The role of treatment beliefs in the placebo effect

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I, Andrew Watkinson confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Andrew Watkinson
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Abstract

Treatment beliefs and related illness representations are important determinants of treatment uptake and adherence. This thesis explores whether these representations might also explain placebo effects. Within this thesis, a literature review outlines placebo mechanisms and summarises theory and research in relation to representations of treatment and illness. The empirical section that follows addresses three research questions identified by the review and explored in four studies.

Study 1 was a randomised controlled trial using the cold pressor paradigm in healthy volunteers (n=167). This demonstrated that treatment beliefs predicted pain responses to two placebos described as pharmaceutical versus natural, consistent with the theoretical model of specific and general treatment beliefs.

Study 2 involved patients (n=136) with symptoms of gastric-reflux, undergoing a diagnostic test. It showed that pain intensity, in response to oesophageal saline perfusion, could be significantly reduced by describing the saline as ‘therapeutic’ rather than as a ‘non-therapeutic’ component of the test procedure. Patients’ beliefs about their condition moderated the effect of framing on pain response to saline with more negative representations of gastric-reflux associated with lower therapeutic response.

Studies 3 and 4 were conducted in parallel to explore whether placebo-related treatment beliefs could be modified by brief interventions designed to change beliefs. Study 3, an analogue study in health volunteers (n=222), found that a brief informational intervention designed to increase coherence between representations of asthma and its treatment did not influence treatment beliefs. In Study 4, placebo effects to cough induction in health volunteers (n= 62) were influenced by treatment beliefs (general pharmaceutical schema), but treatment beliefs were again, not influenced by the intervention used in Study 3.

Despite their limitations the empirical studies suggest that treatment beliefs and illness representations are related to placebo effects, justifying further work to extend the scope and quality of this research.
**Dissemination plan**

**Manuscripts under review**


**Manuscript in preparation**


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### Abbreviations

<table>
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<th>Description</th>
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<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>B-IPQ</td>
<td>Brief Illness Perceptions Questionnaire</td>
</tr>
<tr>
<td>BMQ – G</td>
<td>Beliefs about Medicines Questionnaire – General</td>
</tr>
<tr>
<td>BMQ – S</td>
<td>Beliefs about Medicines Questionnaire – Specific</td>
</tr>
<tr>
<td>BMQ</td>
<td>Beliefs about Medicines Questionnaire</td>
</tr>
<tr>
<td>CAM</td>
<td>Complementary and Alternative Medicines</td>
</tr>
<tr>
<td>CAMBI</td>
<td>Complementary and Alternative Medicines Belief Inventory</td>
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<tr>
<td>CR</td>
<td>Conditioned Response</td>
</tr>
<tr>
<td>CS</td>
<td>Conditioned Stimulus</td>
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<tr>
<td>CSM</td>
<td>Common Sense Model of Self-Regulation</td>
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<tr>
<td>C-TIMP</td>
<td>Clinical Trial of an Investigational Medicinal Product</td>
</tr>
<tr>
<td>ELM</td>
<td>Elaboration Likelihood Model</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced Expiratory Volume in the first second</td>
</tr>
<tr>
<td>GORD</td>
<td>Gastro-oesophageal Reflux Disease</td>
</tr>
<tr>
<td>HRM</td>
<td>High Resolution Manometry</td>
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<tr>
<td>IAU</td>
<td>Information as Usual</td>
</tr>
<tr>
<td>IPQ</td>
<td>Illness Perceptions Questionnaire</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter-Quartile Range</td>
</tr>
<tr>
<td>LOS</td>
<td>Lower Oesophageal Sphincter</td>
</tr>
<tr>
<td>LPR</td>
<td>Laryngo-pharyngeal Reflux Disease</td>
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<tr>
<td>MPQ</td>
<td>Multidimensional Pain Questionnaire</td>
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<tr>
<td>NCF</td>
<td>Necessity Concerns Framework</td>
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<td>NCI</td>
<td>Necessity Coherence Intervention</td>
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<tr>
<td>OPI</td>
<td>Overall Pain Index</td>
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<tr>
<td>PANAS</td>
<td>Positive and Negative Affect Schedule</td>
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<tr>
<td>PCS</td>
<td>Pain Catastrophizing Scale</td>
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<td>PHQ-15</td>
<td>Patient Health Questionnaire 15</td>
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<td>PHQ-9</td>
<td>Patient Health Questionnaire – 9</td>
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<tr>
<td>PIL</td>
<td>Patient Information Leaflet</td>
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<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
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<tr>
<td>PSM</td>
<td>Perceived Sensitivity to Medicines</td>
</tr>
<tr>
<td>PSS</td>
<td>Perceived Stress Scale</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>RSI</td>
<td>Reflux Symptom Index</td>
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<tr>
<td>SF-MPQ</td>
<td>Short Form McGill Pain Questionnaire</td>
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<tr>
<td>STAI – T</td>
<td>State Trait Anxiety Inventory – Trait</td>
</tr>
<tr>
<td>UCLH</td>
<td>University College London Hospital</td>
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<tr>
<td>US</td>
<td>Unconditioned Stimulus</td>
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<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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1. Introduction

Historically, the placebo effect has been considered something of a nuisance, an artefact acting as a barrier, preventing researchers from detecting a true representation of a drug’s efficacy (Barsky, Saintfort, Rogers, & Borus, 2002). Furthermore, current ethical standards forbid practitioners from the deceptive use of placebo in clinical practice as this violates the patient’s right to be fully informed about treatment (De Deyn & D’Hooge, 1996). However, views of the placebo effect are changing. We now know the placebo effect is not simply due to observer or reporting bias and is reflected in neurological changes in the brain (Finniss, Kaptchuk, Miller, & Benedetti, 2010). Moreover, in certain conditions placebo effects can not only influence self-reported changes in symptom severity but also physiological processes in diseases (Goetz, Leurgans, Raman, & Stebbins, 2000a; Kemeny et al., 2007). There is now a resurgence of interest in the psychosocial factors which influence this phenomenon in order to utilize the power of the placebo effect in clinical practice.

Treatment beliefs have been useful in understanding whether patients decide to take a treatment and whether they continue taking a treatment as prescribed. Treatment beliefs include specific beliefs about a particular medicine (treatment necessity and concerns) and more general “background” beliefs about pharmaceuticals (Horne, Chapman, et al., 2013; Horne, Faasse, et al., 2013b; Horne, Weinman, & Hankins, 1999a). There is a small but growing body of evidence which suggests that they may also influence the reporting of side effects (Aikens & Klinkman, 2012; Bautista, Gonzales, & Jain, 2011; De Smedt, Denig, van der Meer, Haaijer-Ruskamp, & Jaarsma, 2011; De Smedt et al., 2012; Horne, Faasse, et al., 2013b; Wendt et al., 2014). However, there is no research exploring the effects of these beliefs on the placebo effect. Treatment beliefs are also informed by representations of illness (Horne & Weinman, 2002), however as of yet the relationship between illness representations and the placebo effect has yet to be investigated. This thesis will therefore explore the role of treatment beliefs and illness representations in the placebo effect. I will start by providing an overview of our understanding of the placebo effect to date followed by a summary of theory and research in relation to representations of treatment and illness. Then I will present the perspective of the present research, outline outstanding research questions and address these questions in 4 studies. Finally I will discuss the implications of my findings, limitations and potential future directions.
2. Literature review

The effect of medicine can be due to two components – the specific effect which is due to direct pharmacological action of the medicine, and the non-specific component (de la Fuente-Fernandez & Stoessl, 2002). Compared to the specific effects of medicine, the non-specific effect cannot be explained by the pharmacological action of the medicine (Manchikanti, Giordano, Fellows, & Hirsch, 2011). There are a number of factors which contribute to the magnitude of this non-specific effect that are often mistaken for placebo effects. These factors can include spontaneous remission and regression to the mean (Kienle & Kiene, 1997). The placebo effect is the proportion of this non-specific therapeutic effect which is attributable to the psychosocial context surrounding the treatment (see Figure 1). Such factors range from the characteristics of the treatment (e.g. colour of pill) to patient characteristics (e.g. desires, hopes and expectations), the attitudes of the physician and psychosocial factors affecting the physician-patient relationship (suggestion, compassion etc.) (Di Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001; Price, Finniss, & Benedetti, 2008).

![Figure 1: Possible factors associated with symptom improvement in patients taking active medication, placebo medication and no medication (control or natural history group) in clinical trials. In studies which lack control group non-specific factors such as regression to the mean and spontaneous remission can get misconstrued as part of the placebo effect, resulting in a placebo effect which seems larger than it actually is (note: not real data).](image-url)
This literature review will begin by reviewing our current understanding of the placebo effect; when and where we see placebo effects, the size of this effect across conditions and psychosocial factors associated with its magnitude.

2.1 Magnitude of the placebo effect

The magnitude of the placebo effect is highly variable, depending on the illness and contextual factors of the treatment, ranging from 0% to 100% (Benedetti, 2010). One aim of this thesis is to investigate the effect of treatment beliefs on the placebo effect in the context of experimentally induced pain, experimentally induced cough, vs in the clinic in patients with gastro-oesophageal reflux disease (GORD) and laryngopharyngeal reflux disease (LPR). Typically the placebo effect is larger in experimental studies compared to clinical trials. In clinical trials information about the medication across conditions are kept constant to prevent biasing results (e.g. active medication group vs. placebo group). However, in experimental studies such as those investigating the effects of expectations, information about the placebo medication is varied in order to manipulate expectations (Vase, Riley, & Price, 2002). Placebo effects have also been found to vary depending on whether subjective outcome measures or objective outcome measures are used, with larger placebo effects being observed in the former (Hrobjartsson & Gotzsche, 2001). There is variability in the magnitude of the placebo across medical conditions. This section will begin by discussing this variability while mechanistic explanations that might contribute to changes in the magnitude of this effect will be discussed in section 2.2.

2.1.1 Pain

The placebo effect in pain has been extensively studied in both healthy individuals and clinical samples of patients suffering from pain disorders (Evers, Bartels, & van Laarhoven, 2014; Flaten, 2014; Vase, Skyt, & Hall, 2016). In a meta-analysis of 5 randomised controlled trials of analgesic medication in postoperative pain, it was found that pain relief from placebo treatment varied from 7% - 37% compared to a 5% - 63% variation in the active drugs (McQuay, Carroll, & Moore, 1996). As previously stated, the magnitude of the placebo effect can vary depending on the type of study. A mean effect size of the effect of placebo treatment on pain
reduction was 0.15 (-0.95 to +0.57) in 23 analgesic studies. In comparison to this, a mean effect size of 0.95 (-0.64 to +2.29) was found in 14 experimental studies investigating placebo mechanisms (Hrobjartsson & Gotzsche, 2001). The difference in effect sizes was found to be significant, thus, the magnitude of placebo analgesia can vary significantly depending on experimental design (Vase et al., 2002). In this thesis I will examine the effect of treatment beliefs on the placebo effect in experimentally-induced pain in section 5.

2.1.2 Respiratory disorders

Respiratory disorders, such as asthma and cough, are known to be particularly susceptible to top-down processes (Rietveld, 1998; Van den Bergh, Van Diest, Dupont, & Davenport, 2012). Cough has been shown to be influenced by a number of psychological factors (e.g. affect, anxiety and depression) and susceptible to very large placebo effects (Lehrer, Feldman, Giardino, Song, & Schmaling, 2002; Van den Bergh et al., 2012). In 5 clinical trials of antitussive medication, the placebo effect was shown to vary from 56% up to 105% with an average effect of 85% (Eccles, 2002a). Similarly, symptoms of asthma are susceptible to placebo effects. A randomised, double blind investigation of salmeterol found a mean improvement in forced expiratory volume (FEV1) of 29% of individuals in the placebo group (Kemeny et al., 2007). The susceptibility of cough to placebo effects provides an excellent model to study the role of treatment beliefs in this phenomenon. The effect of treatment beliefs on the placebo effect will be examined in response to experimentally induced cough (section 8).

2.1.3 Gastrointestinal disorders

Symptom reduction is particularly common in patients with gastrointestinal disorders receiving placebo treatment (Cremonini et al., 2010; Enck & Klosterhalfen, 2005; Patel et al., 2005). In irritable bowel syndrome, responses to placebo treatment in clinical trials range from 3-84%, however, longer studies suggest a placebo effect of 40% (Cremonini, Delgado-Aros, & Camilleri, 2003; Enck & Klosterhalfen, 2005; Spanier, Howden, & Jones, 2003). Similarly, in GORD and LPR large placebo effects are observed. A meta-analysis of clinical trials showed a placebo effect ranging from 3-47% in patients with GORD and LPR (Barry & Vaezi, 2010; Cremonini et al., 2010). Interestingly, the placebo effect was significantly lower for those taking proton pump inhibitor (PPI) medication than H2-receptor antagonists (14.5% vs. 24.7%) (Cremonini et al., 2010). In this thesis, I will examine the
relationship between illness representations and the placebo effect using a sample of GORD and LPR patients (section 6).

2.1.5 Subjective vs. objective outcomes

The use of subjective vs. objective outcomes in placebo research has been highly debated. Subjective measures, such as self-reported pain, can be influenced by biases. For example, patients in clinical trials may feel the need to report favourable outcomes due to the fact that they are participating in a trial or to please the doctor who has spent considerable time with them (Hrobjartsson, Kaptchuk, & Miller, 2011). However, subjective changes in symptoms due to placebo treatment are much more common than objective changes. A meta-analysis of 130 clinical trials found a significant beneficial effect of placebo treatment in trials compared to no treatment, but did not find any beneficial effect in trials using objective outcome measures (Hróbjartsson & Gøtzsche, 2001). However, objective measures of perceived symptoms can be difficult to obtain. For example, pain can be objectively measured using fMRI, a procedure which can be expensive and requires neuroimaging expertise to obtain.

A number of conditions are known to be susceptible to objective measured placebo effects. Substantial improvements in objective measures of motor performance have been well documented in patient with Parkinson’s disease using sham deep-brain stimulation and placebos described as anti-parkinsonian drugs (Benedetti et al., 2003; Goetz, Leurgans, Raman, & Parkinson Study, 2002; Goetz, Leurgans, Raman, & Stebbins, 2000b; Mercado et al., 2006; Pollo et al., 2002; Udupa & Fox, 2015). There is also some evidence for objective placebo effects in the respiratory system and in respiratory disorders such as asthma (Benedetti et al., 1998; Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999; Kemeny et al., 2007). For example, changes in functional expiratory volume due to methacholine (a bronchoconstrictor) were significantly reduced after administration of a placebo bronchodilator compared to baseline (Kemeny et al., 2007). Other conditions where objective placebo effects have been observed include psoriasis (Ellis et al., 2007), hypertension (Asmar, Safar, & Queneau, 2001), and ulcerative colitis (Ilnyckyj, Shanahan, Anton, Cheang, & Bernstein, 1997).

While changes in subjective reports of symptoms are clinically important in the management of conditions, changes in physiological measures are perhaps more as important as these changes cannot be argued as due to reporting bias. Thus,
understanding what conditions are susceptible to both subjective and objective placebo effects and what psychosocial factors influence these effects, is crucial in order to take optimal advantage of the placebo effect in clinical practice. Therefore, one aim of this thesis is to determine whether treatment beliefs influence both subjective and objective placebo effects (section 8).

2.2 Explanatory mechanisms of the placebo effect

There are many different mechanisms which influence the placebo effect (Benedetti & Amanzio, 2013). A complex psychosocial context surrounds the administration of a treatment, such as the patients’ beliefs/expectations of the treatment or the physician, the hospital environment, and what the physician communicates to the patient. Expectations about the outcome of treatment are considered the principle component which influences the placebo. However many other factors within the psychosocial context surrounding treatment interact with expectations. For example, in some circumstances conditioned placebo effects are mediated by expectations (Stewart-Williams & Podd, 2004) (Price et al., 2008). Furthermore, there is evidence to suggest personality factors such as optimism moderate the influence of expectations on the placebo effect. However, this is still not well understood (see Figure 2, and sections 2.2.1 and 2.2.2 for further detail).

This thesis aims to expand our current understanding of the placebo effect by suggesting that other beliefs in addition to efficacy expectations are also involved in this phenomenon. Horne et al. (Horne, 1999) briefly acknowledged a theoretical relationship between treatment beliefs and the placebo effect, however to date there has been no studies testing this relationship.
2.2.1 Expectations

Expectations can be defined as what an individual considers most likely to happen in a situation of uncertainty. For example, when an individual takes a medication for the first time, there is usually some level of uncertainty as to its effects. Individuals will have also have some degree of expectation based on, for example, information received from other sources about said medication or previous experience with similar medications. Expectations can also be explicit (i.e. one that is stated) or implicit (not stated and/or difficult to verbalise). While there is considerable research into how these two types of expectations are associated with beliefs and health behaviour (Blanton H et al., 2016; Campbell et al., 2014) this thesis will not distinguish between the two types as the role of explicit vs. implicit expectations on the placebo effect is out of the scope of this PhD.

Most of the literature on the placebo effect has focused on the role of expectations as the major mechanism in the placebo effect (Benedetti & Amanzio, 2013). It is widely known that expectations are associated with placebo effects which are reflected by changes in neuronal activity in cognitive and emotional areas of the brain (e.g. prefrontal cortex, amygdala and the nucleus accumbens) (Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005). Typically measured using visual analogue scales (VAS), previous studies have provided participants with verbal
cues of expectations, both positive and negative, to modify the placebo effect. For example, if an individual is provided with a verbal suggestion that a placebo cream is inert and will have no effect, before experiencing an experimental pain stimulus, no analgesic effect will occur. If however, another individual is given the suggestion that the placebo cream is an effective analgesic, placebo analgesia will be observed (Price et al., 1999). This is also true for negative expectations. Providing negative expectations before placebo administration leads to increases in pain intensity (Colloca & Benedetti, 2007). A recent meta-analysis of 10 randomised controlled trials (RCT) of adults suffering from pain suggested that providing positive expectations about treatment can lead to significantly reduced pain compared to when positive expectations are not provided (Howick et al., 2016).

Placebo effects can be graded by inducing different expectations of symptom severity after administration of placebo medication (van Laarhoven et al., 2011). Price et al. (Price et al., 1999) applied three placebo creams adjacent to each other on the forearm of participants giving the expectation that cream A was the most effective analgesic, cream B was a weak analgesic and cream C had no analgesic properties. Graded heat stimulation was applied to these areas in order to confirm the expectancies that were given for each cream. The same heat stimulation was then applied to all three areas and pain intensity was measured. This led to a graded magnitude of actual pain (C>B>A). While some have suggested expectations act directly on placebo outcomes, other psychological factors such as anxiety are thought to mediate the relationship between expectations and outcome (Mueller, Bjørkedal, & Kamping, 2012). This will be discussed further in section 2.6.

One issue with some of these studies which examine the relationship between expectations and the placebo effect is that they rely on the assumption that any change in symptom severity after placebo administration is due to the expectation provided in the manipulation and not expectations of the individual. An individuals’ belief in the manipulation may also influence their subsequent response. For example, Handley et al. (Handley, Fowler, Rasinski, Helfer, & Geers, 2013) found that beliefs about expectations of pain moderate the effect of expectations on the experience (e.g. if they believe strongly that expectations can have powerful effects on perception of stimuli). Another issue is that a number of studies did not measure expectations prospectively (Geers, Helfer, Weiland, & Kosbab, 2006; Rose, Geers, Rasinski, & Fowler, 2012). Recalling expectations after outcomes can lead to bias. It is known that individuals typically recall of expectations is biased by current knowledge (e.g. the experience of how effective a medication was in reducing...
symptoms) and so are less accurate compared to prospectively measured expectations (Conway, 1990; Geers, Wellman, Fowler, Helfer, & France, 2010). Thus results from these studies must be interpreted with caution.

Not all conditions are responsive to expectation-induced placebo effects. As previously discussed in section 2.1.5 there is little evidence for the effect of expectations on objectively measured placebo effects compared to subjective measurements. There is also considerable debate as to whether conscious expectations can influence unconscious processes (e.g. hormone secretion) and how expectations interact with other mechanisms such as classical conditioning (Stewart-Williams & Podd, 2004).

2.2.2 Classical conditioning

Classical conditioning is a learning process that occurs through association between naturally occurring stimuli (unconditioned stimuli; US) and environmental stimuli (conditioned stimuli; CS) resulting in a conditioned response (CR). In a clinical context, those who suffer from chronic pain condition and regularly consume paracetamol can associate the shape or taste of the medicine (CS) with a reduction in pain (due to the drug: US). After a number of repeated associations of the medicine occurring with a reduction in pain, a placebo which resembles that medicine can provide symptomatic relief (conditioned response, see Figure 3) (Stewart-Williams & Podd, 2004). Other factors surrounding the context of medicine can provide the same effect, such as syringes, doctors and hospitals (Haour, 2005).

![Classical Conditioning Diagram](image_url)

Figure 3: Classical conditioning.
In the placebo literature the conditioning approach to explaining placebo effects has been typically pitted against the expectation approach. However there is evidence to show that these two mechanisms do not always work in confinement. Certainly, we see conditioning effects in simple organisms such as *Caenorhabditis elegans* where expectations cannot be involved (Erdogan & Sahin, 2013). On the other hand, expectations can provide an understanding for how a CS can lead to a CR. Some suggest that conditioning follows expectation and relies on the success of the first encounter of the US i.e. the effect of the treatment/medication (Finniss et al., 2010). For example, repeated associations between a CS and US leads to expectations that presentation of the CS will be followed by the CR. This is supported by a meta-analysis which found that placebo analgesia is significantly greater in studies where a placebo effect was induced via suggestion and conditioning than in experiments using suggestion alone or conditioning alone (Vase et al., 2002). In another experiment, some participants were told that they were given an inert cream before undergoing a conditioning procedure, whereas others were not informed of this. In the group that were told that the cream was inert, no conditioned placebo effect was observed (Montgomery & Kirsch, 1997). Therefore, in this context, expectations were required to elicit a conditioned placebo effect.

