (e.g. anxious preoccupation and fighting spirit). However, they are dissimilar enough to contribute to the differing models across studies.

6.4.2 Social influences

A common theme observed throughout the research project was the important role of social learning (through indirect observation) on patients' formation of side effect expectancies and their subsequent experiences. It has

been established that social modelling can impact individuals' responses to stimuli through an increase in relevant response expectancies (Lorber et al., 2007). Based on the current research project, this could be extended to indirect social influences in a naturalistic context. In *Study 1,* expectancies of hair loss displayed the strongest relationship with subsequent experience. Hair loss is the most commonly depicted side effect of chemotherapy as represented in the media (FernÁNdez-Morales, 2009), likely contributing to the strength of expectancies of hair loss. The influence of media has also been alluded to many times in the literature (Kirsch, 1985, 1997; Roscoe et al., 2006). Kaptchuk et al. (2010) theorized that patients benefited from open labelled placebos (i.e., non-deceptive placebos), partly because of a focus in the media on the effectiveness of placebos.

Study 4 also revealed the impact of media and social influences. Approximately halfway through the experimental phase of this study a charity event known as the Ice Bucket Challenge became popular worldwide. This drew parallels with the current study, because it involved ice water, and associated discomfort; however, ice water poured over the whole body, rather than the placement of one hand in water, with ice no longer visible as per the experiment, and final temperature (above zero degrees Celsius). Individuals (including celebrities and official personnel who undertook the challenge) appeared across printed and televised news, entertainment, televised sporting matches, and heavily in social media. Because of the extemporaneous timing of the commencement of the Ice Bucket Challenge, it was possible to investigate its effects on participants' response expectancies for related responses and experiences. Individuals participating after the popularity of the Ice Bucket Challenge reported experiencing initial pain later (i.e., a higher pain threshold) and lower average

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levels of pain throughout the experiment than those participating beforehand.

Thus, observation of others participating in a similar, painful challenge, positively

influenced responses. Interestingly, the Ice Bucket Challenge did not predict any

change in expectancies of the related reactions, suggesting the influence of social

modelling may have occurred directly (Lorber et al., 2007).

Social influences have also been found to produce both placebo and

nocebo responses in pain experiments. Healthy female participants viewed a

confederate demonstrate experiencing placebo induced relief from a painful shock

to their hand. When a green light appeared, the participants believed a further

electrode neutralised the effects of the shock. They then underwent the same

process. Despite no objective change to the level of the stimuli, the participants

experiences pain reduction when the green light was visible (Colloca & Benedetti,

2009). Viewing the confederate experience pain relief was significantly more

effective than previous experiencing pain relief associated with the green light,

and then verbal suggestion alone. The impact of social observation has been

replicated with nocebo responding (Vögtle, Kröner-Herwig, & Barke, 2016), with

an inert ointment producing pain after observing this occur in a confederate. The

effects of social observation on pain relief occur to a similar extent whether the

confederate is in the same location (direct) or in a pre-recorded video-clip

(indirect; Hunter, Siess, & Colloca, 2014). These influences may help explain the

occurrence of mass psychogenic illnesses (Lorber et al., 2007; Mazzoni et al.,

2010). When healthy subjects watched a confederate inhale a substance and

display symptoms (i.e., headache, nausea, drowsiness, and itchy skin), they

reported significantly higher levels of all symptoms compared to controls

(Mazzoni et al., 2010). This extends to the indirect observation of others in a

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range of media channels (i.e., news, magazines, online, etc.) which has been found to increase related symptom and side effect reporting (Faasse et al., 2010), including changes to medications, vaccination scares, psychogenic illnesses, and celebrities receiving cancer diagnoses (Faasse, Gamble, Cundy, & Petrie, 2012). Such influences may occur at an even more indirect level. For instance, when patients were primed with the stereotype of cognitive impairments, a late side effect reported by patients treated with chemotherapy (Schagen et al., 2009), patients reported and demonstrated more cognitive impairment following treatment. It is highly likely direct observations of fellow patients during treatment or in support groups, and indirect social learning through media and social media channels could be influencing patients' cancer treatment-related experiences (e.g. hair loss being famously associated with chemotherapy). Thus, the current research adds to this small body of existing evidence about the impact of indirect social observations in responses, in both patients and healthy individuals.

Individuals who completed the CPT with another participant in the room took longer to experience initial pain than individuals either participating in isolation or undertaking the task in groups of three, regardless of the fact that individuals could not see each other and were silent. Potentially, participants could have been listening for any sign of discomfort or pain from the other individual(s) in the room, creating a distraction, which has been shown to reduce perceived pain (Frankenstein, Richter, McIntyre, & Rémy, 2001). Thus, participants may not have noticed their pain until it reached a higher level. However, the fact that this did not occur when three individuals participated in a single session may suggest that the observed phenomenon could also reflect task

competitiveness because having fewer competitors as been linked to increased competitiveness between participants (known as the N-effect; Garcia & Tor, 2009b). Thus, this appears to be another indirect social influence that could have impacted the results of *Study 4*.

A better understanding of the role that response expectancies play in the link between social observation and related experience is needed to determine whether this is a mediating or moderating mechanism. Furthermore, social modelling may be useful for reducing severe toxicities. For example, health care workers could correct stereotypes about treatment side effects; tell new patients stories about previous patients who have had more positive experiences; or suggest attendance at facilitated support groups, before treatment process.

6.5 Clinical implications and future research directions from the findings of the current research project in combination with the literature to date

Based on the results of this research, there are a number of implications for future research direction and clinical practice. The first is the necessary caution when measuring response expectancies. Currently, the only way to determine patients' anticipations is through self-report. Thus, measures need to be accurate, and need to capture the same underlying construct. This is important for research before such measures are able to be clinically utilised as screening tools.

Furthermore, like placebo and nocebo effects, response expectancies differ greatly between side effects. This is even the case with homogenous samples, and treatment modalities. Research should reflect this, and focus on specific side effects, particularly those most problematic to patients. Despite this, response

expectancies appear effective predictors across a wider scope of people than previously established. In this research project alone, they were influential in a variety of patients undergoing different treatment and healthy volunteers. A logical next step is to determine the extent response expectancies predict cancer treatment-related side effects in different cultures. A study by Molassiotis et al. (2002) found pre-treatment expectancies of nausea and vomiting predicted these side effects in a group of Chinese patients being treated with chemotherapy for breast cancer, suggesting they may be universal. However, because response expectancies are produced by experiential learning, verbal instruction including the languages used, the clinical context and meaning behind it, previous experiences, and observation of others, it is highly likely differences would emerge. For example there are cross-cultural differences in the meaning given to different colours, and numbers, as two examples (Madden, Hewett, & Roth, 2000), potentially eliciting different response expectancies about the reaction they will create. Moreover, many regions, particularly those is South-East Asia and Africa, more commonly use traditional and complementary therapies compared to Western (evidence-based) medicine (World Health Organization, 2013). Thus, it is predicted that their response expectancies would be significantly different than in Western countries.

Response expectancies do not require deceit or an altered state of consciousness to influence outcomes. However, interventions and screening need to occur before treatment, as it is apparent response expectancies are influential early in treatment, and appear to become stronger over time. Once treatment has begun there is likely a larger influence of conditioning effects, making response expectancy-based intervention strategies less effective. Although valence framing

did not impact response expectancies (in a healthy sample) in the current research project, response expectancies have been shown to be adjustable in placebo and nocebo research (Colloca, 2014; Vambheim & Flaten, 2017), and directly (Rief et al., 2017). Furthermore, there is potential that social observation, whether direct or indirect may influence patient experiences; signifying an important area for future investigation.

6.6 A critical review of the current research project

Limitations of the current research project have been acknowledged and discussed in each of the journal manuscripts (*Chapters 2-5*) and are summarized more generally in the following section. These have potential to limit the accuracy and interpretability of relevant study findings; thus, research outcomes should be interpreted with these in mind. This discussion will be presented for each study individually, followed by a summary of the strengths of the current project as a whole.

6.6.1 Study 1: Meta-analysis

A considerable limitation of *Study 1* was the interest in categorising studies by measurement differences, and individual side effects. Hence, the number of pooled studies in some sub-group analyses was low, and these analyses were vulnerable to the influence of any investigations reporting extreme results (high or low). Therefore in future research exploring different toxicities, there must be careful consideration of methodology to allow for future research integration.

Another limitation, common to meta-analytic reviews, was that the influence of additional variables (such as anxiety and coping style) could not be

controlled. Thus, although the results of *Study* 1 suggested that increased side effect experiences occurred in individuals with stronger expectancies of those same side effects, no conclusions about causation can be drawn from this study.

6.6.2 Study 2: Psychometric study

A major limitation of *Study 2* was its exploratory nature. Only the two most commonly-used measures were compared, and the validity of the scales could not be assessed in the absence of a gold standard response expectancy measure. Therefore, other response expectancy measurement tools were not included in this investigation; notably, the 3-point response expectancy scale which demonstrated the strongest effect size with subsequent analyses in *Study* 1. Future research determining the interchangeability or utility of all major response expectancy scales is still warranted.

6.6.3 Study 3: Longitudinal clinical study

Study 3 may have been underpowered for the number of variables measured, particularly by the final follow-up (7-weeks into radiotherapy), when not all patients with prostate cancer remained in the study (largely because of treatment changes for patients commencing brachytherapy at the third and final time-point). This was evidenced with some negative adjusted R^2 values. Consequently, significant findings may have been missed (Type II error). Steps were taken to mitigate this problem. All covariates and hypotheses were theoretically-based, and the inclusion criteria were adjusted to include more patients. Larger cut-offs were selected for covariates entered into multivariate models (in order to preserve power), and effect sizes were reported alongside exact *p*-values. Clear patterns were found in the study analyses, supporting the

clinical implications provided. It would be ideal if these could be replicated in larger samples in the future and across different cancer types using radiotherapy.