The question is, are there certain situations when expectations are involved in conditioning and situations when they are not. Benedetti and colleagues (2003) suggested that expectations may mediate conditioned placebo effects when conscious processing is involved (e.g. pain) but not when unconscious processing is involved (e.g. hormone secretion). Benedetti et al. (Benedetti et al., 2003) showed that in patients with Parkinson’s disease placebo conditioning procedures will only work when patients have an expectation that the medication will be effective. Conversely, Benedetti was able to condition hormone secretion through a placebo conditioning procedure regardless of whether participants had an expectation of effectiveness or not. However, it is likely that this is not quite as clear-cut as Benedetti suggests. A recent study has shown that conditioned responses to pain, a consciously processed stimulus, can be acquired using subliminally presented CS (Jensen, Kirsch, Odmalm, Kaptchuk, & Ingvar, 2015). This suggests that cognitively mediated stimuli such as pain are responsive to unconscious conditioning procedures which do not involve expectations. Moreover, to further complicate this debate, we also know that expectations can be activated and acquired outside of conscious awareness (Dienes, Baddeley, & Jansari, 2012). We may therefore be
underestimating the effects of expectations on the conditioned placebo effect particularly when no verbal suggestions are given.
2.2.3 Personality and the placebo effect

Personality is conceptualised as dimensions of individual differences in tendencies to show consistent patterns of thoughts, feelings and actions across different contexts and developmental periods (McCrae & Costa, 2003). Early investigations into the effect of personality produced inconsistent findings. Initial results suggested placebo responders tended to be individuals who were anxious, suggestible, emotionally labile, and dependent on others (Jospe, 1978). However, most studies failed to find strong and consistent findings (Brody, 1980; Shapiro & Morris, 1978; Turner, Deyo, Loeser, Von Korff, & Fordsce, 1994). Interest into the effect of personality on the placebo effect has been renewed in recent years (Jakšić, Aukst-Margetić, & Jakovljević, 2013). A recent study investigating multiple personality traits has shown that 25% of the placebo analgesic response and associated opioid activity within the brain can be explained by ego-resilience, altruism, straightforwardness and hostility (Pecina et al., 2013).

Outside of highly controlled experimental situations, we are often exposed to a multitude of factors which may influence the placebo effect. Thus, it is unlikely that these personality factors work in isolation. Emerging research now suggest that situational factors must be taken into account when assessing the relationship between personality factors (e.g. optimism, pessimism, extraversion and ego-resilience) and the placebo effect (Jakšić et al., 2013). This is because the strength and direction of their effect may change, depending on other factors such as efficacy expectations. For example, we now know that optimists are more likely to exhibit attentional bias towards positive information than pessimists (Isaacowitz, 2005a). Furthermore, optimists tend to elaborate on and be persuaded by positive messages to treatment than pessimists (Geers, Handley, & McLarney, 2003). Geers et al. (Geers, Helfer, Kosbab, Weiland, & Landry, 2005) therefore tested to see whether optimism moderates the relationship between expectations and the placebo effect, and indeed such a relationship was found. A significant interaction effect between dispositional optimism and the expectation manipulation on pain reports was observed. Further research is now required to understand the mechanisms behind how dispositional optimism interacts with expectations e.g. optimisms may be more likely to cognitively elaborate upon suggestions of efficacy and thus experience a larger placebo effect.
2.2.4 The patient-provider relationship

The provider of treatment is an essential part of the psychological context that surrounds the placebo effect. Providers of treatment, albeit a nurse, doctor or surgeon can provide a lot of information about a treatment through their attitudes, behaviour or words. Thus it is not surprising that interactions with care providers can be therapeutic. Although the exact mechanisms are not fully understood, a number of studies have highlighted the importance of this relationship. A recent systematic review of 51 studies covering 5079 patients with acute pain assessed the effect of face-to-face communication styles on pain severity. The review found that providing positive expectations and doing so in an empathetic way can lead to a small but significant reduction in pain. The authors do note, however, that there was large heterogeneity across the studies in terms of content, complexity and delivery of information, in addition to unclear descriptions of control conditions. Thus these results must be interpreted with caution (Mistiaen et al., 2016).

Other factors such as the number of visits a patient receives from a care provider can predict clinical improvement. In a sample of patients with ulcerative colitis and Crohn’s disease taking placebo medication, Ilnyckyj et al. (Ilnyckyj et al., 1997) found greater symptom remission in those who received four or more visits compared to those who had three or fewer. This is supported by a recent study where compared to a standard visit, patients with GORD receiving an extended visit by a doctor were more likely to report a 50% or greater improvement in symptoms. A supportive relationship with a doctor has also been shown to increase symptom reduction in IBS patients undergoing sham acupuncture (Dossett et al., 2015). Furthermore, Kaptchuk et al. (Kaptchuk et al., 2008) found that compared to IBS patients who received limited interactions with their practitioner, those who received a practitioner that exhibited a warm and friendly manner, and actively listened, had significantly greater symptom improvement. How these effects can be utilized in clinical practice remains to be determined. Enhancing the placebo effect through increasing the number of visits from a doctor to each patient may in fact reduce the length and quality of the interaction between them and thus lead to more limited interactions.

There may be also some interplay between personality and the effects of the patient-practitioner relationship. In IBS patients, extraversion and agreeableness was shown to independently predict the magnitude of the placebo effect when in a warm and empathetic therapeutic setting but not in a neutral setting. Thus,
individuals high in extraversion and agreeableness respond better when the therapeutic setting is similar to their personality (Kelley et al., 2009). Furthermore, when patient-provider interaction is minimal or at least neutral (e.g. when medicines are sent by post), then these personality factors may not have such a relevant effect (Kelley et al., 2009). Whether these interactions influence objective measures of the placebo effect has yet to be investigated.

2.3 Summary

Research has shown the placebo effect is driven by many psychological factors, but has largely focused on the effects of conditioning and expectations (Benedetti, 2008b; Benedetti & Amanzio, 2013). Despite many years of research into the effects of expectations, the role of other beliefs about medication and illness have yet to be investigated. Work by Horne and colleagues (Horne, Faasse, et al., 2013b; Horne et al., 1999a) have shown that patients’ perceptions about medicines go beyond efficacy expectations, consisting of specific beliefs about a particular medicine which are in turn informed by more broad social representations of medicines and representations of illness. Treatment beliefs and illness representations may therefore be useful in further understanding variations in the magnitude of the placebo effect.

2.4 The role of treatment beliefs in the placebo effect

Horne et al. (Horne, 1999) has briefly suggested a theoretical relationship between treatment beliefs and the placebo effect, however, there is little research investigating this relationship, with most focussing on side effect reporting (Aikens & Klinkman, 2012; Bautista et al., 2011; De Smedt, Denig, et al., 2011; De Smedt, Haaijer-Ruskamp, Groenier, van der Meer, & Jaarsma, 2011; Horne, Faasse, et al., 2013b; Wendt et al., 2014). This is reflected by a PubMed and PsycInfo search for “beliefs about medicines”[All Fields] OR “treatment beliefs”[All Fields] OR “medication beliefs”[All Fields] AND “Placebo”[All Fields] which produced 3 results, all of which were not relevant. Similarly a PubMed and PsycInfo search for “illness beliefs”[All Fields] OR “illness perceptions”[All Fields] OR “illness
representations"[All Fields] AND “Placebo”[All Fields] produced one result which was not relevant. Current evidence comes from a handful of studies assessing the relationship between treatment beliefs and illness representations and responses to active medications or therapies. Furthermore, these studies are hampered by methodological issues, thus supporting the need for further studies to address a causal relationship between treatment beliefs and the placebo effect. This section begins by defining treatment beliefs following by the examination of current evidence for their role in the placebo effect.

2.4.1 Treatment beliefs

Treatment beliefs are important determinants of whether patients’ decided to take medicines, their choice in treatment and whether they continue to take their treatment as prescribed (Horne, Chapman, et al., 2013; Horne et al., 2004; Horne et al., 1999a). Early work by Horne and colleagues suggested that patients can have quite complex and diverse beliefs about medicines, however, many of these beliefs can be categorized into common themes: specific beliefs pertaining to a particular medicine and more broad pharmaceutical schema (Horne, Faasse, et al., 2013b; Horne et al., 1999a). Specific beliefs about medicines can be grouped under two categories: an individual’s perceived need for a prescribed medication (Specific Necessity) and concerns about its negative effects (Specific Concerns). Specific beliefs are operationalized using the Necessity-Concerns Framework (NCF). The NCF proposes that adherence to a prescribed medication is determined by the interplay between these two sets of specific beliefs. When a patient decides to take a treatment they weigh up their personal need for the medication against any concerns they have about its negative effects (Clatworthy et al., 2009; Horne, Chapman, et al., 2013; Horne, Cooper, Gellaitry, Date, & Fisher, 2007). A recent meta-analysis supported the utility of the NCF in explaining nonadherence in 94 studies involving over 25,000 patients across 24 long-term conditions and 18 countries (Horne, Chapman, et al., 2013).

Specific evaluations of treatments are in turn influenced by the patients’ pharmaceutical schema and illness representations (see section 2.6.3 for relationships between specific beliefs and illness representations). A patient’s pharmaceutical schema consists of broad “social representations” of medicines in general (beliefs about the beneficial effects of pharmaceuticals, their potential to cause harm and their overuse by doctors) and perceptions about self in relation to
medicines (Perceived Sensitivity to Medicines; PSM) (Horne, Faasse, et al., 2013b; Horne et al., 1999a). For example, a patient will have greater personal need for a medication if they believe medicines in general are beneficial. Conversely, a patient will express more concerns about a prescribed medication if they believe medicines are generally harmful, are overprescribed by doctors and have high PSM (Horne, Weinman, & Hankins, 1999b) (see Figure 4).

Figure 4: The influence of pharmaceutical schema on specific beliefs about medicines. Specific Necessity beliefs about a prescribed medication are positively informed by General Benefit beliefs. Conversely, Specific Concerns about a prescribed medication are positively informed by General Harm, General Overuse and PSM beliefs.

Treatment beliefs are measured using the Beliefs about Medicines Questionnaire (BMQ) (Horne et al., 1999a) and the PSM Scale (Horne, Faasse, et al., 2013b). The BMQ was specifically developed as an extension of Leventhal’s CSM and the IPQ (see section 2.6.3 for details on CSM and IPQ), to further understand medication adherence. This validated measure is comprised of the BMQ-General (BMQ-G) and BMQ-Specific (BMQ-S). The BMQ-G consists of 3 scales measuring assessing beliefs about the benefit of medicines in general (General Benefit), their capacity to cause harm (General Harm) and their overuse by doctors (General Overuse). The BMQ-S consists of a 5-item scale measuring Specific Necessity and a 6-item scale measuring Specific Concerns about a particular medication (Horne et al., 1999a). More recently, the PSM was developed as a measure of patients' perceptions about medicines in relation to self i.e. perceptions about their general sensitivity to the negative effects of medicines. The PSM is a short 5-item measure which has recently been validated across a range of conditions (Horne, Faasse, et al., 2013b). These instruments will be used to measure treatment beliefs throughout this thesis (see section 4 for further details on these measures).
2.4.2 Current evidence supporting the role of treatment beliefs in the placebo effect

2.4.2.1 Specific beliefs about medicines

Initial evaluations of treatment necessity are in part formed from our perceptions of the symptoms we experience. If we decide to take a treatment our initial evaluations are then either reinforced or changed depending on whether symptoms improve or do not change/become more severe (Horne, 2003). The appraisal of symptoms is therefore an important determinant of our personal need for medication. For example, in a sample with HIV patients, Cooper et al. (Cooper, Gellaitry, Hankins, Fisher, & Horne, 2009) found that those who experienced persistent symptoms while taking anti-retroviral medication were likely to doubt their personal need for medication. I propose that, in a similar fashion to expectations, evaluations of treatment necessity in turn influence the appraisal of subsequent symptoms. That is, those who have greater treatment necessity beliefs will perceive greater symptom reduction (i.e. a larger placebo effect) after medication use than those who have lower treatment necessity beliefs.

Horne proposes that although treatment necessity is not a form of efficacy belief, it is likely that efficacy expectations, as well as patients’ illness representations, inform evaluations of treatment necessity (Horne, 2003; Horne & Weinman, 2002). However, efficacy expectations are not synonymous with treatment necessity. A patient can have high personal need for a treatment even if they do not believe it to be very effective, for example if there is only one treatment available. Alternatively, a patient may believe a treatment is effective but does not have personal need for it, for example if they believe their illness is not severe enough to warrant medical intervention (Horne, 2003). This is reflected in a study which found 25% of the variance in treatment necessity was explained by efficacy expectations (Horne, Cooper, Gellaitry, Lambert, & Fisher, 2002).

To date there are no studies which have assessed the relationship between treatment necessity and the placebo effect. Aikens et al. (Aikens & Klinkman, 2012) did investigate the effect of prospectively measured treatment beliefs on treatment response in patients with depression taking active medication. Results showed greater perceived need for an anti-depressant at baseline was associated with reduced depressive symptomology after 14 weeks of treatment. They also found concerns about the effects of anti-depressants at baseline significantly predicted the
number of side effects reported. Unfortunately, this study did not have a natural history group and therefore changes in symptomology could be due to spontaneous remission or regression to the mean. In this thesis, I will therefore examine a causal relationship between treatment necessity and the placebo effect in two studies (section 5 and 8). I hypothesise that a) greater perceived need for a treatment is associated with a larger placebo effect and b) this effect will remain independent to that of efficacy expectations.

2.4.2.2 Pharmaceutical schema

Horne proposes that patients’ pharmaceutical schema may inform efficacy expectations as well as treatment necessity. These beliefs are thought to originate from one’s own experiences with specific treatment and information gained from experiences of others (i.e. information from significant others or speculation from the press) which are then incorporated into their general schema (Horne, 2003). For example, in a sample of students, those who had a previous experience of taking prescribed medicine were more likely to believe that pharmaceuticals in general are beneficial than those who did not have any experiences with prescribed medicine (Horne et al., 2004). Whether pharmaceutical schemas in turn influence patients’ evaluation of treatment effectiveness (i.e. the placebo effect) has yet to be investigated.

General beliefs about medicines

Similarly to treatment necessity, there have been no direct studies assessing the role of general beliefs about medicines in the placebo effect, but there is some evidence from studies in patients taking active medication (Bautista et al., 2011) (Glattacker, Heyduck, & Meffert, 2013a, 2013b). In patients with epilepsy, total BMQ-G scores have been associated with an increase in both seizure and side effect frequency after changing from branded to generic anti-epileptic medication (Bautista et al., 2011). Glattacker et al. (Glattacker et al., 2013a, 2013b) investigated the predictive effects of patients’ general beliefs about medicines on treatment outcome in pain and depression. In patients with depression treatment beliefs were measured before rehabilitation. General beliefs were found to predict the severity of depression, as well as general mental health, at 3 and 6 months after rehabilitation (Glattacker et al., 2013b). Similarly, in patients with chronic back pain treatment beliefs were predictive of pain intensity at 3 and 6 months after rehabilitation (Glattacker et al., 2013a). However, relationships between treatment
response and individual BMQ subscales were not reported in these studies. Therefore we cannot determine the effect of individual constructs within patients’ general beliefs about medicines on treatment response. Furthermore, variables which may have influenced treatment response, such as adherence, were not controlled for. Further research on the role of general beliefs about medicines in the placebo effect is clearly warranted.

Patients with negative orientations towards pharmaceuticals in general tend to be suspicious of modern medicines. This is associated with the view that alternative medicines such as natural remedies are safer due to their natural origins (Gupta & Horne, 2001; Horne et al., 1999a). In fact, general beliefs about the harmfulness of pharmaceuticals have been found to predict willingness to use natural remedies (medicines derived from natural sources). In contrast, willingness to use pharmaceuticals are positively predicted by general beliefs about the benefits of pharmaceuticals, and negatively predicted by general beliefs about the harmfulness and overuse of pharmaceuticals (Green, Horne, & Shephard, 2013). Perceptions about different types of medicines are therefore important determinants in the uptake of types of medicines. However, there have been no studies examining the relationship between pharmaceutical schema and the placebo effect, or whether this effect is different depending on the type of medication. For example, those with more positive pharmaceutical schema may exhibit a larger placebo effect when the medication is perceived as a pharmaceutical. In contrast those with more negative pharmaceutical schema may exhibit a larger placebo effect when the medication is perceived as natural. Thus, pharmaceutical may have contrasting relationships with the placebo effect depending on how the treatment is perceived. This will be explored in Study 1 using the cold pressor paradigm where participants will be exposed to a placebo cream described as natural vs. pharmaceutical (section 5). I will also explore the relationship between general beliefs about medicines and the placebo effect in response to a placebo medication, described as having anti-tussive effects, using experimentally induced cough (Study 4, section 8).

**Perceptions about self in relation to medicines**

Perceived sensitivity to medicines reflects how sensitive patients perceive themselves to be to the effects of medicines. Personal judgements of sensitivity are thought to influence how much medicine is necessary to have a beneficial effect or to cause adverse effects. Furthermore, patients with high PSM scores may decide to stop taking their medication sooner than those with low PSM scores (Horne,
Faasse, et al., 2013b). Horne et al. (Horne, Faasse, et al., 2013b) proposes that in a similar fashion to harmful expectations about specific medicines, perceptions about ones sensitivity in relation to medicines may also influence side effect reporting. This idea is supported by a study which found that those with higher PSM scores reported a greater number of symptoms attributed to a vaccine following inoculation (Petrie, Moss-Morris, Grey, & Shaw, 2004). A more recent study confirms these results suggesting those with high PSM scores report more symptoms after taking medication than those with moderate and low PSM scores. Furthermore, it showed that PSM is also associated with the likelihood to seek information about medication and the number of GP visits (Faasse, Grey, Horne, & Petrie, 2015). Is PSM also associated with placebo effect?

For some patients, the positive and negative effects of medicines can come hand in hand. For example, if a medicine is highly efficacious then it implicitly must have more side effects (Gabe & Lipshitz-Phillips, 1982; Leventhal, Easterling, Coons, Luchterhand, & Love, 1986). Therefore those who believe they are particularly sensitive to the effects of medicines may report greater perceived effectiveness as well as a greater number of side effects than those who do not. I will explore the effects of PSM on the placebo effect in Study 1 and 4 (section 5 and 8).

2.4.3 The relationship between illness representations, treatment beliefs and the placebo effect.

Horne (Horne, 2003) proposes a symbiotic relationship between treatment beliefs and illness representations (Figure 6 shows the theoretical relationship between treatment beliefs, illness representations and the placebo effect). Constructs within one’s illness representation can influence specific beliefs about a treatment (Horne & Weinman, 2002; Nicklas, Dunbar, & Wild, 2010a; Ross, Walker, & MacLeod, 2004). Therefore to understand the role of treatment beliefs in the placebo effect we must also explore the role of illness representations on the placebo effect.
Figure 5: Relationship between treatment beliefs, illness representation and treatment response. Key to diagram: 1 – Experience of symptoms trigger perceptions about treatment depending on the cause of illness e.g. illness attribution influences treatment necessity, whereas attribution to medication influences treatment concerns. 2 – Emotional and cognitive representations of medicines are processed in parallel. 3 – The individual strives for common-sense coherence between their beliefs about their illness and treatment. 4 – Treatment perceptions influence the placebo effect 5 – Response to the treatment (e.g. change in symptom severity) is appraised and a subsequent change or reinforcement of treatment beliefs occurs (adapted from Horne (Horne, 2003)).

According to Leventhal’s Common Sense Model of Self-Regulation (CSM), when a person develops an illness, they create their own representation of that illness in order to make sense of and respond to subsequent health problems. This representation is based on the individual’s personal ideas surrounding their illness. These ideas include the identity of the illness, the cause and the timeline, consequences of the illness, and beliefs about curability and controllability of the illness. Identity refers to the patient’s ideas about the nature of their condition, for example, the symptoms associated with it and the links between these. Cause and timeline refers to the patients idea about what is the likely cause of the illness and how long they think this problem will last (i.e. acute, chronic or cyclic/episodic).
Consequences reflect the patient’s belief about the severity, its impact on their physical, social and psychological ability. Finally, curability and controllability represent the patient’s belief in how controllable their health problem is and the extent to which it can be cured. These factors are not independent but individually can have very specific effects on outcomes and coping. Leventhal proposes that these factors are a reflection of the patient’s cognitive responses to their symptoms and illnesses, and can change as their illness progresses, symptoms emerge, and in relation to treatment responses (Hill, 2010; Leventhal, Nerenz, & Purse, 1984).

**Illness representations and the placebo effect**

Illness representations have shown to be important determinants of clinical outcomes such as adherence (Hagger & Orbell, 2003). A number of studies have also found links between patients’ illness representations and symptom perception across a variety of conditions including pain (Glattacker et al., 2013a; Goldstein et al., 2011), asthma (Ohm & Aaronson, 2006), heart disease (Hirani, Pugsley, & Newman, 2006b). In patients with chronic back pain, beliefs about back pain were measured at three time points: two weeks before the start of rehabilitation, at the end of rehabilitation and at a 6 month follow up. Illness beliefs at baseline were found to be more predictive of pain intensity compared to other socio-demographic factors and illness related variables, such as mental health. In particular, beliefs that one’s illness was chronic was associated with greater pain intensity and explained 6% of the variance in pain intensity at follow up (Glattacker et al., 2013a).

Recent evidence, however, suggests illness representations may also be involved in treatment response. Chilcot et al. (Chilcot J et al., 2013) explored the use of Leventhal’s CSM in determining how cognitive behavioural therapy (CBT) influences clinical outcomes in patients with IBS. Illness representations were measured at baseline and after 6 months of CBT. Compared to treatment as usual, patients receiving CBT reported greater symptom improvement after 6 months, an effect which was mediated by a change in illness representations. In other words, CBT led to more positive illness representations (lower total IPQ scores) and in turn greater symptom improvement. Unfortunately this study did not examine the relationship between individual constructs within patients’ illness representation. Furthermore this study did not have a therapy control group and thus we cannot determine whether changes in illness representations were due to the CBT or other factors such as time spent with a clinician. These results were confirmed, however, in a more recent study of patients with functional somatic syndromes undergoing CBT.
This study found that the effect of CBT on symptom severity was primarily mediated by beliefs about perceived control but that reductions in emotional representations of IBS and perceived consequences were also important (Christensen, Frostholm, Ornbol, & Schroder, 2015).

In a study of patients with depression, Glattacker (Glattacker et al., 2013b) found that the effectiveness of rehabilitation in reducing depressive symptoms was predicted by representations of their illness. Beliefs about illness identity, illness chronicity (timeline), and personal and treatment control at the start of treatment were significantly predictors of symptom severity at 6 month follow up after rehabilitation. However, this study did not have a control condition and thus we cannot determine whether change in symptoms were due to factors such as spontaneous improvement or regression to the mean. Further research is clearly warranted to determine whether representations of illness are associated with responses to treatment. In this thesis I will examine the role of illness representations on the placebo effect in patients with GORD and LPR (Study 2, section 6).

The relationship between illness representations and treatment necessity

Illness representations influence specific evaluations of treatment e.g. treatment necessity (Horne, 2003). For example, despite asthma being a chronic condition, those who believe asthma is cyclical (i.e. no symptoms, no asthma) are likely to doubt the necessity of their medication (Horne & Weinman, 2002). Horne and Weinman (Horne & Weinman, 2002) also found that perceived consequences of having asthma was significantly correlated with perceived necessity of their preventer medication. That is, the greater the perceived consequences, the greater the perceived necessity. This result is further supported by a number of other studies in patients with chronic pain (Nicklas, Dunbar, & Wild, 2010b) and hypertension (Ross et al., 2004). Beliefs about the control/curability of an illness also influence perceived need (Leventhal, Leventhal, & Contrada, 1998). Horne and Weinman (Horne & Weinman, 2002) found treatment necessity beliefs to be positively correlated with perceived treatment control but not with other forms of control beliefs such as personal control, in patients taking HIV medication. Interestingly, studies investigating other conditions have reported a significant negative relationship between treatment necessity and perceived personal control but no significant relationship with perceived treatment control (Nicklas et al., 2010b).
There is also evidence for a mediatory effect of treatment necessity in the relationship between illness representations and adherence. Horne and Weinman (Horne & Weinman, 2002) found the effects of illness timeline on adherence to preventer medication in asthma patients was fully mediated by treatment necessity. Furthermore, a partial mediation of treatment necessity was found between illness consequences and adherence. This result is supported by another study which found the effect of illness consequences and emotional representations of illness on adherence to be mediated through treatment necessity and concerns (Nicklas et al., 2010b). Whether this relationship exists with the placebo effect remains to be determined, for example more negative representations of health threats are associated with greater treatment necessity beliefs and in turn a larger placebo effect.

In this thesis I will explore this idea in Study 1 using the cold pressor paradigm in healthy volunteers. As this is experimentally induced pain using a non-clinical sample, participants will not have an illness representation per se. Thus, I will be using a related variable, pain catastrophizing. Pain catastrophizing is a form of negative pain-related cognition. It is described as the tendency to exaggerate the threat value of pain sensations, to ruminate on and feel helpless during pain (Sullivan, Bishop, & Pivik, 1995). Negative illness representations are associated with catastrophic thinking about symptoms (Van Wilgen, Van Ittersum, Kaptein, & Van Wijhe, 2008). For example, in patients with fibromyalgia, those who catastrophize about pain tend to have poor illness coherence, belief that their illness is cyclical and are emotionally affected by their illness (Van Wilgen et al., 2008). Therefore, I propose that as with patients with negative illness representations, participants who tend to catastrophize about pain will have greater need for the placebo medication and in turn experience a larger placebo effect. This will be explored in section 5.

Horne proposes that people aim to find “common-sense” coherence between illness representations and treatment beliefs, and that messages about treatment necessity are likely to be more convincing if they are consistent with their illness representations (Horne, 2003; Petrie et al., 2004). As I hypothesise that treatment necessity is positively associated with the placebo effect, messages about treatment necessity focused around constructs within patients’ illness representations (e.g. cause, timeline and consequences) may be useful in maximising the placebo effect. In this thesis I will test this idea in two studies by developing a micro-intervention which aims to increase the placebo effect by modifying treatment necessity beliefs.
This intervention is designed to increase treatment necessity beliefs by improving coherence between participants’ beliefs about a placebo medication and representations about the health threat. The effect of this intervention on increasing necessity beliefs will be assessed in an analogue scenario where participants are asked to imagine they have been prescribed a medication for asthma (section 7). In a parallel study the effect of this intervention on the placebo effect will be examined using experimentally induced cough (section 8).

2.5 Other psychological factors related to symptom perception and the placebo effect

A range of psychological factors are known to influence symptom perception. These factors include anxiety (Vase, Robinson, Verne, & Price, 2005), depression (Bar et al., 2005), affect (Deary, Chalder, & Sharpe, 2007), somatisation (De Gucht & Maes, 2006) and stress (Salovey, Stroud, Woolery, & Epel, 2002). For example, patients with depression seem to have a general insensitivity toward experimental pain in comparison to healthy controls. This is supported by a number of studies which have shown that depressed individuals have consistently heightened pain thresholds to experimental pain (Adler & Gattaz, 1993; Bar, Greiner, Letsch, Kobele, & Sauer, 2003; Dickens, McGowan, & Dale, 2003). In contrast, the tendency to somatise i.e. to experience and report somatic symptoms, is associated with increased physical symptom reporting as well as increased side effect reporting (Brown et al., 2012; Doering et al., 2015; Uhlenhuth et al., 1998).

The role of affect in symptom perception has also been heavily investigated (Bogaerts et al., 2005; Janssens, Verleden, De Peuter, Van Diest, & Van den Bergh, 2009; Watson & Pennebaker, 1989). Positive and negative affect reflect the extent to which an individual experiences positive (e.g. excited, enthusiastic and alert) and negative (e.g. upset, nervous and afraid) emotions (Watson, Clark, & Tellegen, 1988). The role of affect in symptom perception has been well documented in a variety of conditions such as asthma (Janssens et al., 2009), chronic pain (Gaskin, Greene, Robinson, & Geisser, 1992) and IBS (Crane & Martin, 2002). For example, asthmatics with high negative affect are likely to report more severe asthma symptoms (Put et al., 2004). Furthermore, it is thought that expectations influence the placebo effect through an increase in positive affect and/or reduction in negative affect (Petrovic et al., 2005; Vase et al., 2005). This idea is supported by studies which have shown a reduction in anxiety and stress
after placebo administration. In patients with IBS, Vase et al. (Vase et al., 2005) found a reduction in anxiety after placebo administration. Anxiety along with patients’ expectations and desire for pain relief were found to be significant contributors to variations in the placebo effect. A similar effect of stress after placebo administration has also been observed. For example, reductions in anticipatory stress were observed after placebo administration, an effect which was significantly related to the degree of placebo analgesia (Aslaksen, Bystad, Vambheim, & Flaten, 2011).

Due to their role in symptom perception and associations with the placebo effect I also examine the role of these factors in the placebo effect.
3. Aims of thesis and outstanding questions

Although studies in the current literature have not directly explored the relationship between treatment beliefs, illness representations and placebo effect, they imply that these beliefs may be useful in understanding individual variations in response to treatment. Therefore, this thesis will contribute to knowledge of the placebo effect with the primary aim of understanding the role of treatment beliefs and illness representations in the placebo effect. This thesis will use a range of methodologies to answer the following outstanding questions:

**Do treatment beliefs predict the placebo effect?**

I will determine whether there is a causal relationship between prospectively measured treatment beliefs and the placebo effect across 2 studies:

**Study 1:** Using the cold pressor paradigm, this study aims to predict whether specific beliefs about two placebo creams described as natural and pharmaceutical are associated with the placebo effect. I hypothesise that high perceived need for either cream will be associated with a larger placebo effect, an effect which will remain significant when controlling for efficacy expectations. I will also investigate the effects of participants’ pharmaceutical schema on their placebo effect to placebos described as natural vs. pharmaceutical (section 5).

**Study 4:** Using experimentally induced cough as a model, I will investigate whether treatment beliefs not only influence subjective placebo effects but also objective. I hypothesise that greater personal need, more positive general beliefs about medicines and higher PSM will be associated with a reduced urge-to-cough (subjective) and fewer numbers of coughs (objective) after placebo administration (section 8).

**Are illness representations associated with the placebo effect?**

I will address this question in Study 2 using a sample of GORD and LPR patients. Using a modified Bernstein test participants will be exposed to two conditions where saline described as therapeutic vs. neutral is applied directly to the oesophagus. The effect of baseline illness representations on their responses to each description will then be explored. It is hypothesised that 1) describing the saline as therapeutic will result in significantly lower pain intensity compared to describing the saline as
neutral 2) a greater therapeutic effect will be observed in participants with more positive illness representations (section 6).

**Can treatment necessity beliefs be changed by a brief information-based intervention to increase coherence between representations of the condition and treatment, and does a change in treatment necessity beliefs result in changes in placebo effect?**

Study 3 and 4: In two parallel studies I will assess whether placebo-related treatment beliefs can be modified by brief interventions designed to change belief. This micro-intervention aims to increase participants’ perceived need for a placebo medication by improving coherence between participants’ beliefs about a placebo medication and representations of the condition. The effect of this intervention will assessed in an analogue scenario to determine whether it increased treatment necessity beliefs of a fictitious medication in comparison to a control group (no intervention) (Study 3, section 7). I will also assess the effect of this intervention on the placebo effect using experimentally induced cough. It is hypothesised that participants who receive the intervention will exhibit greater perceived need for the placebo medication and in turn a larger placebo effect, in comparison those who do not (Study 4, section 8).
4. Materials

The following measures will be used across all 4 studies. Study specific measures will be described in detail in each research chapter. Many of the independent variables in this thesis are intercorrelated (see Figure 4 as an example). While the key independent variables of interest in this thesis (e.g. treatment beliefs and illness representations) are highly correlated, it is known that individual constructs can have different effects on medication taking behaviour (see sections 2.4.2–2.4.3). Thus throughout this thesis, the effect of individual constructs within participants representations of treatment and illness on the placebo effect will be examined. Similarly, individual effects of a number of emotion and personality-related variables will also be examined in a similar fashion.

4.1 Beliefs about Medicines Questionnaire (BMQ)

Treatment beliefs were measured using the BMQ-Specific (BMQ-S) and BMQ-General (BMQ-G). The BMQ-Specific consists of two subscales assessing the individuals beliefs about their personal need for (Specific Necessity, e.g. “My health, at present, depends on my medication”) and concerns they have about a medication (Specific Concerns, e.g. “My medication disrupts my life”) about a specific medication or placebo. The BMQ-General comprises of three subscales measuring participant’s beliefs about the benefits of medicines (General Benefit e.g. “Medicines help many people to live longer”), that they are generally harmful (General Harm e.g. “All medicines are poisons”) and that they are overprescribed by doctors (General Overuse, e.g. “Doctors use too many medicines”) (Horne et al., 1999a). Participants must rate how much they agree with each using a 5-point Likert-type scale (1 = strongly disagree to 5 = strongly agree). A scale-adjusted mean score for each scale was computed by dividing the mean scale score by the number of items.

As studies 1 and 4 recruited healthy individual the BMQ-S items were modified to suit the experimental situation. For example “My medicines protect me from becoming worse” was changed to “This pain relieving cream will protect me from feeling pain”. Some items were removed as they were not appropriate for the laboratory scenario such as “My health in the future will depend on this medicine”. Please refer to the measures sections in Study 1 (section 5.2) and 4 (section 8.2) for the modified items.
4.2 Perceived sensitivity to medicines (PSM)

The PSM is a validated 5-item scale measuring perceptions about self in relation to medicines i.e. ones perceived sensitivity to the effects of medicines in general (Horne, Faasse, et al., 2013a). Participants rate how much they agree with each item (e.g. “My body over-reacts to medicines”) using a 5-point Likert-type scale (1 = strongly disagree to 5 = strongly agree). A scale-adjusted mean score for each scale was computed by dividing the mean scale score by the number of items.

4.3 Positive and Negative Affect Schedule (PANAS)

Positive and Negative Affect were measures using the PANAS. The PANAS consists of two 10-item scales measuring state positive and negative affect – a person’s current emotional state (Watson et al., 1988). This questionnaire was chosen to measure affect as it is validated (Watson et al., 1988) and has been widely used in both clinical and healthy populations (Boumparis, Karyotaki, Kleiboer, Hofmann, & Cuijpers, 2016; Crawford & Henry, 2004; Janssens, Verleden, De Peuter, Petersen, & Van den Bergh, 2012; Wong et al., 2015). For each item (e.g. Excited) participants must indicate to what extent they are feeling this way at this moment using a 5-point scale from 0 – very slightly or not at all to 5 – extremely. Total scores for each scale are computed by summing scores from each item.

4.4 State Trait Anxiety Inventory – Trait (STAI-T)

The STAI-T is a 20 item scale measuring trait anxiety – the tendency to report anxiety across many situations (Spielberger, 1983). This measure for trait anxiety has been used extensively in both clinical and healthy populations (Freeman-Gibb, Janz, Katapodi, Zikmund-Fisher, & Northouse, 2016; Gunther, Rufer, Kersting, & Suslow, 2016; Thibodeau, Welch, Katz, & Asmundson, 2013; Van Ryckeghem et al., 2013) and is validated (Metzger, 1976). For each item (e.g. I feel nervous and restless) participants must indicate how they feel in general using a 4-point scale from 0 – almost never to 4 – almost always. A total score is calculated by summing the score from each item (reverse scoring for items 1, 3, 5, 6, 10, 11, 14, 15, and 17).
4.5 Patient Health Questionnaire – 9 (PHQ-9)

The PHQ-9 is a 9-item questionnaire for the assessment of depression severity (Kroenke, Spitzer, & Williams, 2001). Participants must indicate how bothered they have been about 9 problems over the past two weeks (e.g. feeling down, depressed or hopeless) using a 4-point Likert-type scale from 0 – not at all to 3 = nearly every day. A total score is calculated by summing the scores from each item. Higher scores indicate more severe depression (0-4 none/minimal, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe).

4.6 Efficacy Expectations (VAS)

Efficacy Expectations were measured using a VAS where 0 = not effective at all to 100 = highly effective.
5. Beliefs about pharmaceutical medicines and natural remedies predict individual variation in placebo analgesia

5.1 Background and research question

Pain has been the most extensively studied condition in the placebo literature (Holmes, Tiwari, & Kennedy, 2016). This is most likely due to its subjective nature. Prospectively measured expectations have consistently been linked to placebo analgesia as well as nocebo hyperalgesia (Reicherts, Gerdes, Pauli, & Wieser, 2016). As discussed in section 2.6 however, there are currently no studies assessing the effect of prospective treatment beliefs on the placebo effect. This study therefore set out to address whether treatment beliefs are associated with the magnitude of the placebo effect.

Treatment necessity beliefs are influenced by patients’ appraisal of their symptoms. Cooper et al. (Cooper et al., 2009) found that in patients taking anti-retroviral medication, those with persistent symptoms doubted the need for their medication. In section 2.6 I proposed that treatment necessity beliefs inform the appraisal of symptoms. That is, those with greater perceived need for a medication will likely perceive a greater reduction in symptoms after taking the medication. In this study I hypothesise that treatment necessity beliefs will be positively associated with the magnitude of the placebo effect.

According to the Extended CSM, treatment necessity beliefs are informed by patients’ representations of illness (Horne, 2003)(see section 2.6.3). Whether representations of illness influence the relationship between treatment necessity beliefs and the placebo effect remains to be determined. As this study involved healthy individuals and experimentally induced pain, participants would not have an illness representation per se but would have a representation of the experimental pain. Pain catastrophizing is the tendency to exaggerate, ruminate on and feel helpless during pain (Sullivan et al., 1995). In patients with pain conditions such as fibromyalgia, more negative illness representations have been associated with greater pain catastrophizing (Van Wilgen et al., 2008). For this study illness representations were therefore operationalized as ‘pain catastrophizing’.

This study also investigated the effect of participants’ pharmaceutical schema in response to two placebos described as pharmaceutical vs. natural. As I described in
section 2.6.2 negative pharmaceutical schema is often associated with more positive perceptions about natural remedies. A previous study has shown that pharmaceutical schema can influence patients’ preference for and uptake of specific classes of treatment (e.g. as pharmaceutical medicines vs natural remedies). For example, belief that pharmaceutical medicines are harmful is associated with a greater tendency to use natural remedies (in preference to pharmaceuticals use of natural remedies (Green et al., 2013). Whether pharmaceutical schema inform placebo effects in natural remedies remains to be determined. It will also explore how pharmaceutical schema inform specific evaluations of the placebo depending on whether it is described as pharmaceutical vs. natural.

Using the cold pressor task, this study aimed to understand whether treatment beliefs predict the magnitude of the placebo effect. Participants were exposed to three conditions in a random order: No Placebo, Pharmaceutical Placebo and Natural Placebo. This study tested the following hypotheses:

Hypothesis 1: Variation in placebo effects in both conditions will be predicted by the participant’s Specific Necessity beliefs (i.e. their perception of personal need for the specific ‘treatment’ pharmaceutical vs. natural.

Hypothesis 2: High pain catastrophizing will be associated with stronger treatment necessity beliefs and a larger placebo effect.

Hypothesis 3: Specific Necessity will be differentially influenced by general pharmaceutical schema and general beliefs about complimentary medicine. More positive pharmaceutical schema will be associated with stronger beliefs in the necessity for the Pharmaceutical Placebo and more positive beliefs in complementary and natural medicine with stronger beliefs in the necessity for the Natural Placebo.

Hypothesis 4: Negative pharmaceutical schema will be associated with more positive beliefs about complementary and natural remedies and preferences for this type of treatment.
5.2 Method and materials

This study was approved by the UCL Ethics Committee (ref: 4875/002, see Appendix A). The study had a within-subject design. Participants attended a single testing session in which they completed 3 conditions in a random order: Pharmaceutical Condition, Natural Condition and No Placebo Condition.

Sample, recruitment and consent

The sample size was calculated using G Power (G*Power v3.1.9.2), for testing a linear multiple regression model (fixed, $R^2$ increase), 80% power and an alpha error probability of 0.05. I calculated the required sample size based on a study which reported that expectations explained 7.3% of the variance in cold pressor pain intensity (Sullivan, Rodgers, & Kirsch, 2001). A sample size of 168 was required in order to explain a total variance of 7.3% by 5 predictor variables of interest (Necessity, Concerns, General Benefit, General Harm and PSM) in a multiple regression model.

Participants were invited to take part in a study comparing the effectiveness of two new pain-relieving creams via the UCL Announcement Email Service between June and December 2014. Participants were included if aged 18 years and above, and able to sufficiently understand spoken and written English. Participants were excluded if they reported a history of the following medical conditions: fainting/seizures, cardiovascular disease, circulation disorders or if they had the following conditions in the past two weeks: chronic pain, back pain, severe headaches, and arthritis or hand injuries. Participants were also excluded if they were currently taking medication for pain, anti-depressants or sedatives. Potential participants were emailed the information sheet and a screening questionnaire (see Appendix B) to check eligibility and given at least 24 hours to decide whether to participate. Informed consent was obtained on the day of the experiment. Participants were paid £10 for their time. The experiment took 1 hour to complete.
Measures

The following measures were used in this study. Details about measures used throughout this thesis can be found in section 4 with their Cronbach’s alphas in Table 1. Measures specific to this study are described in detail below.

Table 1: Cronbach’s alphas for the BMQ-G, PSM, STAI-T, PHQ-9 and PANAS

<table>
<thead>
<tr>
<th>Measure</th>
<th>Subscale</th>
<th>Cronbach’s Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ-G (Horne et al., 1999b)</td>
<td>General Benefit</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>General Harm</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>General Overuse</td>
<td>0.67</td>
</tr>
<tr>
<td>PSM (Horne, Faasse, et al., 2013b)</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>STAI-T: Trait Anxiety (Spielberger, 1983)</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>PHQ-9: Depression (Kroenke et al., 2001)</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>PANAS: Positive and Negative Affect (Watson et al., 1988)</td>
<td>Positive Affect</td>
<td>0.91 – 0.93</td>
</tr>
<tr>
<td></td>
<td>Negative Affect</td>
<td>0.83 - 0.85</td>
</tr>
</tbody>
</table>

Note: BMQ-G = Beliefs about Medicines Questionnaire – General, PSM = Perceived Sensitivity to Medicines Questionnaire, STAI-T = State Trait Anxiety Inventory – Trait, PHQ-9 = Patient Health Questionnaire – 9, PANAS = Positive and Negative Affect Schedule. Range of Cronbach’s alpha across all three conditions are shown for the PANAS subscales.

BMQ-S (Horne et al., 1999a)

The BMQ-S was developed for examining beliefs about medicines prescribed for chronic illnesses; therefore, each item was modified to apply to healthy individuals in an experimental setting (see Table 2). Please refer to section 4.1 for details on the original BMQ-S scales and scoring. Both modified scales had good internal consistency in both conditions (Pharmaceutical Condition: Necessity α = 0.61, Concerns α = 0.71, Natural Condition: Necessity α = 0.68, Concerns α = 0.64).
Table 2: Modified items of the BMQ-S scales

<table>
<thead>
<tr>
<th>Necessity</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>This cream is necessary to reduce my pain</td>
<td>Using this cream worries me</td>
</tr>
<tr>
<td>I would experience more severe pain without this cream</td>
<td>I am concerned about the long-term effects of this cream</td>
</tr>
<tr>
<td>Using this cream makes me less anxious about the pain in this study</td>
<td>How this cream works is a mystery to me</td>
</tr>
<tr>
<td>This pain relieving cream will protect me from feeling pain</td>
<td>I am concerned that this cream won’t work</td>
</tr>
<tr>
<td></td>
<td>I am concerned that this cream might cause a side effect</td>
</tr>
<tr>
<td></td>
<td>I am concerned this cream will affect my sense of touch in my hand</td>
</tr>
<tr>
<td></td>
<td>It would worry me to feel as though I depended on this cream to tolerate the pain</td>
</tr>
</tbody>
</table>

Note: BMQ-S = Beliefs about Medicines Questionnaire - Specific

**Treatment preference**

Participants were asked to choose which cream they would use if they were suffering from muscle pain.