The nature of the data made it challenging to determine the most appropriate statistical analysis. The assumption of normality was not met for linear regression, and transformations reduced the sample substantially without improving the distribution of the error residuals. However, the assumption of parallel lines was not met for logistic regression either. Accordingly, the decision was made to utilise multiple linear regression analyses because splitting the measurement of response expectancies (measured as severity on VAS) into categories would lose too much data. As specified by Tabchnick and Fidell (2006), although the failure to meet the normality assumption weakens an analysis, because it does not capture the full relationship, it does not invalidate it.

6.6.4 Study 4: Randomised controlled experimental study

Study 4 included recruitment of a healthy sample which prevented direct generalisation of the results to clinical samples, such as cancer patients. The CPT offered no benefits, and although it induced pain, this was momentary and in a safe and controlled context, unlike a real world clinical environment. This prevented a clear picture of whether framing influences patients' expectancies of side effects, or their subsequent experiences.

As mentioned in Section 6.2, the decision to frame and present only one reaction – hand withdrawal - might, in retrospect have had major implications for the results of *Study 4*. Based on the findings of the remaining studies in this research project, and a previous framing study (O'Connor et al., 1996), it could

have been assumed that side effects would need to be framed individually to influence subsequent outcomes.

6.7 Strengths of the current research project

This research project demonstrated a number of strengths, most notably a careful consideration of the current literature, and the investigation of expectancies of cancer toxicities in a range of novel contexts. This included patients who were underrepresented in the previous literature: with a diagnosis and treatment modality, which had not been previously considered, and different patient characteristics (i.e., age and sex) from those commonly represented in the literature. Similarly, the comparison of two popular response expectancy measures, the comparison of individual expectancies of cancer treatment-related side effects, and the investigation of the influence of framings on both response expectancies and experiences simultaneously were all novel investigations in this field. This research can thus add a large body of knowledge in reference to response expectancies of side effects for clinicians, and reinvigorate research in the area by providing novel directions for future investigations.

Another strength of this research was the variety of side effects measured across studies. This allowed clarification of individual toxicity differences, and their relationships with response expectancies and covariates in different circumstances, providing clear direction for prioritising response expectancy reduction research within chemotherapy and radiotherapy. This also meant patterns of side effects could be considered, including any differences between objective and subjective toxicities, and the important finding that nausea, the most commonly measured toxicity, demonstrated a significantly lower relationship

with nausea expectancies than did many other side effects. This suggested that the influence of response expectancies on subsequent experience may be greater than it currently appears in the published literature (consisting mainly of studies using nausea as their outcome variable).

6.8 Conclusion

This research project and thesis successfully addressed many gaps and inconsistencies in the literature surrounding the influence of expectancies of cancer treatment-related side effects on subsequent experiences. Measurement and other methodological differences produced different outcomes; thus, care needs to be taken when designing studies and interpreting results. Furthermore, findings from a previously unrepresented group, older men commencing radiotherapy, showed similarities with the previous literature but also highlighted differences between highly related toxicities. This result was further supported by the current meta-analysis, suggesting any potential intervention needs to be tailored specifically for the patient group and treatment. Moreover, it does not appear that framing impacts the formation of response expectancies or experiences in a healthy sample; however, suggestion requires additional exploration as a simple but effective response expectancy reduction tool. Side effect expectancies appear to be influential but complex predictors of toxicity experiences in patients undergoing cancer treatment. This complexity need not discourage future investigation of response expectancies in this area, with promising directions, including important side effect expectancies to focus on for chemotherapy and radiotherapy, and the potential of social influences to assist with side effect expectancy reduction, revealed in the current project.

Although there is still more to be discovered about their mechanisms, response expectancies show utility as inexpensive, tangible, and simple predictors and interventions for those at risk of severe toxicity experiences. These findings, in associations with others, can aid our understanding of a variety of interventions. Cancer treatment-related side effects are often highly distressing for patients (Curt et al., 2000; Davis et al., 2014; Genre et al., 2002), come at a large economic cost to the healthcare system (Carlotto et al., 2013), and can continue for up to decades beyond the completion of treatment (Curt et al., 2000). A projected increase in the number of individuals who will require treatment in the future (Jemal et al., 2017; Miller et al., 2016), the majority of whom will be older with more comorbidities and risks associated with toxicity experiences (Butkiewicz et al., 2016) signifies the necessity to consider multiple, interdisciplinary approaches to toxicity management. Based on the outcome of this project alone, it is evident that response expectancies are particularly important and promising non-pharmacological predictors that can be harnessed to manage the severity of patients' side effects, benefiting not only the patient, but the entire healthcare system.

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Appendix A

Terms used in Electronic Database Searches (by Database)

PsychInfo

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expecta$.sh OR expecta$.tw OR anticipat$.tw OR response expecta$.tw OR nocebo$.tw OR placebo effect$.tw OR psychological factor$.tw OR psychological aspect$.tw OR psychological variable$.tw OR non pharmacologic$.tw OR nonpharmacologic$.tw	exp neoplasms OR neoplasms.sh OR neopla$.tw OR cancer$.tw OR carcinoma$.tw OR malignan$.tw OR sarcoma$.tw OR tumor$.tw OR tumour$.tw OR oncolog$.tw	exp drug therapy OR exp treatment OR drug therapy.sh OR drug therap$.tw OR treatment$.sh OR treatment$.tw OR medicat$.tw OR chemotherapy$.tw OR radiotherapy$.tw OR radiation therap$.tw OR surger$.tw OR "therapy (drug)".tw	drug adverse reaction$.tw OR side-effect$.tw OR toxicit$.tw OR adverse$.tw OR nonspecific.tw OR non specific.tw OR iatrogenic effect$.tw OR drug effect$.tw OR drug reaction$.tw OR nausea.tw OR vomiting.tw OR fatigue.tw OR pain.tw OR sex.tw OR change$.tw OR sleep.tw OR hair loss.tw OR mood$.tw OR weight$.tw OR diarrhea.tw OR diarrhoea.tw OR constipat$.tw OR fever.tw OR blood$.tw OR bleed$.tw OR concentra$.tw OR weak$.tw OR anticipatory*.tw OR exp "side-effects (treatment)" OR "side-effects (treatment)".sh

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PubMed

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anticipat* [tw] OR placebo effect*[mh] OR nocebo*[tw] OR response expecta*[tw] OR expecta* OR placebo effect*[tw] OR psychology set[tw] OR psychological factor*[tw] OR psychological variable*[tw] OR psychological aspect*[tw] OR non pharmacologic*[tw] OR nonpharmacologic*[tw]	Neoplasms[mh] OR neopla*[tw] OR cancer*[tw] OR tumor*[tw] OR tumour*[tw] OR carcinoma*[tw] OR malignan*[tw] OR oncolog*[tw] OR sarcoma* [tw]	Drug therapy [mh] OR drug therap*[tw] OR treatment* [tw] OR medicat* [tw] OR surger*[tw] OR chemotherap* [tw] OR radiotherap* [tw] or radiation therap* [tw] OR therapy, drug* [tw]	Drug-related side-effects and adverse reactions [mh] OR toxicit*[tw] OR side-effect*[tw] OR iatrogenic effect*[tw] OR non specific*[tw] OR nonspecific*[tw] drug effect*[tw] OR drug reaction*[tw] OR adverse*[tw] OR nausea[tw] OR vomiting[tw] OR fatigue[tw] OR pain[tw] OR sex[tw] OR change*[tw] OR sleep[tw] OR "hair loss"[tw] OR mood*[tw] OR weight*[tw] OR diarrhea[tw] OR diarrhoea[tw] OR

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constipat*[tw] OR
fever[tw] OR
blood*[tw] OR
bleed*[tw] OR
concentra*[tw] OR
weak*[tw] OR
anticipatory*[tw]

CINAHL

MH	MH Neoplasms	MH drug	MH
Psychosocial aspects of illness OR TI psychosocial aspects of illness OR AB psychosocial aspect of illness OR TI expecta* OR AB expecta* OR TI "response expecta*" OR AB "response expecta*" OR TI anticipation* OR AB anticipation* OR nocebo*OR AB nocebo* OR TI "placebo effect*" OR AB "placebo effect*" TI "psychology set" OR AB "psychology set" OR TI "psychological factor*" OR AB "psychological factor*" OR TI "psychological aspect*" OR AB "psychological aspect*" OR TI "psychological variable*" OR AB "psychological variable*" OR TI "non pharmacologic*" OR AB "non pharmacologic*" OR TI nonpharmacologic* OR AB nonpharmacologic*	OR TI neopla* OR AB neopla* OR TI cancer* OR AB cancer* OR TI carcinoma* OR AB carcinoma* OR TI malignan* OR AB malignan* OR TI tumour* OR AB tumour* OR TI tumor* OR AB tumor* OR TI oncolog* OR AB oncolog* OR TI "cancer patient*" OR AB "cancer patient*" OR TI sarcoma* or TI sarcoma*	therapy OR TI drug therap* OR AB drug therap* OR TI treatment* OR AB treatment* OR TI medicat* OR AB medicat* OR TI surger* OR AB surger* OR TI chemotherap* OR AB chemotherap* OR TI radiotherap* OR AB radiotherap* OR TI radiation therap* OR AB radiation therap*	Adverse healthcare event OR TI adverse* OR AB adverse* OR TI Side-effect* OR Ti iatrogenic effect OR AB itrogenic effect OR AB side-effect* OR TI toxicit* OR AB toxicit* OR TI nonspecific* OR AB nonspecific* OR TI non specific OR AB non specific OR TI drug effect* OR AB drug effect* OR AB drug reaction* OR TI drug reaction OR TI nausea OR TI vomiting OR TI fatigue OR TI pain OR TI sex OR TI change* OR TI sleep* OR TI "hair loss" OR TI mood* OR TI weight* OR TI diarrhea OR TI diarrhoea TI constipat* OR TI fever OR TI blood* OR TI bleed* OR TI concentra* OR TI weak*OR AB nausea OR AB vomiting OR AB fatigue OR AB pain OR AB sex OR AB changes OR AB sleep OR AB "hair loss." OR AB mood* OR AB weight* OR AB diarrhea OR AB diarrhoea OR AB constipate* OR AB fever OR AB blood* OR AB bleed* OR AB concentra* OR AB weak*OR TI anticipatory* OR AB anticipatory*