**Complementary and Alternative Medicines Belief Inventory (CAMBI) (Bishop, Yardley, & Lewith, 2005)**

The CAMBI measures beliefs about complementary and alternative medicine. It has four 5-item subscales measuring beliefs about: Holistic Health (health and illness involve the whole person e.g. “Health is about harmonizing your body, mind and spirit”); Holistic Treatments (treatment should focus on the body’s healing mechanisms e.g. “It is important for treatments to boost my immune system”); Natural Treatments (natural treatments are safer than orthodox medicines) e.g. “Treatments should only use natural ingredients”; and Participation in Treatment (patients should be actively involved in their treatment). Items were scored on a 7-point Likert-type scale (0=strongly disagree, 7=strongly agree). Scores for each item were summed to produce a total score for each scale. This questionnaire has shown good validity (Bishop et al., 2005). The Holistic Health, Holistic Treatment and Natural Treatment scales had adequate to good internal consistency in our sample (α = 0.59, 0.61, 0.49 respectively). The Participation in Treatment scale had poor internal consistency (α = 0.28) and so was not used in the analysis.
Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995)

The PCS is a 13-item questionnaire measuring propensity to exaggerate the seriousness or threat value of pain. It can be divided into 3 subscales measuring rumination (e.g. “I can’t stop thinking about how much it hurts”; PCS-Rumination), magnification of pain (e.g. “I worry that something serious may happen”; PCS-Magnification), and feelings of helpless (e.g. “It’s awful and I feel that it overwhelms me”; PCS-Helplessness) during pain. Participants indicate the degree to which they have these thoughts and feelings using a 5 point scale (0=not at all, 4=all the time). Totals for each subscale are calculated by adding scores from each item. This questionnaire has been validated (Osman et al., 1997) and had good internal consistency for all 3 subscales (PCS–Rumination α = 0.75, PCS–Magnification α = 0.85, PCS-Helplessness α = 0.59).

Expectations of drug efficacy and pain intensity (VAS)

Visual Analogue Scales (VAS) were used to measure expectations of drug efficacy (Efficacy Expectations: 0 = Not effective at all, 100 = Highly effective), and Expected Pain Intensity (0 = Least possible pain, 100 = Worst possible pain).

Pain Tolerance

Pain Tolerance was measured by timing how long participants left their hand submerged in the water bath. Pain Tolerance was defined as the time from immersion to withdrawal of the hand from the water.

Short-Form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987)

The SF-MPQ measures Pain Intensity using a visual analogue scale (VAS, 0 = Least possible pain, 100 = Worst possible pain), and Multidimensional Pain Intensity scale (MPQ) using 11 items assessing sensory pain and 4 items assessing affective pain. For each MPQ item, participants rated how much of that quality (e.g. sharp) their pain had from 0 =none to 3 = severe. The scale showed good internal consistency for each condition (Pharmaceutical Condition α = 0.85, Natural Condition α = 0.84, No Placebo Condition α = 0.81). Total scores for each scale were calculated by adding the score from each item. Participants also completed the Overall Pain Intensity measure (OPI) where they are asked to rate their overall pain intensity from 0 = no pain to 5 = excruciating.
Side Effect Frequency

Participants were provided with a list of 6 common side effects to pain medication – Skin irritation, Headache, Nausea, Dizziness, Fatigue, Hot flushes and were asked to report if they had experienced them or not. They were also provided with the option to note any other side effects they had experienced.

Manipulation Checks

Participants were asked what they thought the aim of the study was. Finally using a VAS, they were asked whether they thought they had received a placebo or an active medication for each condition (where 0=placebo and 100=active medication).

Conditions

In the Natural and Pharmaceutical Conditions participant were presented with patient information leaflets (PIL) describing a “natural” and “pharmaceutical” treatment (see Figure 6, 7 and 8). These PILs were developed in order to manipulate participants’ specific beliefs about the placebo cream. The structure of each PIL was based on standard PILs used in pharmacy practice. The content of these PILs were based on two analgesics: 1) extracts from the plant Cassia occidentalis plant (Sini, Karpakavalli, & Sangeetha, 2010) and 2) chlorthenoxazine, a chemical modification of salicylic acid (Hinz, Dorn, Shen, & Brune, 2000). To emphasize the “natural” and “pharmaceutical” aspects, information about how each medication was developed was included along with pictures of the Cassia occidentalis plant and chlorthenoxazine chemical structure.

In the No Placebo Condition participants were provided with the following message: “The purpose of this condition is to compare normal pain intensity/tolerance against the condition where you will receive a medicine to see how effective the drugs are in reducing pain”. Participants received no placebo for the control condition. While designing the study I considered using an open-label placebo for the control condition where participants would receive the placebo cream but would be told that it contains no medication. However, I decided against this for various reasons. Firstly, the majority of the placebo literature use a “no placebo” group as a control condition. This mirrors clinical trials which compare the effect of active medication against a group receiving a “deceptive” placebo and a natural history group (i.e. no placebo). As I mentioned in the literature review there have been no studies examining treatment beliefs on the placebo effect thus I felt it was important to...
develop studies which mirrored studies which have examined other predictors of the placebo effect.

A within subject design was chosen as it is known that individual differences can influence pain and outcomes of the cold pressor paradigm. The within-subject design will help reduce the effect of individual differences on my results.

Figure 6: PIL presented to participants in the Natural Condition.
1. WHAT IS XYLOPTAN AND HOW DOES IT WORK?

Xyloptan is a pharmaceutical cream used to prevent and relieve pain. Its active ingredient, clorhthenoxazine was first synthesised in the laboratory over 40 years ago. It has undergone further development and testing and is licenced for use as Xyloptan pain-relieving cream, which is marketed by an international pharmaceutical company. Studies have shown this medicine to be highly effective in reducing the type of pain you’re about to experience. It works within the central nervous system, reducing pain perception within the brain.

2. BEFORE YOU USE XYLOPTAN

This cream should not be used on the following areas:

- Cuts, grazes or wounds.
- Where there is a skin rash or eczema.
- In or near the eyes.
- Inside the nose, ear or mouth.

3. HOW TO USE XYLOPTAN

In this study, we will ask you to apply this cream to the back of your hand (while wearing a glove on the hand you use to apply the cream). Gently massage the cream into your skin. You may experience a slight tingling on your hand when it takes effect.

Figure 7: PIL presented to participants in the Pharmaceutical Condition.
Figure 8: Pharmaceutical (left) and natural (right) “analgesics” tested in this study.

**Cold pressor task**

The temperature of the water bath (Julabo F-12 Refrigerated Circulator, see Figure 9) was set at 2°C (Forsyth & Hayes, 2014). Participants were instructed to submerge their hand in the water up to their wrist for as long as possible (maximum 2 minutes). The experimenter remained out of view during this task to prevent any audience effects from influencing results.
Figure 9: The Julabo F-12 Refrigerated Circulator used for the cold pressor task. This equipment was chosen for the experiment as it had a temperature resolution of 0.01ºC and provided constant water circulation.

**Filler task**

Between each condition, participants were asked to complete a 'Magic Square' task to keep them engaged while their hand re-acclimatised to normal temperature. The task involved a 3x3 grid where they were required to place numbers from 1-9 in each square so that each row column and diagonal adds up to 15 (Schuh, 1968). Participants were told that this task was to test their cognitive abilities after experiencing pain and to complete it within 5 minutes.

**Procedure**

Participants first completed the Baseline Measures (Sociodemographics, BMQ-G, PSM, CAMBI, PHQ-9, STAI-T, and PCS). Then they were exposed to each condition in a randomized order. Hand order (dominant – non-dominant - dominant hand or vice versa) was also randomized. Randomisation was determined for each participant using an online randomiser (unblind using www.randomizer.net) before
participants came in for the experiment and were not told the order of conditions. In each condition, participants read the PIL, then the completed the Condition-Specific Measures (BMQ-S, PANAS and Expectations) and the cold pressor task. Pain Tolerance was measured during each cold pressor task. Immediately after the task participants completed the Post-Cold Pressor Measures (SF-MPQ, Side Effects). Between each condition participants completed the filler task.

Once all conditions had been completed, participants completed the End of Study Measures (Manipulation Checks). Finally, participants were fully debriefed (see Figure 10).

Figure 10: Overview of procedures for Study 1.BMQ-G = Belief about Medicines Questionnaire – General, PSM = Perceived Sensitivity to Medicines, CAMBI – Complementary and Alternative Medicines Belief Inventory, PHQ-9 = Patients Health Questionnaire – 9, STAI-T = State Trait Anxiety Inventory – Trait, Pain Catastrophizing Scale, PANAS, Positive and Negative Affect Schedule, PIL = Patient information leaflet, BMQ-S = Beliefs about Medicines Questionnaire – Specific, SF-MPQ = Short Form McGill Pain Questionnaire.
**Statistical analysis**

Paired t-tests were performed to determine if there were significant differences in Efficacy Expectation, Expected Pain Intensity, Necessity and Concerns, Pain Intensity (VAS, MPQ, OPI), and Pain Tolerance across conditions. Scores for the BMQ-S subscales were dichotomized at the scale mid-point to describe participants as high or low on each subscale (for descriptive statistics only). Scores for Necessity and Concerns in the Natural Condition were subtracted from the Pharmaceutical Condition to determine whether participants formed different perceptions about the placebo cream in each condition.

The placebo effect for Pain Intensity (MPQ Placebo Effect) and Tolerance (Tolerance Placebo Effect) were calculated by subtracting scores obtained in the Pharmaceutical and Natural Conditions from the No Placebo Condition. I used the placebo effect derived from the MPQ scale as our main outcome measure for pain intensity as it is a multidimensional measure of pain, rather than the VAS and OPI scales (Melzack, 1987). I employed multiple linear regression to determine the effects of Specific Beliefs about the placebo (Necessity and Concerns), participants' Pharmaceutical Schemas (General Benefit, Harm and Overuse, PSM) and Beliefs about CAM (CAMBI: Natural Treatments, Holistic Treatments, Holistic Health) on the MPQ and Tolerance Placebo Effects in each conditions. I then tested the effects of potential confounders (Expectations, Pain Catastrophizing, Anxiety, Depression, Positive and Negative Affect and Sociodemographics) on the MPQ and Tolerance Placebo Effects for each condition. A Sobel test determined whether any effect of beliefs about the impending pain (Pain Catastrophizing) on the placebo effect was mediated by Necessity. Finally I included significant predictors in a regression model to determine the overall variance of the placebo effect by these variables.

Pearson’s correlations were conducted to examine relationships between general beliefs about medicines, PSM, Specific Beliefs about the placebo and Beliefs about CAM. A binomial test was used to determine whether there was a significant preference for either the Natural or Pharmaceutical Placebo within our sample. Independent t-tests were conducted to determine significant difference in treatment beliefs, beliefs about CAM and Pain Intensity in response to each placebo between those who preferred to use the Natural vs. Pharmaceutical Placebo. Analyses were conducted using IBM SPSS Statistics v21.
5.3 Results

Sample characteristics

Of 236 individuals who expressed interest, 21 did not meet the inclusion criteria. Of the 215 who agreed to take part after screening, 47 did not attend their appointment and 168 completed the experiment. The mean age of participants was 25.69 years with the majority being female (63.70%). Just over a third of participants were currently studying an undergraduate degree with the rest studying for a postgraduate degree. Most participants spoke English as their first language (see Table 3).

<table>
<thead>
<tr>
<th>Table 3: Sociodemographics</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.69 (8.40)</td>
</tr>
<tr>
<td>Female</td>
<td>107 (63.70%)</td>
</tr>
<tr>
<td>Currently studying:</td>
<td></td>
</tr>
<tr>
<td>Undergraduate degree</td>
<td>59 (35.10%)</td>
</tr>
<tr>
<td>Postgraduate degree</td>
<td>93 (64.90%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White British/American/European</td>
<td>92 (54.80%)</td>
</tr>
<tr>
<td>Other</td>
<td>75 (45.20%)</td>
</tr>
<tr>
<td>First Language</td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>100 (59.52%)</td>
</tr>
<tr>
<td>Other</td>
<td>64 (40.47%)</td>
</tr>
</tbody>
</table>

Baseline Measures

Most participants expressed positive views about pharmaceutical medicines. All but one participant (99.40%) had high General Benefit beliefs, scoring above the scale mid-point (mean = 3.98 SD= 0.45). The majority of our sample viewed medicines as generally safe (Low General Harm 81.50%, mean = 2.24 SD = 0.59) and had low perceived sensitivity to medicines (93.50%, mean = 2.05 SD = 0.58). However, two thirds of our sample believed that medicines are over prescribed by doctors (66.70%, mean = 3.06 SD = 0.69). Mean scores for the CAMBI – Natural Treatment, Holistic Treatment and Holistic Health scales were 17.45 (SD = 4.51), 20.65 (SD = 3.86) and 15.38 (SD = 3.81), respectively. These scores were around the scale midpoint suggesting participants were ambivalent to whether medication should be
natural, utilize the body’s own mechanisms, and focus on the body “as a whole”. A median Depression score of 3 (IQR = 6) was observed with 18.5% of our sample scoring above the criteria for depression severe enough to warrant medical intervention. Mean scores for PCS – Rumination, Magnification and Helplessness were 5.24 (SD = 3.90), 2.43 (SD = 1.99) and 4.90 (SD = 3.98) suggesting participants generally were low pain catastrophizing tendencies. Finally a mean Trait Anxiety score of 43.18 (SD = 6.49) was observed suggesting moderate levels of anxiety within our sample (see Table 4).

Table 4: Baseline measures

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Benefit</td>
<td>3.98 (0.45)</td>
</tr>
<tr>
<td>General Harm</td>
<td>2.24 (0.59)</td>
</tr>
<tr>
<td>General Overuse</td>
<td>3.06 (0.69)</td>
</tr>
<tr>
<td>PSM</td>
<td>2.05 (0.58)</td>
</tr>
<tr>
<td>CAMBI - Natural Treatment</td>
<td>17.45 (4.51)</td>
</tr>
<tr>
<td>CAMBI - Holistic Treatment</td>
<td>20.65 (3.86)</td>
</tr>
<tr>
<td>CAMBI - Holistic Health</td>
<td>15.38 (3.81)</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>43.18 (6.49)</td>
</tr>
<tr>
<td>PCS - Rumination</td>
<td>5.24 (3.90)</td>
</tr>
<tr>
<td>PCS - Magnification</td>
<td>2.43 (1.99)</td>
</tr>
<tr>
<td>PCS - Helplessness</td>
<td>4.90 (3.98)</td>
</tr>
<tr>
<td>Depression</td>
<td>3.00 (6.00)</td>
</tr>
</tbody>
</table>

Note: PSM – Perceived Sensitivity to Medicines Scale, CAMBI – Complementary and Alternative Medicines Belief Inventory, PCS – Pain Catastrophizing Scale

**Was the placebo cream convincing? Manipulation check and side effect reports**

I conducted paired t-tests to determine whether participants tended to have different beliefs and expectations about the Natural and Pharmaceutical Placebos. Regardless of whether the treatment was described as Pharmaceutical or Natural, Mean Necessity beliefs in each treatment condition were above the scale mid-point, indicating that most participants felt that they needed the treatment, while Concerns were low, with a mean below the scale mid-point. Necessity beliefs were significantly greater in the Pharmaceutical Condition compared to the Natural Condition (mean difference score= 0.19 SD = 0.54) (see Table 4). Concerns about its adverse effects were also typically higher for the Pharmaceutical cream than the
Natural cream (mean difference score 0.20, SD = 0.50). However, there was variation in how participants perceived the placebos, with some participants having higher Concerns and higher perceived need for the Natural cream (see Figure 11).

![Figure 11: Frequency distributions for Specific Necessity (left) and Specific Concerns (right) difference scores.](image)

Participants expected less pain from the cold pressor task when they were given the cream (Pharmaceutical and Natural Conditions) than when they were not given a cream (No Placebo Condition). There was not a significant difference in expected pain between the Natural and Pharmaceutical Conditions. Overall, participants expected the Pharmaceutical Placebo to be more effective than the Natural Placebo (see Table 5).

<table>
<thead>
<tr>
<th>Condition Mean (SD)</th>
<th>No Placebo</th>
<th>Pharmaceutical</th>
<th>Natural</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necessity</td>
<td>--</td>
<td>3.35 (0.57)</td>
<td>3.16 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concerns</td>
<td>--</td>
<td>2.64 (0.62)</td>
<td>2.44 (0.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Efficacy Expectation</td>
<td>--</td>
<td>64.82 (16.60)</td>
<td>57.88 (16.60)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Expected Pain Intensity</td>
<td>67.08 (21.41)</td>
<td>47.07 (18.21)</td>
<td>50.21 (20.54)</td>
<td>&lt;0.001&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note: p values relate to paired t-tests. a = No Placebo – Pharmaceutical Condition, b = No Placebo – Natural Condition.

Most of our participants believed that the cream was, or could be an active drug; only 6 of our 168 participants thought the cream was definitely a placebo (Pharmaceutical Condition: mean = 51.90, SD = 23.77, Natural Condition: mean =
51.39, SD = 25.21). Furthermore, at least one side effect was reported by 38.2% of participants in the Pharmaceutical Condition and 32.3% of participants in the Natural Condition. Skin irritation was the most commonly endorsed side effect in both conditions (Pharmaceutical Condition: 16.1%, Natural Condition: 13.7%) and headache was the least common (0.6% in both conditions).

**Did I observe placebo effects?**

Paired t-tests were conducted comparing Pain Intensity (VAS, MPQ, and OPI) and Pain Tolerance in the Placebo Conditions to the No Placebo Condition to determine whether we observed a placebo effect.

Placebo effects were seen in both the Pharmaceutical and Natural Conditions. VAS Pain Intensity was significantly lower in both Placebo Conditions compared to No Placebo. Similarly, participants were able to tolerate the pain significantly longer in both the placebo conditions compared to the No Placebo Condition. There was no significant difference in Pain Tolerance or VAS Pain Intensity between the Natural and Pharmaceutical Conditions (see Table 6).

Participants reported lower MPQ Pain Intensity when they used the Natural Placebo than when they used No Placebo, but did not when they used the Pharmaceutical Placebo. No significant differences in MPQ Pain Intensity were observed between the Pharmaceutical Condition and the No Placebo Condition or Natural Condition, respectively (see Table 6).

| Table 6: Comparison of Pain Intensity and Pain Tolerance across conditions |
|---------------------------------|------------------|------------------|------------------|------|
| Condition Mean (SD)             |                  |                  |                  |     |
| **Pain Intensity:**             |                  |                  |                  |     |
| MPQ                             | 14.23 (8.32)     | 13.61 (7.73)     | 12.97 (7.51)     | <0.05<sup>b</sup> |
| VAS                             | 69.79 (18.68)    | 65.09 (18.21)    | 63.52 (19.68)    | <0.05<sup>a</sup>, <0.001<sup>b</sup> |
| OPI                             | 3.75 (0.96)      | 3.64 (0.84)      | 3.56 (0.89)      | <0.01<sup>b</sup> |
| **Pain Tolerance (seconds)**    | 55.07 (44.32)    | 61.63 (43.73)    | 63.63 (43.09)    | <0.05<sup>a</sup>, <0.05<sup>b</sup> |

Note: VAS = Visual Analogue Scale, MPQ = McGill Pain Questionnaire, OPI = Present Pain Intensity. p values refer to the results of paired t-tests. Statistical comparisons - a = No Placebo - Pharmaceutical, b = No Placebo – Natural
Hypothesis testing

Hypothesis 1: Variation in placebo effects in both conditions will be predicted by the participant’s Necessity beliefs.

Multiple Linear Regression showed that reduction in MPQ Pain Intensity Scores after each placebo were significantly related to Specific Necessity beliefs for each treatment (Pharmaceutical: F change (2,168) = 10.75, p < 0.01 vs Natural: F change (2,168) = 6.37, p < 0.05), confirming Hypothesis 1. Specific Necessity beliefs explained 6.1% (Pharmaceutical) and 6.9% (Natural) of the variation in MPQ Pain Intensity scores. Participants response increased by 0.25 and 0.19 units per unit increase in Necessity for the Pharmaceutical and Natural Conditions, respectively (see Table 7).

Scores on the Perceived Sensitivity to Medicines Scale (PSM – an aspect of pharmaceutical schema), explained 2.5% of the MPQ Placebo Effect in the Pharmaceutical Condition (F change (2, 168) = 4.17, p < 0.05) but not in the Natural Condition (p> 0.05). The MPQ Placebo Effect increased by 0.14 units per unit increase in PSM in the Pharmaceutical Condition (see Table 7). No other Treatment Beliefs were significant predictors of participants’ response (all p > 0.05).

The effect of Specific Necessity remained significant when Efficacy Expectations were included in the model (Pharmaceutical: F change (2,168) = 8.16, p < 0.01 Natural: F change (2,168) = 5.36, p < 0.05) Conditions (see Table 7 and Figure 12). Sociodemographics, Trait Anxiety, Depression and Affect also had no significant effect on this relationship (all p > 0.05).

Hypothesis 2: High pain catastrophizing will be associated with stronger Necessity beliefs and a larger placebo effect.

Responses to the Pharmaceutical and Natural Placebos were predicted by two of the three components of pain catastrophizing: Feelings of Helplessness (Pharmaceutical: F change (2,168) = 18.93, p < 0.05: 3% variance explained, Natural: F change (2,168) = 18.93, p < 0.05, 2% variance explained) and Magnification of Pain (Pharmaceutical: F change (2,168) = 4.05, p < 0.05, 1.5% variance explained, Natural: F change (2,168) = 6.23, p < 0.05, 2.6% variance explained, see Table 6). Rumination was not significantly related to MPQ Pain Intensity responses in either placebo condition (all p > 0.05).
As I found that personal need for the placebo cream and two components of pain catastrophizing significantly predicted the MPQ Placebo Effect, I investigated whether treatment necessity beliefs mediated the relationship between feelings of Helplessness and Magnification of Pain, and the MPQ Placebo Effect. Personal need for the placebo partially mediated the effect of Feelings of Helplessness on the MPQ Placebo Effect (Pharmaceutical Condition = Sobel test statistic: 2.26, p<0.05, Natural Condition = Sobel test statistic: 1.99, p<0.05). Personal need for the placebo did not significantly mediate the effect of Magnification of Pain on the MPQ Placebo Effect (p>0.05, see Table 7 and Figure 13 for statistics).
Table 7: The effect of a) Necessity b) Necessity while controlling for Efficacy Expectations, c) Magnification of Pain and feelings of Helplessness on the MPQ Placebo Effect and d) independent effects of Magnification of Pain and feelings of Helplessness on Necessity beliefs for each placebo

<table>
<thead>
<tr>
<th>Model</th>
<th>Condition</th>
<th>Pharmaceutical</th>
<th>Natural</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B [95% CI]</td>
<td>p</td>
<td>B [95% CI]</td>
</tr>
<tr>
<td>a)</td>
<td>Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>0.91 [0.67, 1.14]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Condition order</td>
<td>0.01 [-0.01, 0.01]</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Model 1: Baseline plus - Necessity</td>
<td>0.22 [0.09, 0.35]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>b)</td>
<td>Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Condition order</td>
<td>0.01 [-0.01, 0.01]</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Efficacy Expectation</td>
<td>0.01 [-0.01, 0.01]</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Model 1: Baseline plus - Necessity</td>
<td>0.21 [0.06, 0.35]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>c)</td>
<td>Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Condition order</td>
<td>0.01 [-0.01, 0.01]</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Model 1: Baseline plus - PCS: Magnification</td>
<td>0.04 [0.01, 0.08]</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Model 2: Baseline plus - PCS: Helplessness</td>
<td>0.03 [0.1, 0.05]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>d)</td>
<td>Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Condition order</td>
<td>0 [-0.01, 0.02]</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Model 1: Baseline plus - PCS: Magnification</td>
<td>0.01 [-0.04, 0.58]</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Model 1: Baseline plus - 2) PCS: Helplessness</td>
<td>0.03 [0.12, 0.57]</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Note: MPQ = McGill Pain Questionnaire, PCS = Pain Catastrophizing Scale
Figure 12: Relationship between the MPQ Placebo Effect and (a) Specific Necessity and (b) Necessity while controlling for Efficacy Expectations (95% CI).
Figure 13: Necessity significantly partially mediated the effect of Helplessness on the MPQ Placebo Effect but not Magnification of pain. Figure shows regression coefficients. *p<0.05, **p<0.01. PCS = Pain Catastrophizing.

Hypothesis 3: Specific Necessity will be differentially influenced by general pharmaceutical schema and general beliefs about complimentary medicine.

Pearson’s correlations were used to test for relationships between specific beliefs about the placebo, pharmaceutical schemas (general beliefs about medicines and PSM) and Beliefs about CAM (CAMBI). Pharmaceutical schemas influenced evaluations of the specific placebo treatments. Individuals were more likely to endorse the Necessity of the Pharmaceutical Placebo treatment if they believed that pharmaceutical medicines were intrinsically beneficial. Participants were more likely to reported greater Concerns about potential adverse effects of both the Pharmaceutical and Natural Placebos if they believed that pharmaceuticals are
intrinsically harmful (General-Harm) or believed they were particularly sensitive to the effects of medicines (PSM). Perceived need for the Natural Placebo was not influenced by participants' Pharmaceutical Schema. Finally, those who had more positive Beliefs about CAM were more likely to endorse the necessity of the Natural Placebo and report greater concerns about the Pharmaceutical Placebo (see Figure 14 for statistics).

Hypothesis 4: Negative pharmaceutical schema will be associated with more positive beliefs about complementary and natural remedies and preferences for this type of treatment.

A binomial test was used to determine whether there was a significant preference either the Natural or Pharmaceutical Placebo within our sample. There was an overall but non-significant preference for the Natural Placebo (54.49%, p > 0.05). Independent t-tests were conducted to determine whether there were significant differences in Treatment Beliefs and Beliefs about CAM between those who would prefer to use the Natural Placebo and those who would prefer to use the Pharmaceutical Placebo in a real health situation. Those who preferred to use the Natural Placebo tended to believe that pharmaceuticals were less beneficial, more intrinsically harmful and overused and had higher PSM than those who preferred to use the Pharmaceutical Placebo. Those who preferred to use the Natural Placebo
also had significantly higher Concerns about the Pharmaceutical Placebo and more positive beliefs about CAM than those who preferred to use the Pharmaceutical Placebo (see Table 8 for statistics).

Independent t-tests were conducted to determine whether Pain Intensity in response to each placebo was different for those who preferred the Natural vs. Pharmaceutical Placebo. I found that Pain Intensity in response to the Pharmaceutical Placebo was significantly lower in participants who preferred the Pharmaceutical over the Natural Placebo than vice versa (Pharmaceutical: mean reduction = 0.99, SD = 0.27, Natural: mean reduction = 0.01, SD = 0.42, t(167) = 1.93, p < 0.05). No significant difference in Pain Intensity was found in response to the Natural Placebo in those who preferred Natural vs Pharmaceutical Placebo (p > 0.05).

Table 8: Comparison of Treatment Beliefs and beliefs about CAM between those who preferred to use the Pharmaceutical vs. Natural Placebo

<table>
<thead>
<tr>
<th>Preference for:</th>
<th>Pharmaceutical Placebo</th>
<th>Natural Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Benefit</td>
<td>4.08 (0.39)</td>
<td>3.90 (0.48)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>General Harm</td>
<td>2.08 (0.58)</td>
<td>2.54 (0.56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>General Overuse</td>
<td>2.97 (0.70)</td>
<td>3.38 (0.71)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PSM</td>
<td>1.89 (0.53)</td>
<td>2.18 (0.59)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Pharmaceutical Placebo : Necessity</td>
<td>3.41 (0.53)</td>
<td>3.30 (0.65)</td>
<td>0.250</td>
</tr>
<tr>
<td>Pharmaceutical Placebo : Concerns</td>
<td>2.45 (0.53)</td>
<td>2.81 (0.61)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Natural Placebo: Necessity</td>
<td>3.12 (0.59)</td>
<td>3.19 (0.61)</td>
<td>0.458</td>
</tr>
<tr>
<td>Natural Placebo: Concerns</td>
<td>2.37 (0.51)</td>
<td>2.50 (0.57)</td>
<td>0.153</td>
</tr>
<tr>
<td>CAMBI: Holistic Health</td>
<td>14.50 (3.70)</td>
<td>16.18 (3.76)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CAMBI: Holistic Treatment</td>
<td>19.70 (3.76)</td>
<td>21.45 (3.78)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CAMBI: Natural Treatment</td>
<td>15.73 (4.11)</td>
<td>18.91 (4.34)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Note: an adjusted p-value of 0.005 was used to test for multiple comparisons. PSM = Perceived Sensitivity to Medicines, CAMBI = Complementary and Alternative Medicines Belief Inventory
5.4 Discussion

This study confirmed my first research question suggesting that there is a causal relationship between treatment beliefs and the placebo effect. Pain tolerance was significantly higher in both placebo conditions compared to the no placebo condition. Pain intensity in the natural placebo condition was significantly lower compared to no placebo. However there was no significant difference in pain intensity between the pharmaceutical placebo condition and the natural placebo condition or no placebo. I then showed that variations in pain intensity in the pharmaceutical and natural condition were associated with prospectively measured treatment necessity beliefs. Stronger beliefs in the personal need for the treatment predicted larger placebo effects for both pharmaceutical and natural placebos.

Feelings of helplessness and magnification of pain were positively associated with placebo-mediated reductions in pain intensity. Further analysis then showed that treatment Necessity beliefs partially mediated the effects of feelings of helplessness on the placebo effect. Finally I showed that perceptions about pharmaceutical medicines in relation to self (PSM) were associated with changes in pain intensity in the pharmaceutical condition but not the natural condition. That is, the more sensitive participants felt they were to the effects of pharmaceutical medicines, the larger the reduction in pain intensity after using the pharmaceutical placebo.

Treatment necessity beliefs and the placebo effect

This study showed a linear relationship between treatment necessity beliefs about each ‘treatment’ and the placebo effect. This result expands current placebo literature as it shows that placebo effects are susceptible to more complex and diverse beliefs than simple efficacy expectations. Theory suggests that efficacy expectation are likely to contribute to treatment necessity beliefs, however these two constructs are not synonymous (Cameron & Leventhal, 2003). For example, one study showed that 25% of the variance in perceived need of anti-retroviral medication was due to efficacy expectations (Horne et al., 2002). This result was reflected in the current study which found efficacy expectations were significantly positively correlated with treatment necessity beliefs in each condition. Unfortunately I found no significant effect of efficacy expectations on the placebo effect, therefore I cannot determine the variance explained by treatment necessity beliefs when controlling for such expectations.
It is possible that I did not find a significant effect of expectations (efficacy expectations and expected pain intensity) because I did not manipulate expectations directly. Expectation manipulations usually involve inducing different expectancies of efficacy or symptom severity after placebo administration (Schmid et al., 2013; Vase, Robinson, Verne, & Price, 2003). In this study, participants were told that both medicines would be “highly effective”. This may be why I found no effect of expectations on the placebo effect.

In accordance with the Extended Model of Self-Regulation (Horne, 2003), representations about the health threat (feelings of helplessness) informed perceptions about the treatment (necessity beliefs). Furthermore, I found that in a similar fashion to how treatment necessity beliefs mediate the effect of illness representations on adherence (Horne & Weinman, 2002), treatment necessity beliefs also partially mediated the effect of feelings of helplessness on the placebo effect. This result suggests that in addition to more complex beliefs such as necessity and PSM, perceptions about health threats may also contribute to placebo effects.

**Perceived sensitivity to medicines and the placebo effect**

I also showed for the first time an association between PSM and the placebo effect. Previous research has shown that perceptions about how sensitive one is to the effects of medicines is associated with side effect reports. A recent study found that participants receiving a vaccination, those with higher PSM scores attributed a greater number of symptoms to the vaccine (Horne, Faasse, et al., 2013b). Interestingly, I found that the association between PSM and the placebo effect was only significant in the pharmaceutical condition but not the natural condition. Therefore, although pharmaceutical schema may inform specific evaluations of placebos described as pharmaceutical and natural, their effects on the placebo effect may be stronger when a pharmaceutical description is given than natural.

**Relationship between specific beliefs about medicines and pharmaceutical schema**

In common with previous studies I found that specific treatment evaluations were informed by more general beliefs about medicines (Chapman, Horne, Chater, Hukins, & Smithson, 2013; Horne et al., 1999a). However, there was a differential effect of these general beliefs depending on how the placebo cream was described. Pharmaceutical schema informed treatment necessity beliefs when the placebo was
described as “pharmaceutical” whereas general beliefs about CAM informed treatment necessity beliefs when the placebo was described as “natural”. This suggests that the influence of one’s pharmaceutical schema on how specific treatments are evaluated may not be as strong in treatments which are not considered typical pharmaceuticals. Finally, consistent with previous studies, preference for the Natural Placebo was associated with more negative pharmaceutical schema, greater concerns about the Pharmaceutical Placebo and more positive general beliefs about CAM (Bishop et al., 2005; Green et al., 2013).

**Strengths and weaknesses**

This study had a number of limitations. Firstly, this study had a within subject design therefore habituation may have influenced pain reports. However, I minimised the effect of habituation by randomising condition order and hand order and keeping the water bath within ±0.03ºC of 2ºC. I also allowed participants hands to reacclimatise back to room temperature between each condition. Neither I nor the participants were blinded thus my results may have been influenced by experimenter and observer bias. However, I tried to experimenter bias was kept to a minimum by keeping the study protocol constant for each participant i.e. ensuring participants only received information about each placebo from the patient information leaflet. Observer bias was kept to a minimum by conducting the experiment in a private room, remaining out of view when participants undergo each cold pressor task and keeping instructions about the experiment constant. Secondly, my sample consisted of healthy, highly educated and young students which limit the generalizability of my results to a wider population. Furthermore, the majority of my sample had generally positive pharmaceutical schema thus I cannot determine how other samples with more negative schema would have responded.

Pain scores were reflective of the magnitude of pain observed in a number of untreated pain conditions such as chronic pain and diabetic neuropathy (Grafton, Foster, & Wright, 2005; Rosenstock, Tuchman, LaMoreaux, & Sharma, 2004; Woods & Asmundson, 2008). Differences in pain scores between the two placebo conditions and no placebo were also of a similar magnitude to previous placebo studies using the cold pressor task (Geers et al., 2010; Rose et al., 2012; Staats, Staats, & Hekmat, 2001). My manipulation check revealed that the results could not be simply due to bias. Most of my sample believed both placebo creams were active medication. Furthermore, around a third of my participants reported side effect and thus supports the effectiveness of my manipulation. Finally, I recruited a large
sample size for a within-subject design. This maximised statistical power and reduced the effect of individual differences on my result.

**Implications**

In this study I showed that beliefs about pharmaceutical medicines and natural remedies influence the placebo effect. There are many medicines currently used in clinical practice which are derived from natural sources. For example, capsaicin is an analgesic derived from the plant *Capsicum annum* and galantamine derived from *Galanthus caucasicus*, is used for Alzheimer’s disease (Mason, Moore, Derry, Edwards, & McQuay, 2004; Wilcock, Lilienfeld, & Gaens, 2000). As I found that specific evaluations about the placebo medication differed depending on how it was described, examining treatment beliefs in clinical practice and providing tailored medicinal information may provide a way to utilise these effects.

As this study is a laboratory experiment with healthy volunteers, I cannot determine how treatment beliefs change depending on how patients evaluate the effect of their medication as their symptoms increase/decrease. The pain experienced in my study is much more predictable than the pain experienced by patients with long-term conditions for example. Furthermore, patients’ symptoms can carry serious consequences compared to the acute pain experienced in the cold pressor task. Evaluations of treatment necessity and how they influence the placebo effect may differ in a clinical sample. Further research is now required to determine the temporal and longitudinal relationship between treatment beliefs and the placebo effect in clinical conditions.

**Conclusion**

This study answered the following outstanding research question: Do treatment beliefs predict the placebo effect? Prospectively measured treatment necessity beliefs were positively associated with the magnitude of the placebo effect, an effect which was influenced by more general beliefs about pharmaceuticals and complementary and alternative medicines, depending on how the placebo was described. Further research is required to confirm these results in a clinical sample and to determine whether treatment beliefs and in turn the placebo effect are modifiable.
6. The effect of patients’ illness representations and pharmaceutical schema on the placebo effect in GORD and LPR

6.1 Background and research question

In the previous study I showed a relationship between prospectively measured treatment beliefs and variations in the placebo effect. Are beliefs about one’s condition also associated with this phenomenon? In an opportunistic study, using a sample of GORD and LPR patients, I assessed whether the effect of saline applied directly to the oesophagus can be therapeutic or not depending on how it is represented to the patient (described as neutral vs. therapeutic). I then examined whether representations of GORD and LPR influence the magnitude of this therapeutic effect.

GORD and LPR are highly prevalent in the western population with up to 30% of individuals suffering from these conditions (Fass, 2007). Symptoms of GORD include heartburn and regurgitation, whereas symptoms of LPR typically experience symptoms such as globus and difficulty swallowing. It is thought that the cause of these symptoms are due to abnormal acid oesophageal acid exposure, however, many patients can report symptoms even though acid exposure in their oesophagus is within the normal physiological range (True Reflux vs. Non-Reflux) (Martinez, Malagon, Garewal, Cui, & Fass, 2003; Shi, Bruley des Varannes, Scarpignato, Le Rhun, & Galmiche, 1995). Typically, patients are treated with acid suppressant therapy (e.g. PPI medication); however, their effectiveness is highly variable. In GORD, PPI’s have been shown to be highly effective in patients with true reflux; however, in the absence of abnormal acid exposure they are less effective (Lind et al., 1997). Furthermore, their effectiveness in treating LPR has shown disappointing results (Qadeer et al., 2006).

Patients typically undergo a 24-hour ambulatory pH and impedance test for diagnosis, which demonstrates the amount of acid reflux in the oesophagus. This has become the gold standard for diagnosing GORD, however, this approach for diagnosing LPR remains controversial (Noordzij et al., 2002; Vaezi, Hicks, Abelson, & Richter, 2003). Before this test became available, patients typically underwent a Bernstein test to determine whether their symptoms were acid related. This test...
involved the blind perfusion of 0.1N hydrochloric acid and saline. If patients reported heightened symptomology in response to the acid perfusion but not to saline then a positive diagnosis was made. Some patients however also reported heightened symptomology in response to the saline perfusion. As saline has no chemical stimulatory effect, it is believed that there must be other mechanisms at play here. It has been suggested that this could be due to hypersensitivity, i.e. some form of autonomic nerve dysfunction, or due to psychological factors (Bernstein & Baker, 1958)(Trimble, Pryde, & Heading, 1995)(Fass et al., 2008).

Psychological factors have been associated with the perception of GORD symptoms. It is thought that psychological factors may cause patients to perceive low intensity somatic stimuli as painful (Trimble et al., 1995). For example anxiety has been linked to an increase in perceived symptom severity but not with increased oesophageal acid exposure (Fass et al., 2008). Stress on the other hand has been associated with both an increase and decrease in perceived GORD symptom severity. While large placebo effects have been observed in clinical trials of GORD treatment (Cremonini et al., 2010), there have been no studies assessing predictors of the placebo effect in patients with GORD or LPR.

Previous research has investigated the effects of treatment beliefs on treatment decisions (medication vs. surgery) and adherence in GORD patients (Cassell et al., 2015; Francis, Wileman, Bekker, Barton, Ramsay, & Group, 2009), but their relationship with the placebo effect has yet to be examined in GORD or LPR. Similarly, as discussed in section 2.6.3, previous research has shown that illness representations are associated with symptom perception in other GI disorders such as IBS and may be involved in treatment response. However, to date there have been no studies investigating such effects in patients with upper-gastrointestinal symptoms.

From a clinical perspective, understanding 1) whether this heightened symptomatic response to saline can be modified by framing and 2) what psychological factors are involved in this process would have important implications in the management of these conditions. It would show that how information about treatment and illness is described influences symptomatic responses and would indicate potential psychological factors which could be targeted in interventions to improve clinical outcomes.

This will be examined using a modified Bernstein test during patients’ routine oesophageal examination. A requirement for their oesophageal examination is for
patients to stop taking any acid-suppressant medication a week prior. This is because the 24-hour ambulatory pH test is designed to assess the relationship between excessive oesophageal acid exposure and the occurrence of symptoms. If patients were on their medication, any excessive acid production by the stomach would be suppressed, leading to a false negative test result.

As this experiment would be conducted immediately before their 24-hour ambulatory pH test it was decided that describing the placebo saline as a medication may create difficulties between the patient and the clinical team. While I was designing this study I shadowed a number of clinicians conducting usual care for these patients. Many patients found it difficult to live without their medication for a week as they were unable to eat without regurgitating food. Thus, it would have been unethical to ask these patients to take part in a study assessing the effect of a medication on their symptoms after they were instructed to stop taking their medication specifically for the 24-hour ambulatory pH test. It was decided that it was best to describe the saline as a “natural way to remove acid”. Considering my results from Study 1, I found no significant effect of participants’ pharmaceutical schema on responses to the “natural” placebo. Pharmaceutical schema was therefore measured in this study to confirm this result.

Using a modified Bernstein test, this study aimed to determine whether illness representations and treatment beliefs were associated with participants' pain intensity in response to saline described as therapeutic. In two conditions, saline was perfused into the oesophagus via a catheter with different information about its effects presented (Neutral Label vs. Therapeutic Label). Hypotheses:

Hypothesis 1: Describing the saline as therapeutic compared to neutral will lead to a significant reduction in pain intensity.

Hypothesis 2: Reductions in pain intensity in response the Therapeutic Label will be greater in those who have more positive representations of their condition.

Hypothesis 3: Pharmaceutical schema will have no significant effect on pain intensity in response to the Therapeutic Label.

Hypothesis 4: Reductions in pain intensity in response the Therapeutic Label will be greater in those who have more positive expectations (high efficacy expectation, low expected pain intensity, low saline-related anxiety).

This study also explored:
1. The relationship between clinical factors (True Reflux vs. Non Reflux, GORD vs. LPR) and participants’ state/trait psychological variables (trait anxiety, depression, somatization, affect and perceived stress) on Pain Intensity in response to each label.

2. Differences in treatment beliefs, illness representations and other psychological factors (trait anxiety, depression, somatization, perceived stress and affect) in patients with True Reflux vs. Non-Reflux and those with GORD vs. LPR.
6.2 Method and materials

This study gained ethical approval from the NHS Queen Square Research Ethics Committee (ref: 14/LO/0593, see Appendix C). The study had a within subject design where participants completed two conditions in a random order: Neutral Label and Therapeutic Label. It was conducted at the GI Physiology Unit, University College London Hospital (UCLH) between June 2014 and August 2015.

Sample, recruitment procedure and consent

The sample size for the primary aim was calculated using a repeated measures ANOVA (within-between interaction), a power of 80% and a significance of level of 5% (G*Power v3.1.9.2). A partial ETA of 0.08 (condition by expectation interaction) was taken from a study assessed the effects of expectations on the placebo effect (Geers, Weiland, Kosbab, Landry, & Helfer, 2005). This calculation estimated a sample of 24 was required. However, due to a) the smaller frequency of LPR patients coming into the clinic (~25%) and b) the study assessing a number of predictor variables on patients pain responses, a target sample size of at least 100 was needed to ensure I met the sample size for both patient groups. One hundred and thirty six patients were recruited in total.

A recruitment letter and information sheet was sent to potential participants by post at least a week prior to the study day if their medical notes met the inclusion criteria and exclusion criteria. When potential participants came into the clinic for their routine physiology assessment they were provided with another copy of the information sheet and enrolled into the study if they provided informed consent. Inclusion criteria were a clinical diagnosis of LPR or GORD with symptoms severe enough to warrant intervention, previous use of prescribed PPI medication, age over 18 years and with sufficient understanding of written and spoken English. Exclusion criteria were a diagnosis of Barrett’s oesophagus, LA grade C or D oesophagitis, achalasia or any symptomatic oesophageal dysmotility. Anyone with any condition or cognitive impairment which meant they could not give informed consent was not recruited (e.g. dementia). Participants were paid £5 to take part. The experimental protocol took 30 minutes to complete over and above the standard planned physiological assessment.
Measures

The following measures were used in this study. Details about measures used throughout this thesis can be found in section 4 with their Cronbach’s alphas in Table 9. Measures specific to this study are described in detail below.