Embase

| Expecta*:ti,ab OR "RE":ti,ab OR "response expectancy":ti,ab OR | Neoplasm/exp OR neopla*:ti,ab OR carcinoma:ti,ab OR malignan*:ti,ab OR | "Drug therapy"/exp OR "drug therapy":ti,ab OR "drug | "Adverse drug reaction"/exp OR "drug effect":ti,ab OR |

nocebo*:ti,ab OR "placebo effect":ti,ab OR "placebo effects":ti,ab OR anticipat*:ti,ab OR nonpharmacologic*:ti,ab OR "non pharmacologic":ti,ab OR psychological factor*:ti,ab OR psychological variable*:ti,ab OR psychological aspect*:ti,ab	tumor*:ti,ab OR tumour*:ti,ab OR oncolog*:ti,ab OR cancer*:ti,ab	therapies":ti,ab OR treatment*:ti,ab OR medicat*:ti,ab OR chemotherapy$:ti,ab OR radiotherapy$:ti,ab OR 'radiation therapy':ti,ab OR surger$:ti,ab	"drug effects":ti,ab OR "drug reaction":ti,ab OR "drug reactions":ti,ab OR "side-effects":ti,ab OR "side-effect":ti,ab OR "non specific":ti,ab OR nonspecific*:ti,ab OR "iatrogenic effect":ti,ab OR "iatrogenic effects":ti,ab OR adverse*:ti,ab OR toxicit*:ti,ab OR nausea:ti,ab OR vomiting:ti,ab OR fatigue:ti,ab OR pain:ti,ab OR sex:ti,ab OR changes*:ti,ab OR sleep*:ti,ab OR "hair loss.":ti,ab OR mood*:ti,ab OR weight*:ti,ab OR diarrhea:ti,ab OR diarrhoea:ti,ab OR constipat*:ti,ab OR fever:ti,ab OR blood*:ti,ab OR bleed*:ti,ab OR concentra*:ti,ab OR weak*:ti,ab OR anticipatory*:ti,ab
NOT Medline			

Columns represent search terms separated by the 'AND" function

Appendix B

Significant differences between patients who did and did not continue to their

specified final follow-up

Outcome Variable	Continued to specified final follow-up	M	SD	t	df	p	ϕ
Helpless/ Hopeless Coping Style	Yes	9.2	2.7				
	No	7.5	1.8	2.30	41	.03	.28
Baseline Urinary Urgency	Yes	1.7	0.5				
	No	2.0	0.0	-4.21	34	.001	.31
REs of Urinary Urgency (T1)	Yes	2.4	2.4				
	No	0.9	1.1	2.85	41	.01	.28
REs of Urinary Frequency (T1)	Yes	3.3	2.5				
	No	1.0	1.3	3.78	24.99	.001	.39
REs of Hair Loss (pelvis; T1)	Yes	1.9	2.1				
	No	0.7	1.3	2.21	20.61	.04	.26
REs of Bowel Leakage (T1)	Yes	1.6	1.9				
	No	0.6	1.0	2.15	24.28	.04	.28

Appendix C

Correlations between response expectancies, experience, and confounding variables (n = 23-34).

	Age	Stage	Com-orbid	Edu.	Culture	Marital Status	Treat.	Hor-mone	Time since Diag.	Baseline	English	Activity Level	H/H	AV	Fa	FS	AP	Depr-ession	Anxiety	Stress
Response Expectancies										r (p)										
Fatigue	-0.21	0.37	0.01	0.28	0.14	-0.21	-0.10	-0.15	-0.29	-0.05	0.00	-0.22	0.16	0.01	0.05	-0.22	0.08	-0.05	0.18	0.03
	(0.23)	(0.04)	(0.95)	(0.12)	(0.45)	(0.24)	(0.57)	(0.41)	(0.11)	(0.79)	(0.99)	(0.20)	(0.96)	(0.96)	(0.78)	(0.23)	(0.64)	(0.79)	(0.32)	(0.89)
Nausea	-0.40	0.43	0.13	0.49	0.01	-0.17	-0.27	-0.25	-0.16	0.15	0.17	-0.23	0.42	0.21	0.18	-0.01	0.29	0.19	0.34	0.23
	(0.02)	(0.02)	(0.48)	(0.01)	(0.96)	(0.36)	(0.12)	(0.16)	(0.37)	(0.40)	(0.33)	(0.20)	(0.02)	(0.26)	(0.32)	(0.97)	(0.11)	(0.28)	(0.05)	(0.20)
Abdominal Cramps	-0.52	0.41	0.25	0.41	-0.03	-0.09	-0.29	-0.10	-0.16	0.14	0.14	-0.20	0.41	0.23	0.06	-0.05	0.39	0.20	0.33	0.29
	(0.001)	(0.02)	(0.1)	(0.02)	(0.86)	(0.62)	(0.09)	(0.57)	(0.36)	(0.42)	(0.44)	(0.26)	(0.02)	(0.20)	(0.74)	(0.78)	(0.02)	(0.25)	(0.06)	(0.09)
Skin Irritation	-0.26	0.32	0.12	0.36	0.04	-0.15	-0.17	-0.26	-0.21		0.09	-0.30	0.09	-0.11	0.00	-0.17	0.06	0.07	0.17	0.01
	(0.14)	(0.09)	(0.52)	(0.05)	(0.82)	(0.42)	(0.35)	(0.14)	(0.23)	-	(0.60)	(0.09)	(0.61)	(0.56)	(0.99)	(0.34)	(0.75)	(0.70)	(0.34)	(0.95)
Urinary Frequency	-0.20	0.14	-0.08	0.31	0.01	-0.13	-0.33	-0.09	-0.24	-0.38	0.09	-0.04	0.30	0.30	0.22	-0.03	0.30	0.01	0.27	0.12
	(0.26)	(0.46)	(0.65)	(0.09)	(0.97)	(0.48)	(0.06)	(0.61)	(0.19)	(0.03)	(0.63)	(0.82)	(0.09)	(0.10)	(0.23)	(0.89)	(0.09)	(0.97)	(0.13)	(0.49)
Hair Loss (Pelvis)	-0.26	0.23	-0.00	0.44	-0.04	-0.12	-0.23	-0.21	-0.04		0.07	-0.27	0.28	0.14	0.15	0.07	0.32	0.12	0.19	0.10
	(0.15)	(0.24)	(0.98)	(0.01)	(0.83)	(0.52)	(0.07)	(0.24)	(0.90)	-	(0.71)	(0.13)	(0.13)	(0.46)	(0.43)	(0.70)	(0.08)	(0.51)	(0.11)	(0.57)
P/B/D when Urinating	-0.22	0.28	-0.01	0.44	-0.09	-0.04	-0.39	-0.22	-0.08	-0.44	0.18	-0.22	0.33	0.23	0.22	0.06	0.27	0.15	0.31	0.20
	(0.22)	(0.13)	(0.95)	(0.01)	(0.63)	(0.85)	(0.02)	(0.12)	(0.67)	(0.01)	(0.32)	(0.21)	(0.06)	(0.24)	(0.24)	(0.76)	(0.13)	(0.39)	(0.07)	(0.25)
Poor Urinary Stream	-0.25	0.23	0.05	0.33	-0.11	-0.04	-0.33	-0.10	-0.12	-0.14	0.09	-0.04	0.37	-0.37	0.25	-0.01	0.33	0.17	0.31	0.17
	(0.16)	(0.23)	(0.80)	(0.06)	(0.55)	(0.84)	(0.06)	(0.59)	(0.52)	(0.44)	(0.60)	(0.83)	(0.03)	(0.04)	(0.17)	(0.95)	(0.03)	(0.35)	(0.08)	(0.35)
Blood in Urine	-0.48	0.34	0.04	0.48	0.01	-0.02	-0.36	-0.25	-0.14	0.15	0.04	-0.09	0.37	0.11	0.15	0.01	0.30	0.09	0.29	0.35
	(0.004)	(0.06)	(0.82)	(0.01)	(0.94)	(0.93)	(0.04)	(0.15)	(0.45)	(0.39)	(0.60)	(0.63)	(0.03)	(0.55)	(0.41)	(0.95)	(0.09)	(0.61)	(0.1)	(0.04)
Urinary Urgency	-0.23	0.15	-0.05	0.36	-0.08	0.05	-0.25	-0.21	-0.17	-0.77	0.20	-0.04	0.37	0.23	0.33	-0.04	0.20	0.14	0.23	0.19
	(0.20)	(0.43)	(0.78)	(0.04)	(0.64)	(0.76)	(0.16)	(0.23)	(0.35)	(<0.001)	(0.25)	(0.82)	(0.03)	(0.21)	(0.06)	(0.83)	(0.27)	(0.44)	(0.20)	(0.27)
Urinary Incontinence	-0.17	0.39	0.06	0.43	-0.12	-0.11	-0.13	-0.34	-0.10	-0.01	0.12	-0.22	-0.30	0.20	0.21	-0.01	0.17	0.21	0.33	0.24
	(0.34)	(0.04)	(0.74)	(0.01)	(0.51)	(0.55)	(0.47)	(0.05)	(0.59)	(0.94)	(0.51)	(0.21)	(0.10)	(0.28)	(0.25)	(0.94)	(0.35)	(0.24)	(0.06)	(0.17)