Table 9: Cronbach’s alphas for the BMQ-G, PSM, STAI-T, PHQ-9 and PANAS

<table>
<thead>
<tr>
<th>Measure</th>
<th>Subscale</th>
<th>Cronbach’s Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ-G (Horne et al., 1999b)</td>
<td>General Benefit</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>General Harm</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>General Overuse</td>
<td>0.74</td>
</tr>
<tr>
<td>PSM (Horne, Faasse, et al., 2013b)</td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>STAI-T: Trait Anxiety (Spielberger, 1983)</td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>PHQ-9: Depression (Kroenke et al., 2001)</td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>PANAS: Positive and Negative Affect (Watson et al., 1988)</td>
<td>Positive Affect</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>Negative Affect</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Note: BMQ-G = Beliefs about Medicines Questionnaire – General, PSM = Perceived Sensitivity to Medicines Questionnaire, STAI-T = State Trait Anxiety Inventory – Trait, PHQ-9 = Patient Health Questionnaire – 9, PANAS = Positive and Negative Affect Schedule.

Brief Illness Perceptions Questionnaire (B-IPQ) (Broadbent, Petrie, Main, & Weinman, 2006)

The B-IPQ is comprised of a 9-item scale used to assess participant’s cognitive and emotional representations of illness. This measure has demonstrated good validity and reliability in a number of conditions (Broadbent et al., 2006) and showed adequate internal consistency (α = 0.62). For the first 8 items participants are asked about their views about their illness (e.g. “How concerned are you about your illness?”) and respond using a 10-point Likert-type scale (e.g. 0 = not concerned at all to 10 = extremely concerned). A total score was calculated by adding the score from items 1-8 (items 3, 4 and 7 reversed scored). Higher scores represent a more threatening view of their illness. For the final item participants are asked to list in rank-order the three most important factors that they believed caused their illness.

Sociodemographics and medical history

The clinical notes and history taking identified the patients’ age, gender, ethnicity, their first language and educational level. Participants were asked about previous medical conditions, medication use, smoking status and alcohol intake.
Reflux Symptom Index (RSI) (Belafsky, Postma, & Koufman, 2002)

The RSI is a nine-item questionnaire for the assessment of symptoms in patients with GORD and LPR while on their medication. This questionnaire has shown to have validity (Belafsky et al., 2002) and showed excellent internal consistency in this sample (α = 0.81). For each item (e.g. throat clearing) participants rated how much each symptom affected them (0 = No problem to 5 = Severe problem). A total score is calculated by adding the scores from each item. Higher scores indicate more severe symptoms.

Participants were also asked to indicate their most and second most troublesome symptom within the last month (Primary and Secondary Symptom). Participants were defined as having GORD or LPR depending on their Primary Symptom:

GORD
- Heartburn
- Acid regurgitation
- Chest pain
- Epigastric pain
- Abdominal bloating

LPR
- Cough
- Difficulty swallowing
- Choking
- Globus
- Hoarseness
- Post-nasal drip
- Throat clearing
- Retching

Somatisation - Patient Health Questionnaire – 15 (PHQ-15) (Kroenke, Spitzer, & Williams, 2002)

The PHQ-15 is a 15-item questionnaire measuring somatisation – the tendency to report medical symptoms in the absence of any physical cause. This measure has shown to be valid and reliable in patients with a variety of conditions (Kroenke et al., 2002) and has excellent internal consistency (α = 0.86). Participants are asked to
indicate how bothered they have been by 15 symptoms (e.g. stomach pain, headache) over the past 4 weeks from 0 = not bothered at all to 2 = bothered a lot. A total score is calculated by adding the score from each item. Higher scores indicate more severe somatisation disorder.

Perceived Stress Scale (PSS) (Cohen, 1988)

This 10-item scale was used to measure perceived stress. The scale showed good internal consistency (α = 0.86), has been validated and is reliable (Cohen, 1988). Participants were asked to respond to 10 questions asking their thoughts and feelings over the past month (e.g. “In the last month, how often have you felt nervous or “stressed?”). For each question, participants responded using a 5-point Likert-type scale from 0 = never to 4 = very often. A total score is calculated by adding the score from each item together.

Baseline Pain Intensity (VAS)

Participants were asked to rate how intense any symptom-related pain was using a VAS from 0 = no pain to 100 = worst possible pain.

Efficacy Expectation, Expected Pain Intensity and Saline-Related Anxiety (VAS)

For each solution participants were asked to rate their Expected Pain Intensity (0 = no pain to 100 = worst possible pain), Efficacy Expectation (0 = not effective at all to 100 = highly effective) and how anxious they were about the effects of the solution (Saline-Related Anxiety: 0 = not anxious at all to 100 = extremely anxious) using VAS.

Short Form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987)

The SF-MPQ measures Pain Intensity using a visual analogue scale (VAS, 0 = Least possible pain, 100 = Worst possible pain), and Multidimensional Pain Intensity scale (MPQ) using 11 items assessing sensory pain and 4 items assessing affective pain. For each MPQ item, participants rated how much of that quality (e.g. sharp) their pain had from 0 = none to 3 = severe. The scale showed poor internal consistency for each condition (Neutral Condition α = 0.40, Therapeutic Perfusion α = 0.41) however due to the heterogeneity of symptoms across our sample we were not expecting participants responses to show high consistency. Total scores for each scale were calculated by adding the score from each item. Participants also
completed the Overall Pain Intensity measure (OPI) where they are asked to rate their overall pain intensity from $0 =$ no pain to $5 =$ excruciating.

**High Resolution Manometry (HRM)**

Participants completed HRM as part of their usual care. This test involves inserting a catheter down the oesophagus, resting just past the lower oesophageal sphincter (LOS, see Figure 15) (van Hoeij & Bredenoord, 2016). Along the catheter are pressure sensors, allowing clinicians to study motor function from the throat down to the LOS. Data from this test was used to identify any participants who had specific oesophageal dysmotility such as achalasia, Nutcracker’s oesophagus, or diffuse oesophageal spasm. Peristalsis is affected in these conditions where contraction of the oesophageal smooth muscle is abnormal. For example, Nutcracker’s oesophagus is characterized by contraction of oesophageal smooth muscle in a normal sequence but for a longer duration or excessive amplitude. This leads to difficulty swallowing and problems clearing acid back into the stomach (van Hoeij & Bredenoord, 2016). Any participants who exhibited such dysmotility were excluded from the analysis.

![HRM catheter](image_url)

*Figure 15: HRM catheter used to examine specific oesophageal dysmotility.*
Conditions

Depending on the condition participants were presented with a message:

Neutral Label –

“A liquid will be poured into your gullet through the plastic tube which will mimic your body’s normal response to food or drink. This liquid should not change any heartburn/pain you are feeling at this moment. This means you should feel nothing, or at most a gentle tingling, in response to this solution.”

Therapeutic Label -

“A liquid will be poured into your gullet through the plastic tube which will mimic the body’s natural way of removing acid. This liquid should soothe any heartburn/pain you are feeling at this moment. This means you should feel better, or at least some slight relief in response to this solution.”

A within-subject design was deemed the most appropriate for this study due to the high variability in the clinical presentation of GORD and LPR symptoms. A between-subject design would likely lead to high variability in symptoms and responses across independent and dependant variables.

Modified Bernstein Test

The HRM catheter was pulled out so that the tip sat 7cm above the superior border of the LOS. Physiological saline was administered in each condition at a rate of 6.7ml/min for 5 minutes.

24-hour ambulatory oesophageal pH and impedance recording

The 24-hour impedance test (usual care) is a physiological test to demonstrate the amount of acid reflux in the distal oesophagus. This test also requires insertion of a catheter into the oesophagus. Along the length of the catheter are a number of pH sensors which record the levels of oesophageal acid during a 24 hour period. The catheter is attached to a recording device which patients wear on their belt. This recording device also has a number of buttons which patients are asked to press to monitor their normal activity – when they experience a symptom, when they start and stop eating meals and when they go to bed. This allows clinicians to 1)
determine whether there are abnormal levels of acid within the oesophagus and 2) determine whether patients' symptoms are associated with changes in oesophageal pH (Ravi & Katzka, 2016). Data from this test was used to determine whether participants had True Reflux or Non-Reflux (Hypersensitive or Functional Heartburn). True Reflux was defined if the total percentage of time pH<4 is more than 5% during the 24-hour pH test.

Procedure

Participants provided informed consent before medical history was taken and then completed the Baseline Measures. HRM was then performed as part of their usual care. Participants then completed the baseline measures. They were then exposed to each condition in a randomized order. Randomization was determined for each participant before they came in for the experiment using an online randomizer (unblind using www.randomizer.org). In each condition, participants read the Condition Specific Message then completed measures for Expectations about the saline. The saline was then perfused for 5 minutes. Immediately after perfusion, participants completed the SF-MPQ. Once all conditions had been completed participants were fully debriefed. Finally, participants completed the 24-hour impedance test as part of their usual care (see Figure 16 for procedure).
Figure 16: Study procedure. BMQ-G = Beliefs about Medicines Questionnaire – General, RSI = Reflux Symptom Index, B-IPQ = Brief Illness Perceptions Questionnaire, PHQ-9 = Patient Health Questionnaire – 9, PHQ-15 = Patient Health Questionnaire – 15, STAI-T = State Trait Anxiety Inventory Questionnaire – Trait, PANAS = Positive and Negative Affect Schedule, PSS = Perceived Stress Scale, HRM = High Resolution Manometry.
Statistical analysis

Pearson’s correlations were used to determine significant correlations between treatment beliefs and expectations about the saline solution. Paired t-tests and Wilcoxon-signed rank test were used to determine whether expectations and pain scores differed across conditions. Expectations scores (Efficacy Expectation, Expected Pain Intensity and Saline-Related Anxiety) about the Therapeutic Label were subtracted from those in the Neutral Label to create expectation difference scores for subsequent analyses. VAS Pain Intensity scores in each condition were subtracted from the baseline pain intensity to obtain a change in VAS Pain Severity for the Neutral and Therapeutic Label. Repeated measures ANOVA were conducted to determine whether a) illness representations, b) pharmaceutical schema c) expectations, d) other psychological factors and e) clinical factors were associated with Pain Intensity scores. The VAS Pain Intensity outcome variable was used for the main analysis as this was measured at baseline and due to the poor internal validity of the MPQ scale. Paired t-tests and Wilcoxon-signed rank tests were conducted to determine whether sociodemographics and baseline measures differed across patient subgroups (true reflux vs. non-reflux, GORD vs. LPR). Analyses were conducted using IBM SPSS Statistics v21.
6.3 Results

Out of 177 patients who were invited to take part in the study, 22 did not want to take part and 18 could not tolerate the HRM catheter. Four participants who did take part were excluded from the results because their HRM results revealed specific oesophageal dysmotility. One hundred and thirty six participants were included in the analysis.

Sociodemographics

The mean age of participants was 48.77 years and the majority were female (60.6%), white British/American/European (70.6%), had a university degree or higher (38.2%) and spoke English as their first language (79.4%, see Table 10).

Table 10: Sociodemographics

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.77 (14.83)</td>
</tr>
<tr>
<td>Female</td>
<td>80 (60.6)</td>
</tr>
<tr>
<td>Educational level:</td>
<td></td>
</tr>
<tr>
<td>Secondary School</td>
<td>32 (23.5)</td>
</tr>
<tr>
<td>College/6th Form</td>
<td>35 (25.7)</td>
</tr>
<tr>
<td>University Degree</td>
<td>52 (38.2)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White British/American/European</td>
<td>96 (70.6)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (29.4)</td>
</tr>
<tr>
<td>First Language</td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>108 (79.4)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (20.5)</td>
</tr>
</tbody>
</table>

Clinical characteristics

Most of the sample had GORD (58.10%) while 41.90% had LPR. Of those who reported a GORD-related symptom (heartburn, regurgitation, bloating, nausea and chest pain) as their primary symptom (58.10%), 24-hour impedance results revealed 44 had excessive reflux (True Reflux i.e. total percentage of time pH<4 is greater than 5%) and 35 did not exhibit excessive reflux (Non-Reflux). Of those who reported an LPR-related symptom (hoarseness, throat problems, difficulty swallowing and breathing, choking issues and a troublesome cough) as their primary symptom (41.90%), 29 were defined as having True Reflux and 28 Non-
Reflux (see Table 11). Just under two-thirds of the sample was experiencing symptoms at the time of the study (62.24%).

<table>
<thead>
<tr>
<th>Table 11: Clinical characteristics</th>
<th>n (%)</th>
<th>Mean RSI score (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GORD-related Primary Symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True reflux</td>
<td>44 (56)</td>
<td>11.31 (7.38)</td>
</tr>
<tr>
<td>Non-reflux</td>
<td>35 (44)</td>
<td>15.52 (8.76)</td>
</tr>
<tr>
<td>LPR-related Primary Symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True reflux</td>
<td>29 (51)</td>
<td>20.69 (10.28)</td>
</tr>
<tr>
<td>Non-reflux</td>
<td>28 (49)</td>
<td>18.52 (11.22)</td>
</tr>
</tbody>
</table>

Note: GORD = Gastro-oesophageal reflux disease, LPR = Laryngopharyngeal reflux disease

Baseline measures

Pharmaceutical Schema and Perceived PPI Efficacy

The majority of participants were accepting of the need for PPI medication, scoring above the scale mid-point (PPI Necessity: 53.30%, Mean = 2.93, SD = 0.73), and expressed low concerns for their PPI medication, scoring below the scale mid-point (PPI Concerns: 63.30%, Mean = 2.65, SD = 0.73). The majority also expressed strong beliefs about the benefit of medicines in general but also believed they are generally overused by doctors (General Benefit: 96.00%, Mean = 3.90, SD = 0.52, General Overuse: 69.1%, Mean = 3.10, SD = 0.69). Furthermore, most expressed low beliefs about the harmfulness of medicines in general and low beliefs about personal sensitivity to the effects of medicines (General Harm: 24.40%, Mean = 2.30, SD = 0.66, PSM: 39.80%, Mean = 2.72, SD = 0.81). Finally, most participants viewed their PPI medication as effective scoring above the scale mid-point (Perceived PPI Efficacy: 52.50%, Mean = 45.98, SD = 29.06, see Table 12).
Table 12: Pharmaceutical Schema and Perceived PPI Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI Necessity</td>
<td>2.93 (0.73)</td>
</tr>
<tr>
<td>PPI Concerns</td>
<td>2.65 (0.73)</td>
</tr>
<tr>
<td>General Benefit</td>
<td>3.90 (0.52)</td>
</tr>
<tr>
<td>General Harm</td>
<td>2.25 (0.52)</td>
</tr>
<tr>
<td>General Overuse</td>
<td>3.10 (0.69*)</td>
</tr>
<tr>
<td>PSM</td>
<td>2.73 (0.81)</td>
</tr>
<tr>
<td>Perceived PPI Efficacy</td>
<td>45.97 (29.06)</td>
</tr>
</tbody>
</table>

Note: PPI = Proton Pump Inhibitor, PSM = Perceived Sensitivity to Medicines

**Illness Representations**

Based on the Brief-Illness Perceptions Questionnaire (B-IPQ), 50% believed their illness severely affects their life (Consequences), 45% believed that their illness will continue for a long time (Timeline) and 47% believed that there was little that can be done to improve their illness (Personal Control). Forty four percent believed that treatment can be effective in curing their condition (Treatment Control), 47% of participants experience many severe symptoms from their illness (Identity) and 56% had high concerns about their illness (Concerns). Finally, 56% believed they understood their condition and 49% reported their illness affects them emotionally (Emotional Representation, see Table 13).

Table 13: Beliefs about GORD/LPR

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>% Low / High (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consequences</td>
<td>6.69 (2.36)</td>
<td>50 (68) / 50 (68)</td>
</tr>
<tr>
<td>Timeline</td>
<td>7.18 (2.24)</td>
<td>55 (75) / 45 (61)</td>
</tr>
<tr>
<td>Personal Control</td>
<td>4.75 (3.00)</td>
<td>53 (72) / 47 (64)</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>6.22 (2.47)</td>
<td>56 (76) / 44 (60)</td>
</tr>
<tr>
<td>Identity</td>
<td>7.34 (1.98)</td>
<td>53 (72) / 47 (64)</td>
</tr>
<tr>
<td>Concern</td>
<td>7.46 (2.36)</td>
<td>44 (60) / 56 (76)</td>
</tr>
<tr>
<td>Coherence</td>
<td>6.06 (2.85)</td>
<td>44 (60) / 56 (76)</td>
</tr>
<tr>
<td>Emotional Representation</td>
<td>5.84 (2.89)</td>
<td>51 (69) / 49 (67)</td>
</tr>
</tbody>
</table>

Note: Low / High based on median split of scores for each item. GORD = gastro-oesophageal reflux disease, LPR = laryngo-pharyngeal reflux disease
Other Psychological Factors

The sample demonstrated mild to moderate levels of trait anxiety, depression, negative affect, and somatization, with high levels of positive affect and perceived stress (see Table 14).

<table>
<thead>
<tr>
<th>Table 14: Other Psychological Variables</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Affect</td>
<td>29.44 (9.10)</td>
</tr>
<tr>
<td>Negative Affect</td>
<td>16.34 (6.22)</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>40.69 (9.36)</td>
</tr>
<tr>
<td>Perceived Stress</td>
<td>18.21 (5.50)</td>
</tr>
<tr>
<td>Somatisation</td>
<td>11.16 (5.77)</td>
</tr>
<tr>
<td>Depression</td>
<td>7.32 (3-9)</td>
</tr>
</tbody>
</table>

Relationship between participants’ treatment beliefs and expectations about the saline solution

Participants’ specific evaluations about their PPI medication were informed by their pharmaceutical schema. Participants expressed greater perceived need for their PPI medication if they had strong concerns about their potential harm, believed pharmaceutical medicines in general were beneficial and believed their PPI medication was effective. Participants expressed greater concerns about their PPI medication if they believed pharmaceuticals were harmful, were not beneficial generally overused, and if they believed they were particularly sensitive to the effects of medicines.

Participants were more likely to report greater Efficacy Expectations about the saline solution if they expected less pain after saline administration or if they were not particularly anxious about the effects of the saline solution (see Figure 17 for statistics). No significant relationships were observed between participants’ treatment beliefs and expectations about the saline solution.
Figure 17: Significant relationship between treatment beliefs and expectations about the saline solution. * p < 0.05, ** < 0.01.

**Were the messages convincing? Manipulation check**

Wilcoxon signed rank tests were conducted to determine whether expectations differed between conditions. When the saline was described as neutral, Pain Intensity Expectations and Saline-Related Anxiety were significantly higher (Pain Intensity Expectation: median = 20, IQR = 50, Saline-Related Anxiety: median = 10, IQR = 50) than when the saline was described as therapeutic (Pain Intensity Expectation: median = 0, IQR = 0, Saline-Related Anxiety: median = 0, IQR = 20, p < 0.001). When the saline was described as therapeutic participants reported significantly higher Saline Efficacy Expectations (median = 30, IQR = 50) than when it was described as neutral (median = 0, IQR = 0, p < 0.001).

**Hypothesis testing**

**Hypothesis 1: Describing the saline as therapeutic compared to neutral will lead to a significant reduction in pain intensity.**

VAS Pain Intensity scores were subtracted from either Baseline Pain Intensity or the previous condition to obtain a change in VAS Pain Intensity for each condition. After the Neutral Label, 62 participants reported no change in pain, 49 experienced hyperalgesia and 22 experienced hypoalgesia. After the Therapeutic Label
participants reported no change in their symptoms, 15 experienced hyperalgesia and 49 experienced hypoalgesia.

Paired t-tests and Wilcoxon signed-rank tests were conducted to determine whether I observed a significant change in pain after each condition. VAS Pain Intensity was significantly lower after the Therapeutic Label compared to the Neutral Label and Baseline Pain Intensity. MPQ and OPI Pain Intensity were also significantly lower after the Therapeutic Label compared to Neutral. This indicated a significant placebo effect was observed (see Figure 18).

Figure 18: Change in Pain Severity (a), Pain Intensity (b) and Overall Pain Intensity (c) after the Neutral Label and Therapeutic Label Saline Perfusion (+SE). ** p < 0.01, *** p < 0.001.
Repeated measures ANCOVA were used to test the following hypotheses. VAS Pain Intensity scores in each condition were used as dependant variables. Condition order and Baseline Pain Intensity was controlled for before testing each variable.

**Hypothesis 2: More positive illness representations are associated with a greater reduction in Pain Intensity in response to the Therapeutic Label.**

The following Illness Representations significantly moderated the relationship between condition and Pain Intensity: Consequences (F (3, 130) = 2.40, p < 0.05), Timeline (F (3, 130) = 3.44, p <0.01), Concerns (F (3,130) = 2.10, p < 0.05). Those whose believed their GORD/LPR was temporary or had many severe consequences reported a greater increase in Pain Intensity after the Neutral Label than those who believed their GORD/LPR was more permanent or had few severe consequences. After the Therapeutic Label those whose believed their GORD/LPR was temporary or had few severe consequences reported a greater reduction in Pain Intensity than those who believed their GORD/LPR was permanent or had many severe consequences. A greater increase in Pain Intensity was observed after the Neutral Label in participants who had high concerns about their GORD/LPR compared to those who had low concerns. A greater reduction in Pain Intensity was observed after the Therapeutic Label in participants who had low concerns about their GORD/LPR compared to those who had high concerns. Simple effects within these interactions were not found to be significant (all p > 0.05). No other significant interactions between illness representations and condition on Pain Intensity were found (all p > 0.05, see Figure 19).
Hypothesis 3: Pharmaceutical schema will have no significant effect on pain intensity in response to the therapeutic message.

No significant effect of participants’ pharmaceutical schema on Pain Intensity was observed (all p > 0.05).

Hypothesis 4: More positive expectations (high Efficacy Expectation, low Expected Pain Intensity and low Saline-Related Anxiety) will be associated with a larger reduction in pain intensity in response to the Therapeutic Label.

Saline Efficacy Expectations (F (3, 130) = 3.36, p < 0.001), Pain Intensity Expectation (F (3, 130) = 1.96, p < 0.05) and Saline-Related Anxiety (F (3 (130) = 1.77, p < 0.05) significantly moderated the relationship between condition and Pain Intensity. An increase in Pain Intensity was observed after the Neutral Label irrespective of the difference in Saline Efficacy Expectations between each condition. A greater reduction in Pain Intensity was observed after the Therapeutic Label if they had higher Saline Efficacy Expectations in the Therapeutic Label compared to Neutral Label. If participants were equally anxious about the effects in each condition or expected similar Pain Intensity, a similar decrease in Pain Intensity was observed. If participants were more anxious about the effects of the Therapeutic Label compared to the Neutral Label, a larger change in Pain Intensity was observed between conditions (see Figure 20).
Figure 20: Interaction effects between Expectations and Condition on VAS Pain Intensity (+S.E.).*** p < 0.001.

Exploratory analysis – Associations between participants’ clinical factors (True Reflux vs. Non-Reflux, Sociodemographics) and state/trait psychological factors (trait anxiety, depression, somatization, affect and perceived stress) on Pain Intensity.

No significant effect of participants clinical or state/trait psychological factors on Pain Intensity was observed (all p > 0.05).

Exploratory analysis – Differences in baseline measures across patient subgroups (True Reflux vs. Non Reflux and GORD vs. LPR).

Adjusting for multiple comparisons (adjusted p-value of 0.025), beliefs that treatment could control one’s illness were significantly greater in participants with True Reflux (mean = 7.24, SD = 2.40) vs. those with Non-Reflux (mean = 6.98, SD = 2.43, t = 2.33, p < 0.025). No other significant differences between participants' baseline measures were observed (all p > 0.05, see Appendix D).
6.4 Discussion

This study is the first to investigate the role of treatment belief and illness representations in patients with GORD and LPR. Furthermore, it is the first to assess predictors of the placebo effect in GORD and LPR and to utilise a modified Bernstein test to investigate this. This study set out to address the following research questions: are illness representations associated with the placebo effect?

Pain intensity was significantly lower in response to the therapeutic label compared to the neutral label. Participants’ illness representations - beliefs about chronicity, consequences and concerns – moderated the effect of the information provided on participants’ pain responses. Efficacy expectations and expected pain intensity also significantly moderated the effect of the information provided in each condition on participants’ pain intensity. In conjunction with my results from Study 1, pharmaceutical schema was not associated with pain intensity in response to the therapeutic message as it was described as “natural”. Pain intensity was not associated with clinical (True Reflux and Non-Reflux) or state/trait psychological factors (trait anxiety, affect, depression, somatization or perceived stress).

Illness representations and expectations

Previous research has shown associations between illness representations and symptom severity in a variety of conditions such as pain, IBS, asthma, heart disease (Chilcot & Moss-Morris, 2013; Glattacker et al., 2013a; Goldstein et al., 2011; Hirani, Pugsley, & Newman, 2006a; Ohm & Aaronson, 2006). For example in IBS, more positive illness representations at baseline (pre-treatment) predicted lower symptom severity after treatment (Chilcot & Moss-Morris, 2013). This study is the first to investigate illness representations in GORD and LPR patients, but also the first to assess their relationship with the placebo effect. My results suggest that therapeutic messages about treatment are more effective if patients have more positive illness representations – that is beliefs that their illness is temporary, has few consequences and in those who have less concern about their illness.

Framing of an ambiguous stimulus can influence the perception of that stimulus in accordance with ones expectations (Anderson & Pennebaker, 1980). In practice, how information provided by physicians about symptom triggers (e.g. certain food types) and treatment impact perceived symptom severity, may be influenced by the patients’ expectations. Negative expectations about potential symptom triggers (e.g. food types, smoking) and treatment may result in heightened symptom reporting.
On the other hand, positive expectations may lead to reduced GORD/LPR symptomology but potentially a lack of risk awareness (Rothman & Salovey, 1997) i.e. continuing poor health behaviour such as a poor diet. This could potentially result in poorer clinical outcomes and increased re-consultation rates. Similarly, representations about GORD/LPR may have similar effects. In accordance with my results, messages about symptom triggers and treatment effects may be more influential on those with more positive illness representations.

Consistent with previous placebo literature I found a significant effect of expectations on the placebo effect (Benedetti, 2008a). However this study is the first to show this relationship in patients with GORD and LPR. Studies in other GI disorders such as IBS have found similar results. For example, two studies by Vase et al. (Vase et al., 2003, 2005) found expected pain intensity predicted variation in pain intensity during rectal distention after placebo administration.

**Relationship between psychological functioning and symptom perception**

Although psychological factors such as anxiety and stress are thought to play a role in GORD and LPR symptomology (Bradley et al., 1993; Choi, Jung, Song, Shim, & Jung, 2013; Kessing, Bredenoord, Saleh, & Smout, 2015; Sharma, Van Oudenhove, Paine, Gregory, & Aziz, 2010), I found no significant effect on participants’ state/trait psychological factors on the placebo effect. A recent prospective study found patients with more severe depression tended to have poorer therapeutic response to PPI therapy (Matsuhashi et al., 2015), however other studies have found no significant effect on PPI responsiveness (Boltin et al., 2013). There is evidence to suggest that changes in such factors (e.g. reduced negative emotions) after placebo administration may mediate the effects of expectations on the placebo effect (Aslaksen et al., 2011; Vase et al., 2005). However, from this data I am unable to determine whether such effects exist in this sample.

**Differences in treatment and illness representations across patient subgroups**

To my knowledge only two studies to date have investigated treatment beliefs in this population (Cassell et al., 2015; Francis, Wileman, Bekker, Barton, Ramsay, & Grp, 2009), with currently no studies which have assessed representations of GORD and LPR. Patients with True Reflux reported greater treatment control beliefs than those with Non-Reflux. This may be reflective of the fact that PPI therapy has been shown to be more effective in those with True vs. Non-Reflux (Lind et al., 1997). On the other hand, there was no significant difference in treatment beliefs or perceived PPI
effectiveness across these two groups which contradict this point. We may not be seeing the full picture here though. Within this Non-Reflux group lies patients who report symptoms due to normal changes in acid within the oesophagus (hypersensitive) and those who report symptoms which do not correlate with changes in oesophageal acid exposure (functional heartburn) (Martinez et al., 2003). Given the findings of the present study and those in Study 1 it would be interesting to examine how illness and treatment representations differ between these groups of patients. Due to the small number of functional heartburn patients in this study I was unable to do this.

Strengths and weaknesses of study

This study has a number of limitations. Firstly, I excluded participants with known structural abnormalities such as Barrett’s oesophagus and erosive oesophagitis and thus it is difficult to extrapolate these results to this subset of patients. I did, however, recruit a large sample size of LPR and GORD patients who expressed symptoms in the presence of abnormal and normal oesophageal acid exposure. These results are therefore generalizable to a significant proportion of this patient population. Secondly, the within-subject design may have led to carry over effects; however, this was minimized by a 3 minute “washout” period between each condition. The within-subject design also minimised the effect of individual variation on pain intensity scores, which is particularly important in this patient population who have a diverse range of symptoms. Similarly to Study 1, participants were not blind to the conditions. Thus the results of this study may have been influenced by experimenter and observer bias. For example, during the therapeutic condition participants may have felt the need to report a reduction in symptom severity to please myself and the GI team who were present. Blinded study designs are required to determine whether the significant results I found in this study remain significant in the absence of such bias

Implications

These results have clinical implications on how information about GORD and LPR and its treatment is framed. Firstly, large placebo effects have been observed in GORD clinical trials (Cremonini et al., 2010). It is possible that the therapeutic response I observed in this study may contribute to patients’ responses to active medication. Secondly, it is common for GORD/LPR patients to report symptoms postprandially. Dietary modification can therefore be proposed a potential line of therapy (Kubo, Block, Quesenberry, Buffler, & Corley, 2014). Not all patients,
however, report heightened symptomology to the same food types (El-Serag, Satia, & Rabeneck, 2005). Labelling potentially neutral stimuli as harmful could therefore lead to increased symptomology.

Recent attempts to reduce GORD symptomology through improving the patient-provider interactions have shown promising results (Dossett et al., 2015). Furthermore, a recent meta-analysis indicates that illness representations can be changed through behaviour change techniques such as problem solving and action planning (Jones, Smith, & Llewellyn, 2015). Developing interventions aimed to address patients’ illness representations could provide additional ways to maximise the placebo effect and reduce symptomatic responses to potentially neutral stimuli (e.g. food types). This may be particularly important in patients who are unresponsive to PPI therapy.

**Conclusion**

This study set out to address the following research question: are illness representations associated with the placebo effect? This study is the first to demonstrate that representations of illness influence the magnitude of the placebo effect in particular beliefs about illness chronicity, illness consequences and concerns about one’s illness. Further research is now required to assess these results in other clinical samples. Interventions aimed at modifying maladaptive illness representations may also provide a way to utilize this effect in clinical practice.
7 The effect of a Necessity Coherence Intervention (NCI) on changing beliefs about an asthma medication – an analogue study

7.1 Background and research questions

In recent years there has been a great deal of interest into how we can utilize the placebo effect ethically in clinical practice (Colloca, Jonas, Killen, Miller, & Shurtleff, 2014; Colloca & Miller, 2011). The question is can we develop ways to effectively shape the psychosocial context surrounding the treatment while providing the most appropriate treatment to maximise perceived efficacy. This could be achieved in two potential ways. Firstly we could shape the environment surrounding the patient. As discussed in section 2.4 providing extended consultations, actively listening and having a warm and friendly manner may provide a way to incorporate the placebo effect in clinical practice. We could also address specific factors that increase the placebo effect; for example modifying any maladaptive beliefs patients have about their treatment.

There have been numerous attempts to modify both treatment beliefs and illness representations. The effectiveness of these interventions, however, has been mixed (Chapman et al., 2015; Chilcot & Moss-Morris, 2013; Knoop, van Kessel, & Moss-Morris, 2012; O'Carroll, Chambers, Dennis, Sudlow, & Johnston, 2014; Petrie, Cameron, Ellis, Buick, & Weinman, 2002). For example, in stroke survivors, treatment necessity beliefs were significantly increased by identifying and modifying maladaptive beliefs about their medication and illness in addition to helping establish better medication taking routines. This led to a 10% greater adherence compared to that seen in the control group (O'Carroll et al., 2014). In another example, doubts about necessity and concerns towards inhaled corticosteroids were significantly reduced in asthma patients by providing asthma nurse specialists with a 1.5 day training programme on how to address treatment necessity beliefs and concerns (Chapman et al., 2015). In contrast, a recent study using motivational interviewing techniques to improve treatment necessity and reduce concerns in patients with rheumatoid arthritis found no significant superiority over treatment as usual (Zwikker et al., 2014). In this analogue study I will attempt to increase treatment necessity beliefs through a theory-based approach by increasing
coherence between beliefs about a fictitious asthma medication and representations about asthma.

In Study 1 and 2 I found that treatment necessity beliefs and illness representations were associated with the placebo effect. As I described in section 2.6.3 Horne has proposed that messages about treatment necessity may be more effective if it addresses patients’ illness representations (Horne, 2003). These include the identity of the illness, the cause (e.g. environmental/genetic), the time-line (e.g. acute/cyclical/chronic), consequences of having the illness (e.g. on their physical, social and psychological abilities) and whether the illness is curable or controllable (either through treatment or behaviour change) (Leventhal et al., 1998). Therefore I designed a micro-intervention aimed to increase coherence between treatment necessity and constructs within participants’ illness representation.

In standard PIL information about the therapeutic effect of a medicine is typically fairly brief with the majority of information about the medicine about potential side effects. The NCI included additional information about the therapeutic effect of a fictitious asthma medication based around illness representations of asthma. For example, I provided information about how the medicine works to stop environmental triggers leading to asthma symptoms (cause) and how it reduces the impact asthma has on daily life (consequences).

I assessed the effect of this intervention in an analogue scenario. In this scenario I asked participants to imagine they had recently been diagnosed with asthma and that their doctor was going to prescribe them a medication called Molair. While analogue studies have their limitations, it was decided that this was the most suitable method to assess the effect of a belief change intervention to recruit a large enough sample. Assessing the effect of the intervention using a sample of asthma patients and measuring subjective and objective outcomes measures (e.g. perceived symptom severity and lung function) would have been the most ideal study design. However, due to the time constraints of a PhD this would not have been possible. Furthermore, there may have been legal and ethical issues around modifying treatment information in a clinical population.

In this study participants were asked to imagine they had been diagnosed with asthma and that they had been prescribed an asthma medication for treatment. Participants were randomly assigned to receive either the NCI, standard information (information as usual; IAU) given in PILs or no information about the asthma medication (Control). The hypotheses were:
Hypothesis 1: Participants receiving the NCI will express greater treatment necessity beliefs and efficacy expectations compared to participants in the IAU and Control Condition.

Hypothesis 2: Treatment necessity beliefs will be associated with participants’ representations of asthma.

In addition to these hypotheses, relationships between efficacy expectations, pharmaceutical schema and specific beliefs about the asthma medication will be explored.
7.2 Method and materials

This study was exempt from REC approval as conformed by the UCL Research Ethics Committee as the study collected anonymous information from healthy volunteers. This study had a between-subject design where participants were randomly assigned to one of the following conditions: NCI, IAU or Control Condition.

Sample, recruitment procedure and consent

The sample was recruited using the online job board Crowdflower where subscribers completed surveys for monetary reward. Participants were provided with an information sheet about the study and then asked to provide consent before completing the survey. Inclusion criteria included anyone over the age of 18 who had not been diagnosed with asthma in the past as this may have influenced their representation of asthma and specific beliefs about the fictitious medication. The only exclusion criterion was participant who could not sufficiently understand written English. Participants were paid $1 to take part and the survey took 30 minutes to complete.

The sample size was calculated using a paired t-test, aiming for a power of 80% to detect an effect that was significant at the level of 5% (3.1.9.2). The effect size was estimated from a study which modified specific concerns about a medication through an intervention (Pre-intervention concerns: mean = 17.90, SD = 4.00, post-intervention concerns: mean = 15.60, SD = 4.40) (Magadza, Radloff, & Srinivas, 2009). It was calculated that at least 54 participants were required in each condition to be powered to detect a significant change in specific beliefs. 74 participants in each condition were recruited (n = 222).

Measures

The following measures were used in this study. Details about measures used throughout this thesis can be found in section 4 with their Cronbach’s alphas in Table 15. Measures specific to this study are described in detail below.
Table 15: Cronbach’s alphas for the BMQ-G, BMQ-S, PSM, STAI-T and PANAS

<table>
<thead>
<tr>
<th>Measure</th>
<th>Subscale</th>
<th>Cronbach’s Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ-G (Horne et al., 1999b)</td>
<td>General Benefit</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>General Harm</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>General Overuse</td>
<td>0.78</td>
</tr>
<tr>
<td>BMQ-S (Horne et al., 1999a)</td>
<td>Specific Necessity</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>Specific Concerns</td>
<td>0.82</td>
</tr>
<tr>
<td>PSM (Horne, Faasse, et al., 2013b)</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>PANAS: Positive and Negative Affect</td>
<td>Positive Affect</td>
<td>0.91</td>
</tr>
<tr>
<td>(Watson et al., 1988)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative Affect</td>
<td>0.85</td>
</tr>
<tr>
<td>STAI-T (Spielberger, 1983)</td>
<td></td>
<td>0.72</td>
</tr>
</tbody>
</table>

Note: BMQ-G = Beliefs about Medicines Questionnaire – General, PSM = Perceived Sensitivity to Medicines Questionnaire, STAI-T = State Trait Anxiety Inventory – Trait, PANAS = Positive and Negative Affect Schedule.

Brief Illness Perceptions Questionnaire (B-IPQ) (Broadbent et al., 2006)

The B-IPQ is comprised of an 8-item scale used to assess participant’s cognitive and emotional representations of illness. This measure has demonstrated good validity and reliability in a number of conditions (Broadbent et al., 2006) and showed adequate internal consistency (α = 0.62). For the first 8 items participants are asked about their views about their illness (e.g. “How concerned would you be about your asthma?”) and respond using a 10-point Likert-type scale (e.g. 0 = not concerned at all to 10 = extremely concerned). A total score was calculated by adding the score from items 1-8 (items 3, 4 and 7 reversed scored). Higher scores represent a more threatening view of the illness.

Efficacy Expectation

Participants were asked to rate how effective they thought the asthma medication would be in relieving their symptoms using a VAS (0 = not effective at all, 100 = extremely effective).

Conditions

Depending on the condition participants were presented with a PIL. In the Control condition participants were provided with no specific information about the medication other than that it is a medication used to treat asthma.

In the IAU condition participants were presented with a PIL (see Figure 21). Those in the NCI were also provided with the same PIL but with additional information (see Figure 22). The PIL presented in the IAU condition was based on a current medication used for asthma – Montelukast. The additional information provided in
the NCI condition was tailored to provide information on how the medication impacts the cause and controllability of asthma, consequences and concerns, and asthma timeline.

Figure 21: PIL provided to participants in the IAU condition
Figure 22: Additional information presented in the NCI condition. This additional information was intended to increase coherence between treatment necessity and representations of asthma (cause and control - red, asthma concerns and consequences - green and asthma timeline – blue).
As the aim of this study was to examine the effect of an intervention on necessity beliefs, a between-subject design was used. A control group is required in order to determine whether a significant change in outcomes have been observed as a result of the intervention.

**Procedure**

After providing consent, participants were presented with information about asthma obtained from the National Health Service (NHS) website (see Appendix E) first completed the Baseline Measures (BMQ-G, PSM, PANAS, PHQ-9, STAI-T, and B-IPQ). They then were randomised to one of three conditions (NCI, IAU, Control) using Qualtrics randomiser. In each condition participants read the condition-specific information before completing the BMQ-S and Efficacy Expectations. Finally, participants were debriefed (see Figure 23).

Figure 23: Overview of procedures for Study 3. BMQ-G = Belief about Medicines Questionnaire – General, PSM = Perceived Sensitivity to Medicines, B-IPQ = Brief Illness Perceptions Questionnaire, STAI-T = State Trait Anxiety Inventory – Trait, PANAS, Positive and Negative Affect Schedule, BMQ-S = Beliefs about Medicines Questionnaire – Specific.
Statistical analysis

One-way ANOVAs were conducted to determine whether there were significant differences in baseline measures across conditions. One-way ANOVAs were used to determine significant differences in specific evaluations (Specific Necessity and Concerns) and Efficacy Expectations about the asthma medication, across conditions. Pearson’s correlations were used to determine significant relationship between treatment beliefs, illness representations, expectations and state/trait psychological factors.

7.3 Results

Sociodemographics

The mean age of participants was 40 years; just over half were female and employed, were of a white British/American/Irish ethnicity and were educated to at least college level (see Table 16).

<table>
<thead>
<tr>
<th>Table 16: Sociodemographics</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.84 (12.12)</td>
</tr>
<tr>
<td>Female</td>
<td>118 (53.20)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>138 (62.20)</td>
</tr>
<tr>
<td>Other</td>
<td>84 (37.80)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White British/Irish/American</td>
<td>174 (78.40)</td>
</tr>
<tr>
<td>Other</td>
<td>84 (11.60)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>75 (33.80)</td>
</tr>
<tr>
<td>College/6th Form</td>
<td>47 (21.20)</td>
</tr>
<tr>
<td>University Degree</td>
<td>73 (45.10)</td>
</tr>
</tbody>
</table>

Baseline measures

Pharmaceutical Schema

The majority of the sample expressed strong beliefs about the benefit of medicines in general (84.20%) but also believed they are generally overused by doctors (56.40%). Most expressed low beliefs about the harmfulness of medicines in general (69.70%) and low beliefs about personal sensitivity to the effects of
medicines (70.90%, see Table 17). No significant differences between participants in the different conditions were observed (all p > 0.05, see Table 17).

**Illness Representations**

Examining the individual IPQ dimensions, the majority believed asthma would severely affect their life (Consequences: 56.80%), that it would continue for a long time (Timeline: 72.20%) but that asthma was controllable (Personal Control: 65.40%, Treatment Control: 79.10%). Around half of participants believed they would experience many severe symptoms from asthma (Identity) and expressed they would have high concerns if they had asthma (Concerns), scoring on the scale mid-point or higher. Around 70% of participants scored on the scale mid-point or higher for and Coherence indicating that most of our sample felt they understood the causes of asthma to some degree. Finally, around half the sample believed that having asthma would affect them emotionally (Emotional Representation, see Table 17). No significant differences between conditions were observed (all p > 0.05).

**Other Psychological variables**

A mean score of 26.14 (SD = 8.21) for Positive Affect and 13.20 (SD = 6.82) for Negative Affect was observed suggesting moderate and low levels of Positive and Negative Affect respectively. A mean score of 43.70 (SD = 6.40) for Trait Anxiety was observed reflecting moderate levels of Trait Anxiety within the sample. No significant differences between conditions were observed (see Table 17, all p > 0.05).
Hypothesis testing

Hypothesis 1: Participants receiving the NCI will express greater treatment necessity beliefs and efficacy expectations compared to participants in the IAU and Control Condition.

ANOVA were conducted to determine whether specific evaluations about the medication and Efficacy Expectations were significant different across conditions. The NCI significantly increased Efficacy Expectations compared to the Control Condition, however Efficacy Expectations were not significantly different between the NCI and IAU condition. There were no significant differences between the IAU and either the Control Condition or NCI (p > 0.05). No significant differences in specific evaluations about the medication were found (Specific Necessity or Specific Concerns, all p > 0.05, see Table 18).