Rectal Urgency	-0.22	0.49	0.17	0.43	-0.12	-0.01	-0.12	-0.29	-0.15	0.23	0.27	-0.23	0.36	0.23	0.24	0.08	0.29	0.13	0.25	0.25
	(0.21)	(0.01)	(0.35)	(0.02)	(0.53)	(0.98)	(0.49)	(0.10)	(0.42)	(0.21)	(0.13)	(0.20)	(0.04)	(0.22)	(0.19)	(0.67)	(0.10)	(0.46)	(0.16)	(0.16)
Painful Bowel Movement	-0.35	0.36	0.17	0.49	-0.08	-0.11	-0.22	-0.34	-0.11	0.14	0.18	-0.15	0.35	0.10	0.21	0.09	0.33	0.08	0.16	0.13
	(0.05)	(0.05)	(0.35)	(0.004)	(0.66)	(0.54)	(0.21)	(0.05)	(0.54)	(0.42)	(0.32)	(0.39)	(0.05)	(0.57)	(0.25)	(0.61)	(0.06)	(0.67)	(0.36)	(0.46)
Bowel Leakage	-0.20	0.38	0.15	0.40	-0.03	-0.12	-0.17	-0.43	-0.10	-0.19	0.47	-0.13	0.19	0.02	0.19	0.14	0.18	0.06	0.17	0.22
	(0.25)	(0.04)	(0.40)	(0.03)	(0.88)	(0.51)	(0.34)	(0.01)	(0.57)	(0.29)	(0.13)	(0.46)	(0.30)	(0.93)	(0.30)	(0.45)	(0.31)	(0.74)	(0.34)	(0.21)
Blood in Stools	-0.35	0.35	0.16	0.49	-0.07	-0.12	-0.19	-0.35	-0.14	0.15	0.16	-0.19	0.38	0.15	0.20	0.10	0.34	0.09	0.16	0.18
	(0.05)	(0.06)	(0.37)	(0.01)	(0.70)	(0.51)	(0.29)	(0.04)	(0.46)	(0.42)	(0.38)	(0.30)	(0.03)	(0.42)	(0.27)	(0.60)	(0.06)	(0.61)	(0.36)	(0.32)
Reduced Desire for Sex	0.01	-0.06	-0.28	0.22	0.01	-0.27	-0.16	-0.26	-0.22	-0.36	0.06	0.09	0.13	0.15	0.35	-0.05	0.10	-0.07	0.14	0.05
	(0.96)	(0.75)	(0.12)	(0.23)	(0.95)	(0.14)	(0.37)	(0.15)	(0.24)	(0.04)	(0.73)	(0.64)	(0.50)	(0.42)	(0.06)	(0.81)	(0.61)	(0.70)	(0.45)	(0.79)
Inability to Reach Orgasm	-0.03	0.02	-0.15	0.33	0.05	-0.18	-0.36	-0.12	-0.11	-0.24	-0.20	-0.27	0.05	0.00	0.09	0.02	0.09	-0.00	0.27	0.06
	(0.88)	(0.94)	(0.43)	(0.08)	(0.79)	(0.34)	(0.05)	(0.54)	(0.56)	(0.19)	(0.28)	(0.15)	(0.80)	(0.99)	(0.65)	(0.91)	(0.64)	(0.99)	(0.14)	(0.75)
Inability to Have or Maintain Erection	0.07	-0.10	-0.20	0.21	-0.05	-0.17	-0.36	-0.04	0.10	-0.37	0.07	-0.22	-0.02	0.09	0.10	0.05	0.06	-0.04	0.21	0.21
	(0.71)	(0.61)	(0.27)	(0.27)	(0.78)	(0.36)	(0.04)	(0.85)	(0.60)	(0.04)	(0.70)	(0.22)	(0.91)	(0.63)	(0.59)	(0.79)	(0.77)	(0.83)	(0.26)	(0.26)
Experienced toxicities										r (p)										
Fatigue	-0.21	0.12	0.27	-0.23	0.13	-0.03	-0.04	-0.11	-0.18	-0.10	-0.14	-0.09	-0.17	-0.24	-0.28	-0.28	-0.14	-0.04	0.09	0.18
	(0.24)	(0.53)	(0.13)	(0.21)	(0.47)	(0.85)	(0.81)	(0.53)	(0.32)	(0.56)	(0.42)	(0.60)	(0.35)	(0.19)	(0.11)	(0.12)	(0.43)	(0.81)	(0.62)	(0.62)
Nausea	-0.51	-0.04	0.50	-0.22	-0.02	0.02	-0.30	-0.11	-0.06	0.07	-0.10	0.10	0.21	0.08	-0.02	-0.01	-0.02	0.12	0.22	0.43
	(0.002)	(0.83)	(0.003)	(0.23)	(0.93)	(0.91)	(0.10)	(0.55)	(0.77)	(0.71)	(0.59)	(0.59)	(0.25)	(0.68)	(0.90)	(0.96)	(0.90)	(0.49)	(0.22)	(0.01)
Abdominal Cramps	-0.35	0.09	0.27	-0.10	0.09	0.13	-0.25	-0.15	-0.06	0.04	-0.08	0.18	0.20	0.17	0.03	0.08	0.06	0.26	0.25	0.47
	(0.04)	(0.65)	(0.13)	(0.61)	(0.62)	(0.48)	(0.15)	(0.39)	(0.76)	(0.81)	(0.66)	(0.31)	(0.25)	(0.36)	(0.88)	(0.66)	(0.73)	(0.14)	(0.17)	(0.01)
Skin Irritation	-0.04	-0.13	0.03	-0.14	-0.10	0.05	-0.03	-0.20	-0.08		0.08	0.07	-0.19	-0.19	0.02	-0.03	-0.29	0.06	-0.03	0.10
	(0.84)	(0.49)	(0.86)	(0.45)	(0.58)	(0.77)	(0.88)	(0.24)	(0.65)	-	(0.64)	(0.69)	(0.29)	(0.29)	(0.93)	(0.85)	(0.10)	(0.73)	(0.86)	(0.59)
Urinary Frequency	-0.07	-0.23	-0.22	-0.07	-0.45	0.08	-0.43	0.09	0.17	-0.14	0.33	0.19	-0.03	0.05	0.00	-0.04	0.16	0.00	0.01	-0.07
	(0.71)	(0.22)	(0.20)	(0.69)	(0.01)	(0.65)	(0.01)	(0.61)	(0.34)	(0.42)	(0.06)	(0.27)	(0.85)	(0.77)	(1.00)	(0.85)	(0.36)	(0.99)	(0.97)	(0.69)
Hair Loss (Pelvis)	-0.14	0.10	-0.16	0.31	-0.03	0.06	-0.30	0.12	-0.09		0.13	-0.09	0.22	0.13	-0.01	-0.18	0.13	-0.29	0.12	0.17
	(0.42)	(0.59)	(0.38)	(0.09)	(0.86)	(0.73)	(0.09)	(0.48)	(0.63)	-	(0.48)	(0.62)	(0.21)	(0.47)	(0.94)	(0.33)	(0.48)	(0.10)	(0.50)	(0.33)
P/B/D when Urinating	-0.13	-0.46	0.02	-0.25	0.02	0.02	-0.39	0.15	0.13	-0.06	-0.17	0.35	-0.25	-0.25	-0.12	0.01	0.03	0.16	-0.19	-0.10
	(0.44)	(0.01)	(0.92)	(0.16)	(0.90)	(0.90)	(0.02)	(0.40)	(0.46)	(0.73)	(0.30)	(0.04)	(0.16)	(0.16)	(0.52)	(0.96)	(0.86)	(0.36)	(0.29)	(0.57)

Measure																			
Poor Urinary Stream	-0.02	-0.21	-0.18	-0.04	-0.39	0.07	-0.38	-0.03	0.09	-0.60	0.31	0.16	-0.11	-0.04	0.02	-0.02	0.01	-0.01	-0.04	-0.02
	(0.92)	(0.26)	(0.31)	(0.81)	(0.03)	(0.70)	(0.03)	(0.87)	(0.62)	(<0.001)	(0.07)	(0.37)	(0.54)	(0.85)	(0.91)	(0.93)	(0.94)	(0.95)	(0.82)	(0.90)
Blood in Urine	-0.19	0.02	0.05	-0.21	0.11	0.06	-0.16	-0.23	0.02	0.04	-0.08	0.30	-0.02	-0.08	-0.09	0.03	-0.00	-0.02	0.03	0.27
	(0.29)	(0.90)	(0.80)	(0.25)	(0.56)	(0.73)	(0.36)	(0.19)	(0.90)	(0.81)	(0.67)	(0.08)	(0.91)	(0.67)	(0.63)	(0.87)	(0.99)	(0.93)	(0.85)	(0.11)
Urinary Urgency	-0.11	-0.04	-0.23	0.07	-0.30	0.19	-0.53	-0.09	0.21	-0.37	0.20	0.15	0.06	-0.07	0.12	0.06	0.15	0.09	0.03	0.07
	(0.55)	(0.82)	(0.19)	(0.72)	(0.10)	(0.28)	(0.001)	(0.63)	(0.24)	(0.03)	(0.26)	(0.39)	(0.74)	(0.71)	(0.53)	(0.70)	(0.41)	(0.60)	(0.86)	(0.70)
Urinary Incontinence	-0.26	-0.16	-0.14	0.11	-0.12	-0.22	-0.58	-0.02	0.14	0.07	-0.20	-0.26	-0.05	-0.16	-0.02	-0.04	0.18	0.06	0.05	-0.04
	(0.13)	(0.40)	(0.41)	(0.56)	(0.51)	(0.21)	(<0.001)	(0.93)	(0.43)	(0.70)	(0.26)	(0.14)	(0.78)	(0.38)	(0.93)	(0.82)	(0.32)	(0.74)	(0.80)	(0.83)
Rectal Urgency	0.15	-0.27	-0.18	-0.22	-0.28	0.47	-0.26	0.04	0.63	0.13	0.11	0.03	-0.08	0.15	-0.00	0.11	0.08	-0.14	-0.16	-0.12
	(0.41)	(0.15)	(0.31)	(0.24)	(0.12)	(0.01)	(0.14)	(0.81)	(<0.001)	(0.46)	(0.54)	(0.87)	(0.68)	(0.41)	(0.98)	(0.55)	(0.66)	(0.43)	(0.36)	(0.500)
Painful Bowel Movement	0.02	-0.15	-0.10	0.04	0.10	0.29	-0.10	0.09	-0.11	0.05	0.62	-0.03	-0.03	-0.11	-0.09	0.04	-0.03	-0.05	0.02	-0.04
	(0.90)	(0.43)	(0.56)	(0.81)	(0.58)	(0.10)	(0.56)	(0.63)	(0.55)	(0.79)	(<0.001)	(0.87)	(0.88)	(0.57)	(0.63)	(0.83)	(0.86)	(0.78)	(0.94)	(0.80)
Bowel Leakage	0.27	-0.23	-0.14	-0.17	-0.17	-0.11	-0.13	0.04	-0.15	-0.19	0.40	-0.03	-0.32	0.01	0.15	0.25	-0.29	-0.14	-0.13	-0.07
	(0.12)	(0.22)	(0.42)	(0.34)	(0.34)	(0.52)	(0.47)	(0.84)	(0.39)	(0.27)	(0.02)	(0.87)	(0.07)	(0.94)	(0.40)	(0.16)	(0.09)	(0.41)	(0.46)	(0.70)
Blood in Stools	-0.36	0.02	0.19	-0.02	0.07	0.15	-0.32	-0.16	-0.04	0.03	-0.05	0.21	0.18	0.05	-0.04	-0.05	0.11	0.08	-0.03	0.30
	(0.03)	(0.93)	(0.28)	(0.93)	(0.69)	(0.40)	(0.07)	(0.37)	(0.81)	(0.87)	(0.76)	(0.22)	(0.30)	(0.78)	(0.84)	(0.78)	(0.55)	(0.65)	(0.89)	(0.08)
Reduced Desire for Sex	0.04	-0.07	-0.35	0.11	-0.25	-0.26	-0.03	-0.39	-0.06	-0.43	0.11	-0.03	0.08	-0.05	0.13	-0.21	-0.05	-0.22	-0.20	-0.21
	(0.84)	(0.73)	(0.05)	(0.58)	(0.17)	(0.16)	(0.85)	(0.03)	(0.75)	(0.01)	(0.56)	(0.89)	(0.68)	(0.80)	(0.48)	(0.27)	(0.78)	(0.22)	(0.27)	(0.24)
Inability to Reach Orgasm	0.16	-0.15	-0.33	0.09	-0.33	-0.17	-0.07	-0.22	-0.01	-0.37	0.10	-0.11	0.06	0.08	0.11	-0.20	-0.09	-0.12	-0.04	-0.14
	(0.40)	(0.47)	(0.07)	(0.64)	(0.08)	(0.37)	(0.70)	(0.23)	(0.97)	(0.04)	(0.59)	(0.56)	(0.76)	(0.68)	(0.56)	(0.30)	(0.63)	(0.53)	(0.84)	(0.44)
Inability to have or Maintain Erection	0.22	-0.21	-0.39	0.03	-0.43	-0.11	-0.01	-0.25	-0.24	-0.41	0.10	-0.10	0.03	0.06	0.05	-0.21	-0.14	-0.26	-0.20	-0.27
	(0.24)	(0.29)	(0.04)	(0.88)	(0.02)	(0.57)	(0.94)	(0.18)	(0.21)	(0.02)	(0.61)	(0.59)	(0.90)	(0.76)	(0.79)	(0.28)	(0.47)	(0.17)	(0.28)	(0.15)

	Age	Stage	Comorb -idity	Edu.	Culture	Marit al Status	Treat- m-ent	Hor- mone	Time since Diag.	Baseline	English	Activity Level	H/H	AV	Fa	FS	AP	Depr- ession	Anxie ty	Stress
T2 Response Expectancies										r (p)										
Fatigue	-0.48	0.24	0.21	0.19	0.11	-0.19	-0.15	-0.14	0.23	-0.10	-0.14	-0.14	0.25	-0.22	0.14	-0.02	0.23	0.09	0.11	0.36
	(0.01)	(0.20)	(0.24)	(0.31)	(0.56)	(0.31)	(0.40)	(0.43)	(0.19)	(0.57)	(0.44)	(0.45)	(0.16)	(0.23)	(0.44)	(0.91)	(0.20)	(0.63)	(0.53)	(0.04)
Nausea	-0.41	0.22	0.11	0.35	0.02	0.35	-0.34	-0.10	0.11	0.12	-0.02	-0.15	0.42	0.04	0.21	0.03	0.15	0.09	0.19	0.33
	(0.02)	(0.24)	(0.52)	(0.05)	(0.93)	(0.05)	(0.05)	(0.56)	(0.54)	(0.51)	(0.90)	(0.41)	(0.02)	(0.83)	(0.26)	(0.88)	(0.41)	(0.62)	(0.30)	(0.06)
Abdominal Cramps	-0.28	0.41	0.03	0.28	-0.01	0.28	-0.24	-0.22	0.08	0.10	0.03	-0.03	0.30	0.10	0.12	-0.02	0.19	0.10	0.26	0.35
	(0.12)	(0.02)	(0.86)	(0.12)	(0.96)	(0.12)	(0.18)	(0.21)	(0.65)	(0.58)	(0.87)	(0.88)	(0.10)	(0.60)	(0.50)	(0.91)	(0.30)	(0.59)	(0.15)	(0.04)
Skin Irritation	-0.15	0.23	-0.00	0.34	0.08	-0.04	-0.11	-0.29	0.20		0.14	-0.07	0.16	-0.05	0.23	-0.01	0.00	0.18	0.11	0.26
	(0.42)	(0.22)	(0.99)	(0.06)	(0.67)	(0.81)	(0.53)	(0.10)	(0.25)	-	(0.44)	(0.68)	(0.37)	(0.79)	(0.21)	(0.97)	(0.99)	(0.31)	(0.55)	(0.15)
Urinary Frequency	-0.37	-0.16	-0.21	0.13	0.12	0.00	-0.60	0.10	0.03	-0.16	0.02	0.20	0.12	-0.13	0.16	0.08	0.18	-0.10	-0.01	0.13
	(0.04)	(0.40)	(0.23)	(0.48)	(0.50)	(1.00)	(<0.001)	(0.67)	(0.88)	(0.35)	(0.92)	(0.27)	(0.49)	(0.47)	(0.38)	(0.67)	(0.31)	(0.57)	(0.57)	(0.46)
Hair Loss (Pelvis)	-0.22	0.35	0.09	0.42	0.08	-0.19	-0.31	0.02	-0.02		-0.14	-0.09	0.30	0.07	0.04	-0.00	0.26	0.44	0.38	0.41
	(0.22)	(0.06)	(0.61)	(0.02)	(0.66)	(0.28)	(0.07)	(0.92)	(0.90)	-	(0.42)	(0.62)	(0.09)	(0.70)	(0.82)	(0.98)	(0.15)	(0.01)	(0.03)	(0.02)
P/B/D when Urinating	-0.29	-0.14	-0.00	0.09	-0.03	0.10	-0.54	0.10	-0.06	-0.18	0.18	0.15	0.09	-0.05	0.07	0.20	0.22	-0.07	-0.05	0.09
	(0.11)	(0.47)	(0.99)	(0.62)	(0.86)	(0.60)	(0.001)	(0.58)	(0.74)	(0.30)	(0.32)	(0.38)	(0.63)	(0.78)	(0.69)	(0.28)	(0.21)	(0.68)	(0.78)	(0.61)
Poor Urinary Stream	-0.26	0.10	-0.14	0.22	0.06	0.08	0.60	0.04	-0.03	-0.36	0.05	0.10	0.09	-0.10	0.10	0.10	0.17	-0.11	-0.03	0.07
	(0.14)	(0.59)	(0.42)	(0.23)	(0.77)	(0.65)	(<0.001)	(0.80)	(0.87)	(0.04)	(0.78)	(0.58)	(0.63)	(0.58)	(0.61)	(0.60)	(0.34)	(0.52)	(0.86)	(0.71)
Blood in Urine	-0.18	0.34	-0.07	0.32	0.08	-0.28	-0.26	-0.09	0.14	0.12	-0.05	-0.04	0.14	-0.13	0.02	0.07	0.25	0.18	0.26	0.27
	(0.32)	(0.07)	(0.72)	(0.08)	(0.65)	(0.12)	(0.14)	(0.61)	(0.43)	(0.52)	(0.78)	(0.83)	(0.45)	(0.48)	(0.91)	(0.70)	(0.17)	(0.32)	(0.14)	(0.21)
Urinary Urgency	-0.39	-0.11	-0.19	0.10	0.14	0.03	-0.65	-0.10	-0.06	-0.39	-0.08	0.25	0.10	-0.18	0.17	0.12	0.24	-0.16	-0.04	0.05
	(0.02)	(0.57)	(0.28)	(0.59)	(0.45)	(0.86)	(<0.001)	(0.97)	(0.75)	(0.02)	(0.64)	(0.15)	(0.57)	(0.31)	(0.35)	(0.51)	(0.17)	(0.38)	(0.81)	(0.77)
Urinary Incontinence	-0.15	0.29	-0.27	0.35	0.14	-0.32	-0.31	-0.12	0.07	0.12	-0.12	-0.05	0.12	-0.14	0.08	0.09	0.24	0.14	0.27	0.17
	(0.41)	(0.13)	(0.35)	(0.05)	(0.45)	(0.05)	(0.07)	(0.50)	(0.68)	(0.51)	(0.51)	(0.78)	(0.53)	(0.43)	(0.68)	(0.64)	(0.19)	(0.43)	(0.13)	(0.33)
Rectal Urgency	-0.06	0.33	-0.13	0.19	-0.14	-0.03	-0.19	-0.15	-0.17	0.10	-0.01	0.06	0.01	0.03	-0.08	0.11	0.17	-0.13	0.17	0.11
	(0.73)	(0.09)	(0.46)	(0.30)	(0.44)	(0.89)	(0.30)	(0.41)	(0.35)	(0.60)	(0.97)	(0.73)	(0.95)	(0.86)	(0.66)	(0.57)	(0.35)	(0.47)	(0.33)	(0.53)
Painful Bowel Movement	-0.09	0.18	-0.11	0.28	-0.04	-0.03	-0.17	-0.08	0.14	0.10	0.31	-0.15	0.13	0.01	0.05	0.04	0.10	-0.06	0.19	0.12
	(0.63)	(0.33)	(0.54)	(0.13)	(0.83)	(0.87)	(0.34)	(0.65)	(0.43)	(0.57)	(0.07)	(0.39)	(0.47)	(0.97)	(0.79)	(0.84)	(0.60)	(0.75)	(0.29)	(0.51)
Bowel Leakage	-0.04	-0.17	-0.17	0.25	-0.13	-0.10	-0.20	-0.30	-0.04	-0.22	0.08	-0.03	0.02	-0.10	0.07	0.09	0.13	-0.18	0.08	0.10
	(0.83)	(0.38)	(0.33)	(0.18)	(0.48)	(0.57)	(0.26)	(0.08)	(0.82)	(0.21)	(0.67)	(0.84)	(0.93)	(0.60)	(0.70)	(0.63)	(0.48)	(0.31)	(0.66)	(0.59)

Blood in Stools	-0.35 (0.04)	-0.20 (0.31)	0.08 (0.66)	0.27 (0.13)	0.11 (0.54)	-0.24 (0.18)	-0.38 (0.03)	-0.05 (0.78)	0.08 (0.65)	0.09 (0.60)	-0.09 (0.60)	-0.14 (0.43)	0.25 (0.16)	-0.11 (0.54)	0.16 (0.39)	0.12 (0.51)	0.05 (0.78)	-0.11 (0.53)	0.08 (0.65)	0.17 (0.33)
Reduced Desire for Sex	0.11 (0.57)	-0.17 (0.38)	-0.31 (0.08)	0.07 (0.72)	-0.09 (0.64)	-0.21 (0.25)	-0.26 (0.15)	-0.22 (0.22)	0.06 (0.74)	-0.36 (0.04)	0.06 (0.74)	-0.03 (0.88)	0.01 (0.95)	-0.19 (0.32)	0.17 (0.38)	0.01 (0.94)	-0.08 (0.69)	-0.24 (0.20)	-0.11 (0.54)	-0.04 (0.82)
Inability to Reach Orgasm	0.09 (0.63)	-0.20 (0.31)	-0.24 (0.19)	0.18 (0.35)	-0.17 (0.37)	-0.14 (0.44)	-0.29 (0.10)	-0.10 (0.58)	0.12 (0.51)	-0.45 (0.01)	0.03 (0.89)	-0.17 (0.37)	0.02 (0.91)	-0.09 (0.63)	0.12 (0.53)	0.03 (0.86)	-0.15 (0.41)	-0.27 (0.13)	-0.04 (0.81)	-0.10 (0.95)
Inability to have or Maintain Erection	0.08 (0.65)	-0.17 (0.34)	-0.22 (0.24)	0.19 (0.30)	-0.18 (0.35)	-0.15 (0.42)	-0.25 (0.16)	-0.13 (0.47)	0.11 (0.54)	-0.51 (0.003)	0.03 (0.88)	-0.20 (0.38)	0.04 (0.81)	-0.16 (0.39)	0.11 (0.55)	0.00 (0.99)	-0.07 (0.72)	-0.26 (0.16)	-0.06 (0.77)	0.00 (1.0)

T3 Experienced toxicities									r (p)											
Fatigue	0.02 (0.93)	0.41 (0.06)	0.30 (0.14)	-0.07 (0.77)	0.07 (0.74)	0.01 (0.97)	0.21 (0.30)	-0.37 (0.07)	0.15 (0.49)	-0.36 (0.08)	-0.02 (0.91)	-0.09 (0.66)	-0.38 (0.07)	-0.49 (0.02)	-0.16 (0.48)	-0.07 (0.77)	-0.25 (0.25)	0.22 (0.29)	0.16 (0.45)	0.39 (0.05)
Nausea	0.10 (0.63)	0.34 (0.10)	0.06 (0.79)	-0.02 (0.93)	-0.04 (0.86)	0.14 (0.49)	0.07 (0.75)	0.06 (0.76)	-0.00 (0.99)	0.07 (0.75)	0.15 (0.47)	0.02 (0.94)	0.08 (0.71)	0.05 (0.83)	0.09 (0.68)	0.09 (0.68)	0.07 (0.74)	0.01 (0.96)	0.15 (0.47)	0.38 (0.05)
Abdominal Cramps	-0.17 (0.40)	0.16 (0.46)	0.54 (0.004)	-0.46 (0.02)	-0.14 (0.52)	-0.17 (0.42)	0.06 (0.77)	-0.25 (0.21)	-0.31 (0.12)	0.06 (0.77)	-0.11 (0.70)	0.09 (0.67)	0.30 (0.10)	-0.37 (0.07)	-0.16 (0.44)	-0.08 (0.71)	-0.27 (0.18)	0.26 (0.19)	0.60 (0.001)	0.35 (0.08)
Skin Irritation	-0.06 (0.78)	0.14 (0.50)	0.28 (0.15)	-0.19 (0.35)	-0.14 (0.51)	0.25 (0.21)	0.09 (0.65)	-0.15 (0.46)	-0.08 (0.69)	- (-)	0.33 (0.09)	-0.10 (0.61)	-0.15 (0.45)	-0.05 (0.83)	0.04 (0.85)	0.10 (0.62)	0.06 (0.76)	0.22 (0.28)	0.51 (0.01)	0.25 (0.20)
Urinary Frequency	0.02 (0.92)	0.02 (0.92)	0.13 (0.51)	-0.05 (0.81)	-0.29 (0.17)	-0.47 (0.02)	-0.26 (0.19)	-0.29 (0.14)	-0.11 (0.59)	-0.26 (0.19)	0.01 (0.95)	0.05 (0.80)	-0.19 (0.36)	-0.23 (0.28)	-0.03 (0.89)	-0.11 (0.59)	-0.20 (0.33)	0.44 (0.02)	0.30 (0.14)	0.23 (0.25)
Hair Loss (Pelvis)	0.02 (0.91)	0.18 (0.39)	0.01 (0.95)	0.28 (0.17)	0.09 (0.66)	-0.06 (0.79)	0.06 (0.75)	-0.03 (0.87)	0.08 (0.68)	- (-)	-0.04 (0.84)	-0.12 (0.57)	0.08 (0.71)	-0.12 (0.58)	0.13 (0.54)	-0.01 (0.97)	0.21 (0.32)	-0.04 (0.84)	-0.06 (0.76)	0.21 (0.30)
P/B/D when Urinating	-0.07 (0.73)	-0.15 (0.48)	0.17 (0.41)	0.07 (0.76)	-0.40 (0.05)	-0.46 (0.02)	-0.31 (0.12)	-0.18 (0.38)	-0.11 (0.57)	-0.12 (0.55)	0.10 (0.62)	0.03 (0.90)	-0.03 (0.87)	-0.17 (0.42)	-0.01 (0.96)	-0.03 (0.91)	0.07 (0.72)	0.30 (0.13)	0.10 (0.64)	0.04 (0.85)
Poor Urinary Stream	0.02 (0.94)	0.01 (0.95)	0.23 (0.25)	0.05 (0.82)	-0.30 (0.15)	-0.47 (0.02)	-0.30 (0.13)	-0.11 (0.58)	-0.06 (0.78)	-0.43 (0.03)	0.03 (0.89)	-0.01 (0.97)	-0.12 (0.58)	-0.22 (0.30)	0.02 (0.94)	0.06 (0.77)	0.00 (1.00)	0.38 (0.05)	0.25 (0.23)	0.27 (0.17)

Blood in Urine	0.04 (0.84)	0.04 (0.86)	0.26 (0.18)	-0.19 (0.36)	-0.39 (0.06)	-0.25 (0.22)	0.06 (0.76)	0.06 (0.77)	-0.23 (0.25)	0.06 (0.76)	-0.11 (0.58)	0.08 (0.70)	-0.17 (0.41)	-0.14 (0.51)	-0.04 (0.86)	-0.09 (0.66)	-0.20 (0.34)	0.01 (0.96)	-0.04 (0.84)	0.13 (0.53)
Urinary Urgency	0.14 (0.49)	0.03 (0.91)	0.10 (0.62)	0.04 (0.84)	-0.31 (0.13)	-0.46 (0.02)	-0.26 (0.18)	-0.20 (0.32)	-0.06 (0.79)	-0.16 (0.44)	-0.01 (0.95)	0.11 (0.58)	-0.13 (0.51)	-0.18 (0.39)	-0.13 (0.55)	-0.27 (0.19)	-0.29 (0.16)	-0.43 (0.02)	0.21 (0.31)	0.20 (0.32)
Urinary Incontinence	-0.05 (0.81)	0.04 (0.85)	0.17 (0.40)	0.30 (0.16)	-0.32 (0.12)	-0.44 (0.03)	-0.11 (0.59)	-0.08 (0.69)	-0.11 (0.58)	-0.20 (0.33)	-0.09 (0.67)	0.06 (0.79)	0.21 (0.32)	0.04 (0.87)	0.25 (0.25)	-0.04 (0.86)	-0.06 (0.78)	0.65 (<.001)	0.28 (0.18)	0.34 (0.09)
Rectal Urgency	0.32 (0.11)	0.09 (0.67)	0.17 (0.41)	-0.01 (0.97)	-0.01 (0.97)	-0.18 (0.37)	0.03 (0.88)	0.19 (0.34)	0.20 (0.31)	0.12 (0.54)	0.17 (0.40)	0.00 (1.00)	-0.14 (0.49)	-0.01 (0.95)	-0.00 (1.00)	0.31 (0.13)	-0.11 (0.60)	0.48 (0.01)	0.23 (0.26)	0.41 (0.04)
Painful Bowel Movement	0.24 (0.24)	0.19 (0.37)	-0.10 (0.63)	0.19 (0.36)	0.11 (0.59)	0.43 (0.03)	-0.17 (0.40)	0.10 (0.63)	0.29 (0.14)	0.10 (0.62)	0.47 (0.01)	-0.02 (0.93)	-0.04 (0.86)	-0.11 (0.61)	-0.00 (0.98)	0.17 (0.42)	-0.10 (0.98)	-0.10 (0.63)	0.00 (0.98)	0.01 (0.96)
Bowel Leakage	0.09 (0.67)	0.34 (0.10)	0.05 (0.79)	0.09 (0.66)	0.06 (0.79)	-0.03 (0.89)	-0.12 (0.56)	-0.03 (0.90)	0.07 (0.74)	-0.17 (0.40)	0.8 (0.71)	-0.06 (0.77)	0.08 (0.69)	-0.12 (0.57)	0.15 (0.47)	0.24 (0.24)	0.10 (0.63)	0.33 (0.09)	0.26 (0.20)	0.50 (0.01)
Blood in Stools										-										
Reduced Desire for Sex	0.18 (0.40)	-0.24 (0.28)	-0.45 (0.02)	0.08 (0.73)	-0.34 (0.11)	-0.41 (0.05)	-0.20 (0.33)	-0.45 (0.02)	-0.22 (0.29)	-0.36 (0.08)	0.04 (0.85)	-0.02 (0.94)	-0.01 (0.98)	-0.14 (0.52)	0.14 (0.52)	-0.16 (0.46)	-0.13 (0.55)	-0.27 (0.20)	-0.26 (0.20)	-0.29 (0.16)
Inability to Reach Orgasm	0.37 (0.08)	-0.25 (0.27)	-0.49 (0.01)	0.06 (0.79)	-0.41 (0.05)	-0.28 (0.20)	-0.21 (0.33)	-0.28 (0.19)	-0.24 (0.25)	-0.32 (0.13)	-0.24 (0.25)	-0.15 (0.48)	-0.06 (0.79)	-0.03 (0.91)	0.07 (0.77)	-0.24 (0.28)	-0.24 (0.26)	-0.25 (0.23)	-0.09 (0.66)	-0.19 (0.37)
Inability to have or Maintain Erection	0.41 (0.06)	-0.20 (0.38)	-0.46 (0.02)	0.09 (0.68)	-0.36 (0.09)	-0.31 (0.15)	-0.16 (0.45)	-0.36 (0.09)	-0.22 (0.31)	-0.41 (0.05)	0.04 (0.87)	0.09 (0.69)	-0.18 (0.40)	-0.36 (0.09)	-0.06 (0.80)	-0.16 (0.47)	-0.02 (0.95)	-0.35 (0.87)	-0.22 (0.30)	-0.24 (0.27)

All response expectancies were measured using Visual Analog scales (VAS) ranging from 0 –100, and 0-180 for Pain Threshold and Hand Withdrawal, higher scores indicate greater anticipated severity or time elapsed; All experienced responses measured using Visual Analog scales (VAS) ranging from 0 –100; [a] = Objectively measured time variables, ranging from 0-180 seconds, higher scores indicating more time elapsed (participants' hand immersion in the ice-water for CPT).

Correlations between response expectancies, experience, and covariates (n = 116-129)

	Age	Gender	Degree	English	Culture	Previous Injury	Cold Response	Monito-ring	Blunting	Depres-sion	Anxiety	Stress
Response Expectancies							r (p)					
Numbness	-0.04	-0.15	-0.09	-0.12	-0.03	0.04	-0.08	0.09	0.02	0.17	0.16	0.20
	(0.65)	(0.10)	(0.29)	(0.18)	(0.75)	(0.65)	(0.38)	(0.32)	(0.80)	(0.05)	(0.06)	(0.03)
Throbbing	0.08	-0.19	0.02	-0.06	0.001	0.07	-0.14	0.10	0.01	0.05	0.17	0.15
	(0.37)	(0.03)	(0.83)	(0.54)	(0.99)	(0.42)	(0.12)	(0.26)	(0.94)	(0.56)	(0.05)	(0.09)
Discomfort	-0.06	-0.09	-0.10	0.001	0.12	0.03	-0.17	0.09	-0.01	0.18	0.28	0.24
	(0.52)	(0.29)	(0.24)	(0.99)	(0.17)	(0.77)	(0.06)	(0.32)	(0.89)	(0.04)	(0.001)	(0.01)
Crushing	-0.08	-0.05	-0.06	-0.20	-0.08	0.003	-0.09	0.09	-0.06	0.14	0.23	0.10
	(0.37)	(0.60)	(0.48)	(0.03)	(0.38)	(0.98)	(0.34)	(0.30)	(0.53)	(0.11)	(0.01)	(0.28)
Average Pain	-0.01	0.07	-0.07	-0.11	0.05	0.08	-0.07	0.05	-0.12	0.07	0.08	0.17
	(0.88)	(0.43)	(0.43)	(0.24)	(0.60)	(0.40)	(0.46)	(0.59)	(0.16)	(0.44)	(0.38)	(0.06)
Maximum Pain	-0.16	-0.02	0.12	-0.14	-0.08	0.05	-0.05	0.07	-0.10	0.15	0.17	0.12
	(0.08)	(0.79)	(0.18)	(0.11)	(0.40)	(0.56)	(0.55)	(0.47)	(0.27)	(0.10)	(0.05)	(0.17)
Redness of Hand	0.04	-0.32	-0.11	-.02	0.16	-0.06	-0.09	0.06	-0.05	0.01	0.002	0.01
	(0.64)	(<0.001)	(0.20)	(0.86)	(0.07)	(0.50)	(0.34)	(0.47)	(0.60)	(0.91)	(0.98)	(0.88)
Headache	0.09	-0.06	-0.10	-0.21	-0.05	0.19	-0.17	0.02	0.03	0.08	0.28	0.17
	(0.31)	(0.54)	(0.28)	(0.02)	(0.62)	(0.03)	(0.05)	(0.81)	(0.71)	(0.36)	(0.001)	(0.06)
Heart Rate Increase	0.03	-0.04	0.08	-0.12	-0.07	0.20	-0.08	-0.03	0.04	0.03	0.12	0.02
	(0.75)	(0.68)	(0.39)	(0.18)	(0.41)	(0.03)	(0.36)	(0.71)	(0.68)	(0.75)	(0.19)	(0.81)

Itching	0.04	-0.16	-0.03	-0.11	-0.07	0.14	-0.09	-0.10	0.02	-0.03	0.07	-0.02
	(0.69)	(0.07)	(0.77)	(0.23)	(0.41)	(0.11)	(0.30)	(0.25)	(0.80)	(0.73)	(0.45)	(0.80)
Pain Threshold	0.09	0.08	0.14	-0.15	-0.10	-0.08	0.20	0.02	0.09	-0.10	-0.07	-0.16
	(0.30)	(0.38)	(0.12)	(0.09)	(0.27)	(0.35)	(0.35)	(0.84)	(0.29)	(0.27)	(0.47)	(0.08)
Hand Withdrawal	0.01	0.25	0.13	-0.04	-0.08	-0.06	0.31	-0.05	-0.01	-0.07	-0.16	-0.21
	(0.95)	(0.01)	(0.14)	(0.66)	(0.39)	(0.52)	(<0.001)	(0.59)	(0.90)	(0.43)	(0.08)	(0.02)

Side-Effects
Experienced

r (p)

Numbness	-0.19	-0.07	-0.28	-0.16	-0.07	-0.02	-0.01	0.08	0.03	0.18	0.14	0.10
	(0.03)	(0.41)	(0.001)	(0.07)	(0.44)	(0.81)	(0.88)	(0.35)	(0.76)	(0.05)	(0.12)	(0.24)
Throbbing	-0.03	-.026	-0.18	-0.22	-0.05	0.04	-0.24	0.09	0.01	0.05	0.16	0.17
	(0.76)	(0.003)	(0.04)	(0.01)	(0.58)	(0.69)	(0.01)	(0.29)	(0.95)	(0.60)	(0.08)	(0.06)
Discomfort	-0.18	0.01	-0.07	-0.13	-0.05	0.03	-0.16	0.18	-0.01	0.22	0.23	0.23
	(0.05)	(0.90)	(0.44)	(0.14)	(0.57)	(0.77)	(0.07)	(0.04)	(0.88)	(0.01)	(0.01)	(0.01)
Crushing	-0.15	0.004	-0.10	-0.27	-0.11	0.10	-0.06	0.21	-0.07	0.21	0.21	0.07
	(0.08)	(0.97)	(0.28)	(0.002)	(0.22)	(0.26)	(0.49)	(0.02)	(0.46)	(0.02)	(0.02)	(0.43)
Average Pain	-0.11	-0.03	0.07	-0.12	0.02	-0.004	-0.08	0.12	-0.002	0.12	0.16	0.15
	(0.23)	(0.70)	(0.43)	(0.19)	(0.82)	(0.96)	(0.36)	(0.18)	(0.98)	(0.19)	(0.07)	(0.09)
Maximum Pain	-0.23	-0.03	0.04	-0.15	-0.04	0.02	-0.11	0.22	-0.01	0.14	0.16	0.11
	(0.01)	(0.71)	(0.63)	(0.09)	(0.65)	(0.85)	(0.20)	(0.01)	(0.92)	(0.13)	(0.08)	(0.21)
Redness	-0.25	-0.16	-0.07	-0.05	0.06	0.04	-0.07	0.15	0.03	0.15	0.09	0.03
	(0.004)	(0.06)	(0.41)	(0.61)	(0.50)	(0.64)	(0.43)	(0.10)	(0.77)	(0.09)	(0.29)	(0.75)
Headache	-0.07	-0.003	-0.05	-0.08	-0.002	0.14	-0.10	0.11	0.02	-0.05	-0.03	0.02
	(0.42)	(0.97)	(0.58)	(0.37)	(0.98)	(0.12)	(0.26)	(0.23)	(0.87)	(0.62)	(0.70)	(0.87)
Heart Rate Increase	-0.04	0.03	-0.04	0.001	0.04	0.14	-0.05	0.03	0.12	-0.04	0.003	0.05
	(0.67)	(0.70)	(0.64)	(0.99)	(0.63)	(0.11)	(0.55)	(0.75)	(0.18)	(0.68)	(0.97)	(0.59)
Itching	-0.02	0.02	-0.16	-.017	-0.06	0.12	0.06	0.10	0.20	-0.03	-0.02	-0.05
	(0.87)	(0.82)	(0.08)	(0.06)	(0.51)	(0.19)	(0.51)	(0.24)	(0.03)	(0.76)	(0.87)	(0.56)

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Pain Threshold[a]	0.04	0.05	0.22	-0.02	-0.12	0.02	0.05	-0.04	0.10	-0.05	-0.10	-0.08
	(0.64)	(0.62)	(0.02)	(0.80)	(0.20)	(0.84)	(0.62)	(0.66)	(0.29)	(0.62)	(0.28)	(0.37)
Hand Withdrawal[a]	-0.004	.019	0.01	0.14	-0.02	-0.03	0.19	-0.007	-0.01	-0.07	-0.11	-0.12
	(0.96)	(0.03)	(0.91)	(0.10)	(0.83)	(0.71)	(0.03)	(0.94)	(0.88)	(0.45)	(0.21)	(0.17)

All REs were measured using Visual Analog scales (VAS) ranging from 0 –100, and 0-180 for Pain Threshold and Hand Withdrawal, higher scores indicate greater anticipated severity or time elapsed; All side-effect experiences measured using Visual Analog scales (VAS) ranging from 0 –100; [a] = Objectively measured time variables, ranging from 0-180 seconds, higher scores indicating more time elapsed (participants' hand immersion in the ice-water for

Appendix E

Examiners Feedback (Unconditional award of degree)

Report on Elise Devlin PhD Thesis
by Irving Kirsch PhD
Harvard Medical School

This is without a doubt one of the very best (if not the best) PhD thesis of the many that I have examined over the past 40 years. Despite being very knowledgeable about response expectancies and having published on the topic of side effects in cancer treatment, I learned a lot from this dissertation. It is well written and suitably documented, displays substantial original and critical thought, and provides a number of important contributions to the literature. One of the chapters is already published. The others certainly merit publication. I feel confident in predicting that these publications will make a substantial impact on the field.

In the opening chapter of her thesis, Ms. Devlin shows a very sophisticated understanding of the subtleties of response expectancy theory. She then relates the focus of the research (expectancies in the generation of side-effects related to cancer treatment) to the broader framework of response expectancy theory, cogently showing that these expectancies affect the degree and number of side effects that patients experience. This opens the way for reducing treatment-related side effects by targeting relevant response expectancies. Thus, the thesis expands on and provides new theoretical knowledge, while at the same time pointing to possible translation of this research to clinical practice.

Ms. Devlin has shown original and critical thought, connecting theory with previous empirical data, identifying shortcomings of those data, and finding methods of overcoming them. Most impressively, she identified that different measures of response expectancy were used in various previous studies. This original critique is then followed by a meta-analysis evaluating and supporting her hypothesis. She then builds on this with two experimental studies, one with healthy volunteers and the other with cancer patients.

Among the contributions to knowledge made in this thesis the most important are the following:

- Response expectancies can be strong predictors of side effects related to cancer treatment.
- Differences in the reported associations between response expectancy and cancer treatment side effects are partially due to the use of samples that are heterogenous with respect to specific diagnosis and type of treatment.
- These differences are also dependent on the nature of the scale used to assess response expectancies. Specifically:

o The use of a midpoint indicating that the person is unsure of whether the side effect will be experienced attenuates the association.

o Visual analogue scales (VAS) are more sensitive than the most commonly used scale, even when the problematic midpoint is removed.

These scale differences were found in the meta-analysis and verified in an experimental study with a homogenous sample.

- Contrary to my predictions, response expectancy was at least as good as predicting objective symptoms (e.g., hair loss) than subjective symptoms.

- Also contrary to my predictions, response expectancies were as influential among patients without previous cancer treatments as those who had experienced previous treatment.

These two findings will change my thinking about these issues.

The only suggestion for the candidate is that some additional analyses be done in the psychometric study reported in chapter 3. Specifically, the analyses based on trichotomized and dichotomized variables be supplemented or replaced by analyses using the continuous scores from which they were derived. I cannot fault Ms. Devlin for having used artificially dichotomized variables, as this is commonly done in articles published in top medical and psychological journals, nor do I recommend revisions to the thesis. However, statisticians have been virtually unanimous in condemning this practice, as it is akin to discarding 1/3 or more of the data and can produce erroneous results (see, for example, Altman & Royston (2006), BJM, "The cost of dichotomising continuous variables"). Therefore, this change might be considered before submitting the ms. for publication.

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Irving Kirsch

**Review of Ph.D. Thesis by Elise Devlin
"The Role of Response Expectancies in Cancer Treatment"
Standard of work completed**

**Joseph Roscoe
University of Rochester Medical Center**

This dissertation represents a substantial scholarly undertaking as the author conducted a meta-analysis and two research studies, one of which was a longitudinal clinical trial with difficult-to-study subjects in a challenging environment, i.e., men undergoing radiotherapy for prostate cancer; no mean feat for a doctoral candidate. This clinical study is the first in the literature to examine the association between response expectancies and radiotherapy-related side effects, as well as the first to examine response expectancies in a homogenous male patient sample. These finding are reported in Chapter 4. A finding of note, and one that is a significant contribution to current knowledge, is that expectancies of sexual side effects robustly predicted subsequent experience of those toxicities. Ms. Devlin correctly states that these findings have important implications clinically, and that there is a need for additional research on how potential side effects can be discussed with patients without heightening response expectancies (and hence, potentially increasing the risk of their occurrence). Many of these same prostate cancer patients also took part in her study investigating the psychometric properties of 5-point scales for assessing response expectancies of cancer side effects compared to visual analogue scales (Chapter 3). While this may sound like much ado about nothing, it has significance in this field of research, and she importantly discovered that the 5-point scales and the VAS are not interchangeable and should be considered independent when used in analyses. In addition to the above clinical trial, she introduced her thesis with an exceptionally well written, comprehensive, and insightful review of all the major elements related to response expectancies (Chapter 1) and followed that with an already published meta-analysis of the relationship between response expectancies and the experience of cancer-related side effects (Chapter 2).

Her second study (Chapter 5) was a randomized controlled experiment in University students (N=134) examining whether pre-intervention valence framing could reduce negative response expectancies and thus negative experiences. While this concept is not novel, there is very little published research on the topic, and a positive finding from this study could have had important clinical implications for how information about potential treatment side effects is presented to patients.

Taken together, the above works are a tribute to both the scholar and her scholarship and clearly show Ms. Devlin's abilities to contribute to the field of response expectancies in multiple ways. She writes clearly and accurately throughout the thesis, and all work is thoroughly documented. The statistical analyses were appropriate and the results, their implications, and probable causes for non-positive findings cogently discussed.

Possibility of Publication

Ms. Devlin used four manuscripts as the backbone for her thesis that included one

published manuscript, two submitted manuscripts, and one un-submitted work written in manuscript style. As it turns out, I was a reviewer on her published meta-analysis manuscript and gave it a very favorable review (below).

"This is an excellent meta-analysis of the current literature examining the relationship between response expectancies (REs) and cancer treatmentrelated side-effects. The authors have culled the existing English-language literature on this subject and have provided a thorough and useful background section. Details regarding the analyses are clear, and the choices for study inclusion are sound and well described. The manuscript is well-written and timely, and their discussion section comprehensive. The only concern I have with the manuscript is its length. I believe a judicious editing could cut 10-20 percent of the text without weakening the manuscript."

My assessment of her other three manuscripts mirror that review in that I consider her work outstanding in all respects but one, that is, in general, it would benefit by being shortened.

Further work that may arise from the research completed

In her thesis, Ms. Devlin laid out two key areas for future research. The first is the need to make sure that response expectancy measures are accurate, reliable, and easy to use clinically. The second is to determine if modifications of how information is presented to patients and/or incorporating non-deceptive and non-hypnotic suggestion to influence individuals' expectancies of side effects can reduce toxicity. Related to this is the need to research whether current practice (including the provision of informed consent) is exacerbating patients' negative response expectancies. These are all important areas of research. As Ms. Devlin's concluding sentence states, "… it is evident that response expectancies are particularly important and promising nonpharmacological predictors that can be harnessed to manage the severity of patients' side effects, benefiting not only the patient, but the entire healthcare system." Judging by the quality of this thesis, I am particularly keen about Ms. Devlin's research potential and her ability to make significant contributions to this research.