Table 17: Baseline measures

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmaceutical Schema</strong></td>
<td></td>
</tr>
<tr>
<td>General Benefit</td>
<td>3.83 (0.74)</td>
</tr>
<tr>
<td>General Harm</td>
<td>2.43 (0.74)</td>
</tr>
<tr>
<td>General Overuse</td>
<td>3.25 (0.82)</td>
</tr>
<tr>
<td>PSM</td>
<td>2.43 (0.92)</td>
</tr>
<tr>
<td><strong>Illness Representations</strong></td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>5.16 (2.91)</td>
</tr>
<tr>
<td>Timeline</td>
<td>6.54 (3.22)</td>
</tr>
<tr>
<td>Personal control</td>
<td>5.64 (2.65)</td>
</tr>
<tr>
<td>Treatment control</td>
<td>6.76 (2.72)</td>
</tr>
<tr>
<td>Identity</td>
<td>4.97 (2.65)</td>
</tr>
<tr>
<td>Concerns about asthma</td>
<td>5.64 (3.10)</td>
</tr>
<tr>
<td>Coherence</td>
<td>6.23 (2.74)</td>
</tr>
<tr>
<td>Emotional representation</td>
<td>4.64 (2.93)</td>
</tr>
<tr>
<td><strong>Other Psychological variables</strong></td>
<td></td>
</tr>
<tr>
<td>Positive affect</td>
<td>26.14 (8.21)</td>
</tr>
<tr>
<td>Negative affect</td>
<td>13.20 (6.82)</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>43.70 (6.40)</td>
</tr>
</tbody>
</table>

Note: PSM = Perceived Sensitivity to Medicines
Hypothesis 2: Treatment necessity beliefs and efficacy expectations will be associated with participants’ representations of asthma

Pearson’s correlations were used to determine relationships between treatment necessity beliefs and participants’ representations of asthma. Participants expressed greater treatment necessity beliefs if they believed asthma was chronic, had severe consequences on their life and experienced a lot of symptoms. Treatment necessity and Efficacy Expectations were positively associated with a better understanding of asthma, that asthma could be controlled, that asthma had severe consequences, concerns about having asthma, and the belief that asthma would affect one emotionally. Efficacy Expectations were also significantly positively associated with perceptions of personal control over asthma (see Figure 24).

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th></th>
<th>p</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCI (n=74)</td>
<td>IAU (n=74)</td>
<td>Control (n=74)</td>
<td>Omnibus</td>
</tr>
<tr>
<td>Specific Necessity</td>
<td>3.17 (0.58)</td>
<td>3.20 (0.44)</td>
<td>3.10 (0.46)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Specific Concerns</td>
<td>2.82 (0.71)</td>
<td>2.90 (0.78)</td>
<td>2.81 (0.71)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Efficacy Expectation</td>
<td>71.43 (24.93)</td>
<td>70.35 (20.14)</td>
<td>62.28 (23.40)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Note: NCI = Necessity Coherence Intervention, IAU = Information as Usual. p values refer to post-hoc pairwise comparisons.
** Figure 24: Significant associations between representations of asthma, Treatment necessity beliefs and Efficacy Expectations. ** p < 0.01.

**Exploratory analysis – relationships between efficacy expectations, pharmaceutical schema and specific beliefs about the asthma medication.**

Pearson’s correlations were used to determine significant relationships between treatment beliefs and Efficacy Expectations. Efficacy Expectations were significantly associated with both specific and general treatment beliefs. Participants were more likely to report higher Efficacy Expectations if they believed they would need the asthma medication, believed pharmaceuticals in general were beneficial and if they believed they were particularly sensitive to the effects of medicines. Individuals were more likely to report lower Efficacy Expectations if they expressed high concerns about the asthma medication. Participants were more likely to report greater treatment necessity beliefs if they held strong beliefs about the beneficial effect of pharmaceuticals in general. Participants were more likely to express greater concerns about the asthma medication if they believed pharmaceuticals were harmful in general, were overprescribed and if they believed they were particularly sensitive to the effect of medicines (see Figure 25).
Participants who reported greater Positive Affect tended to endorse the necessity of the asthma medication ($r(234) = 0.27$, $p < 0.01$) and have greater Efficacy Expectations ($r(234) = 0.16$, $p < 0.05$). Participants who reported greater Negative Affect tended to have greater Concerns about the asthma medication ($r(234) = 0.18$, $p < 0.01$) and believe that medicines are generally overused ($r(234) = 0.14$, $p < 0.05$).

Figure 25: Significant relationship between Efficacy Expectations and treatment beliefs. ** = $p < 0.01$. 
7.4 Discussion

This study set out to address the following research question: Can treatment necessity beliefs be changed by a brief information-based intervention to increase coherence between representations of the condition and treatment? I found no significant effect of the intervention on participants’ specific beliefs about the asthma medication. I did find that the NCI significantly increased participants Efficacy Expectations in comparison to those who received no information (Control). However, there was no significant difference in Efficacy Expectations between those who received the intervention and those who received standard drug information. Finally participants’ pharmaceutical schema and representations of asthma were associated with specific evaluations of treatment according to the Extended Model of Self-Regulation.

The effect of the intervention

There may be a number of reasons for why the intervention was not effective in changing treatment necessity beliefs. While the use of an analogue scenario allowed a comparatively rapid examination of the intervention on treatment necessity beliefs, this was a hypothetical scenario. Participants may not have been fully engaged with the information and hypothetical situation they were asked to imagine in comparison to a sample of patients with diagnosed asthma who experience symptoms.

It is also possible that the information given in the NCI was not understandable to everyone. At present there is considerable research into understanding how health literacy influences health outcome and how to present information to obtain the best outcomes. Health literacy is in part dependant on both the lay skills professional providing the information and the patient receiving this information (Diviani, van den Putte, Giani, & van Weert, 2015; Sorensen et al., 2012). Information given in the NCI tried to explain how the medication would reduce leukotriene expression caused by genetic and environmental factors with the aid of a diagram. However, this may still have been difficult to understand for some. In hindsight proving more simplistic information may have been more understandable and thus more effective in modifying beliefs. The reading age for the intervention material was 14 years which is higher 5 years higher than the UK average (Wheater et al., 2013). This may have therefore affected participants understanding of the intervention content. It would also have been useful to have examined what participants thought about the
medical information provided. This would have given some insight into whether the information was of the right level of complexity.

Alternatively, we may need to tailor treatment information around the individual’s representation of their condition for this type of intervention to be effective. Over the years the effects of tailoring health information on behaviour change have been of great interest (Noar, Benac, & Harris, 2007; Wanyonyi, Themessl-Huber, Humphris, & Freeman, 2011). Tailoring of health information tries to enhance the audience’s attention or motivation to process the message by conveying, either explicitly or implicitly, that the information is designed specifically for them, thus making the message more relevant and meaningful (Kreuter & Holt, 2001). The Elaboration Likelihood Model (ELM) provides a theoretical rationale for the effects of tailoring/personalising health communication. This theory proposes that in many circumstances, we are active information processors, comparing information to other messages we have encountered before and our own beliefs. If a message is tailored, individuals are more likely to thoroughly and actively process the information provided, if the information is perceived as personally relevant. Studies have shown that messages which are elaborated upon in this way (centrally processed) are more likely to permeate change than messages not elaborated upon (peripheral processing) (Cacioppo, Stratham, & Priester, 1994). As this study was an analogue scenario with healthy individuals it is likely that participants did not find the information presented personally relevant and thus not likely to actively processes the information provided. Furthermore, representations about asthma varied within the sample. If we tailor treatment information based around the patient’s personal representation of their condition, they may be more likely to elaborate upon the information and equate to greater belief change. Thus further research may wish to assess the effect of a more tailored NCI on changing treatment necessity beliefs.

**Relationship between treatment beliefs and representations of asthma**

While this was an analogue scenario, relationships between participants’ representations of asthma, treatment beliefs and expectations of efficacy were as predicted by the extended-CSM and similar to previous research. Participants’ treatment necessity beliefs about the asthma medication were informed by their pharmaceutical schema and their cognitive representation of asthma. This is reflected in previous research in patients with asthma where treatment necessity beliefs about inhaler medication are informed by perceptions of whether asthma is
acute/cyclical or chronic (Illness timeline) and the impact of asthma on one’s life (Illness Consequences) (Horne & Weinman, 2002). Treatment necessity beliefs were significantly positively associated with efficacy expectations as in studies 1 and 2 in this thesis, and in addition to previous literature (Cooper et al., 2009). This suggests that participants were engaged in this hypothetical situation to some degree.

**Strengths and weaknesses**

This study has a number of limitations. Firstly, the use of an analogue scenario and a non-clinical population limits the external validity of my findings as patients’ representations of asthma and beliefs about asthma medication may differ to those without the condition. I also did not ask participants to complete the B-IPQ after providing the intervention therefore I cannot determine whether the intervention had an effect on participants’ representations of asthma. While I had a large sample size, it was of a non-clinical population. Further work is therefore required to examine the effect of this intervention in clinical populations.

**Conclusion**

This study set out to address the following research question: Can treatment necessity beliefs be changed by a brief information-based intervention to increase coherence between representations of the condition and treatment? The NCI was not successful in modifying treatment necessity beliefs; however this may have been due to a number of reasons outlined above. Efficacy expectations were significantly greater in patients receiving the NCI vs. control but not when compared to IAU. Participants’ specific beliefs were informed by illness representations and their pharmaceutical schema as predicted by the Extended CSM suggesting that these results are valid to some degree. Further research is now required to assess this intervention in a clinical sample and examine whether a tailored NCI is more effective.
8 Modifying treatment necessity beliefs: A pilot study assessing the effect of an NCI to improve the placebo effect in cough

8.1 Background and research question

In parallel to the previous study I examined the effect of the NCI on the effect of a placebo inhaler used to 'treat' cough induced using the capsaicin cough challenge. This study set out to address the following research questions: 1) can treatment necessity beliefs be changed by a brief information-based intervention to increase coherence between representations of the condition and treatment and 2) does a change in treatment necessity beliefs result in changes in placebo effect?

A cough induction was chosen to examine the effect of the NCI on the placebo effect as this would be reflective of the condition I asked participants to imagine they had in the previous study. Cough is a key symptom in many respiratory disorders such as COPD. A recent population-based survey in the UK reported that 16% of individuals suffer from chronic cough (defined as a persistent cough of eight weeks or more), with the prevalence of non-persistent coughs likely to be higher (Kaushik, Smith, Linehan, & Frank, 2015). Secondly cough is influenced by a number of psychological factors (e.g. affect, anxiety and depression) and susceptible to very large placebo effects (Van den Bergh et al., 2012). In five clinical trials of antitussive medication, the placebo effect was shown to vary from 56% up to 105% with an average effect of 85% (Eccles, 2002b). A more recent review of efficacy of treatments for chronic cough (49 studies) suggests opiates, dextromethorphan and moguisteine show effectiveness over placebo, however, due to limited number of studies their relative efficacy to other agents cannot be determined (Yancy et al., 2013). Furthermore, experimentally-induced cough also allowed me to examine the relationship between treatment beliefs, as well as the intervention on subjective and objective measures of the placebo effect (e.g. urge-to-cough and number of coughs) (Morice et al., 2007).

As discussed in section 2.1.5 there is currently limited but growing evidence that placebo effects can influence physiological measures of disease. Parkinson’s disease has been shown to be responsive to objective placebo effects in a number
of studies (Benedetti et al., 2003; Udupa & Fox, 2015). However, there is currently either limited or contrasting results in other conditions such as asthma (Kemeny et al., 2007; Wechsler et al., 2011) and hypertension (Asmar et al., 2001). If the placebo effect is to be used to our advantage effectively in clinical practice it is important to determine what conditions are susceptible to both subjective and objective placebo effects and what psychological factors influence these effects. To my knowledge there has only been one previous study investigating the placebo effect in cough where they found urge-to-cough was susceptible to placebo conditioning, however objective measures were not investigated (Leech, Mazzone, & Farrell, 2012). This study determined whether treatment beliefs are associated with both subjective and objective placebo effects.

The capsaicin cough challenge is the most extensively used method to experimentally induce cough in a safe, reproducible and dose-dependent manner. It has been extensively used for over two decades in clinical and non-clinical populations (Dicpinigaitis & Alva, 2005; Morice et al., 2007). The capsaicin cough challenge allows researchers and clinicians to assess efficacy of antitussive agents and cough reflex sensitivity (Dicpinigaitis et al., 2015; Dicpinigaitis, Tibb, Ramsey, Carr, & Poore, 2014; Faruqi, Wright, Thompson, & Morice, 2014). It involves the administration of tussive agents such as capsaicin or citric acid and the recording of resulting cough. While there are a number of methods which are used throughout the literature, this study will use the dose-response method. This method involves the inhalation of incremental concentrations of capsaicin to produce a dose-dependent response in terms of objective (number of coughs) and subjective (urge-to-cough) outcome measures (Morice, Kastelik, & Thompson, 2001). Urge-to-cough is typically measured using a modified Borg category scale ranging from 0 – no discernible urge to 10 – maximum urge (Davenport et al., 2007). Objective outcome measures are typically expressed as C2 and C5 which mean the lowest concentration of tussive agent required to elicit two or more, or five or more coughs, per inhalation (Morice et al., 2001).

Using the capsaicin cough challenge, this study aimed to test the effect of the revised NCI on the placebo effect. This study also aimed to examine the effects of treatment beliefs on objective measures of the placebo effect. Participants were randomised to one of the following conditions: NCI, IAU or Control Condition. The hypotheses were:
Hypothesis 1: Participants receiving the NCI will exhibit greater perceived need for the placebo medication and greater efficacy expectations in comparison to those receiving IAU.

Hypothesis 2: A larger placebo effect will be observed in the NCI condition compared to those receiving IAU and control.

Hypothesis 3: Perceived need for the placebo medication will be associated with a larger subjective (urge-to-cough) and objective (number of coughs) placebo effect.

Hypothesis 4: More positive general beliefs about medicines (high General Benefit, low General Harm and Overuse) and greater PSM will be associated with a larger subjective and objective placebo effect.

This study also explored the relationship between other psychological variables (trait anxiety, depression, somatisation and affect) on cough sensitivity and the placebo effect.
8.2 Method and materials

This study was approved by the UCL Ethics Committee (ref: 4875/003, see Appendix F). The study had a between-subject design. Participants were randomized to complete one of three conditions: NCI Condition, IAU Condition, Control Condition.

Sample, recruitment procedure and consent

Potential participants were invited to take part in a study comparing the effectiveness of a new cough medication via the UCL Announcement Email Service between December 2015 and March 2016. People were included if they were over the age of 18 and could sufficiently understand written and spoken English. Exclusion criteria included anyone who had smoked in the past 4 weeks or had any of the following conditions: asthma, chronic obstructive pulmonary disorder, bronchitis, pneumonia or allergies related to the lungs over the past 4 weeks. Participants were also excluded if they were taking any of the following medication: bronchodilators or inhaled corticosteroids, sedatives, ACE inhibitors. Potential participants were emailed the information sheet and a screening questionnaire (see Appendix G) to check eligibility and given at least 24 hours to decide whether to participate. Informed consent was obtained on the day of the experiment. Participants were paid £10 to compensate them for their time. The experiment took 1 hour to complete.

Measures

The following measures were used in this study. Details about measures used throughout this thesis can be found in Section 4 with their Cronbach’s alphas in Table 19. Measures specific to this study are described in detail below.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Subscale</th>
<th>Cronbach’s Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ-G (Horne et al., 1999b)</td>
<td>General Benefit</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>General Harm</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>General Overuse</td>
<td>0.66</td>
</tr>
<tr>
<td>PSM (Horne, Faasse, et al., 2013b)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>PANAS: Positive and Negative Affect (Watson et al., 1988)</td>
<td>Positive Affect</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>Negative Affect</td>
<td>0.65</td>
</tr>
<tr>
<td>STAI-T (Spielberger, 1983)</td>
<td>0.45</td>
<td></td>
</tr>
</tbody>
</table>

Note: BMQ-G = Beliefs about Medicines Questionnaire – General, PSM = Perceived Sensitivity to Medicines Questionnaire, STAI-T = State Trait Anxiety Inventory – Trait, PANAS = Positive and Negative Affect Schedule.
Beliefs about Medicines Questionnaire – Specific Scale (BMQ-S) (Horne et al., 1999a)

The BMQ-Specific was used to assess perceptions of the cough medication. It comprises two scales: a 5-item Specific Necessity scale assessing perceptions of personal need for the cough medication and a 6-item Specific Concerns scale assessing concerns about potential negative effects of the cough medication. The BMQ-S was developed for examining beliefs about medicines prescribed for chronic illnesses; therefore, we modified each item to apply to healthy individuals in an experimental setting (see Table 20). Items were scored on 5-point Likert-type scales (where 1=strongly agree, 5=strongly agree). A scale-adjusted mean score for each scale was computed by dividing the mean scale score by the number of items. BMQ-S scales had poor to adequate reliability (Specific Necessity α = 0.46, Specific Concerns α = 0.68).

Table 20: Modified items of the BMQ-S scales

<table>
<thead>
<tr>
<th>Specific Necessity</th>
<th>Specific Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proxadrol is necessary to reduce my cough</td>
<td>Using Proxadrol worries me</td>
</tr>
<tr>
<td>My cough would be more severe without Proxadrol</td>
<td>I am concerned about the long-term effects of Proxadrol</td>
</tr>
<tr>
<td>Using Proxadrol makes me less anxious about the effects of capsaicin</td>
<td>How Proxadrol works is a mystery to me</td>
</tr>
<tr>
<td>Proxadrol protects me from having a severe cough</td>
<td>I am concerned that Proxadrol won’t work</td>
</tr>
<tr>
<td></td>
<td>I am concerned Proxadrol may cause a side effect</td>
</tr>
<tr>
<td></td>
<td>It would worry me to feel as though I depended on this on Proxadrol to tolerate</td>
</tr>
<tr>
<td></td>
<td>the effects of capsaicin</td>
</tr>
</tbody>
</table>

Note: BMQ-S = Beliefs about Medicines Questionnaire - Specific

Sociodemographics

I asked participants to provide their age in years, gender, ethnicity, current qualification they were studying (undergraduate or postgraduate degree) and first language.

Depression - Patient Health Questionnaire – 9 (PHQ-9) (Kroenke et al., 2001)

The PHQ-9 is a 9-item screening assessment for depression severity. Participants indicated how bothered they had been about 9 features of depression, over the past 2 weeks (e.g. “Little interest or pleasure in doing things”). Items were scored on a 4-point Likert-type scale (0=not at all, 1=several days, 2=more than half the days,
A total score was calculated by summing item scores. It has been validated in clinical and general populations (Kroenke et al., 2001; Martin, Rief, Klaiber, & Braehler, 2006), and had good internal consistency (α = 0.75).

**Somatization – Patient Health Questionnaire – 15 (PHQ-15) (Kroenke et al., 2002)**

The PHQ-15 is a 15-item questionnaire measuring somatization. This measure has shown to be valid and reliable in patients with a variety of conditions (Kroenke et al., 2002) and has good internal consistency (α = 0.75). Participants are asked to indicate how bothered they have been by 15 symptoms (e.g. Stomach pain) over the past 4 weeks from 0 = not bothered at all to 2 = bothered a lot. A total score is calculated by adding the score from each item. Higher scores indicate more severe somatization disorder.

**Forced Expiratory Volume 1 (FEV1)**

FEV1 was measured before each capsaicin cough challenge.

**Expectations of drug efficacy and Cough Intensity/Frequency (VAS)**

Visual Analogue Scales (VAS) were used to measure expectations of drug efficacy (Efficacy Expectations: 0 = Not effective at all, 100 = Highly effective), Expected Cough Intensity (0 = Not intense at all, 100 = Extremely intense) and Expected Cough Frequency (0 = Not at all, 100 = Quite a lot).

**Urge-to-cough**

Urge-to-cough was measured after each inhalation using a modified Borg category scale where 0 = No discernible cough and 10 = Maximum urge (Davenport et al., 2007; Davenport, Sapienza, & Bolser, 2002). The capsaicin concentration required to produce a discernible urge-to-cough was defined as Cu.

**Number of coughs**

The number of coughs produced in the first 15 seconds after each inhalation was recorded. For each test, the capsaicin concentration required to trigger the cough reflex (Cr), two or more coughs (C2) and five or more coughs (C5) was determined.

**Side effects**

Participants were provided with a list of side effects (rapid pulse, throat irritation, headache, nausea, light-headedness, diarrhoea, vomiting, tremor, muscle cramps)
and taste disturbances) and were asked to report if they had experienced each side effect.

**Manipulation check**

Participants were asked what they thought the aim of the study was. Finally using a VAS, they were asked whether they thought they had received a placebo or an active medication for each condition (where 0=placebo and 100=active medication).

**Capsaicin cough challenge**

Capsaicin (30.5mg) was dissolved in 1ml pure ethanol followed by 1ml of polyoxyethylene sorbitan and then further diluted in 8ml physiological saline to obtain a stock solution of 0.01M. The stock solution was then serially diluted to produce doubling concentrations ranging from 0.98µM - 1000µM.

The capsaicin solutions were delivered in ascending order of concentration using a compressed air-driven nebulizer controlled by a KoKo Digidoser (Nspire Health, see Figure 26). The nebulizer output was set at 1.007ml/min-1 and programmed to deliver aerosol for 1.2 seconds. There was interval of 30 seconds between each challenge. Coughs occurring in the first 15 seconds after each inhalation were recorded using Audacity software. The cough challenge was terminated once the participant had coughed 5 or more times unless the participant wished to terminate the procedure earlier.
Figure 26: Koko Digidoser used for the capsaicin cough challenge. This equipment was chosen for the study as it is recommended by the European Respiratory Society (Morice et al., 2007).

Conditions

Depending on the condition participants were presented with a PIL or a message. In the control condition participants were presented with the following message: “You have been randomly allocated to the control condition. This means you will not receive any medication and repeat the sensitivity test.” In a similar fashion to Study 1 I used a “no placebo” group for the control condition. This was because the majority of previous placebo literature uses this method. Furthermore, the “no placebo” group would mirror that of clinical trial i.e. natural history group.

Participants in the NCI and IAU condition were presented with a PIL. In the IAU condition the PIL was modelled on standard information received in an inhaler medication for asthma (see Figure 27). In a similar fashion to the previous study, the NCI PIL was developed to increase coherence between the effects of the medication and beliefs about the capsaicin (see Figure 28).

Similarly to Study 3, a between-subject design was used for this experiment. To assess the effect of an intervention it is important to compare any observed effect with a group of individuals where the intervention is not provided.
Proxadrol is a cough suppressant. It is used to relieve dry and tickly coughs that do not produce phlegm or mucus on the chest. It is also used to prevent cough brought on by “triggers” such as irritants in the air, and substances such as capsaicin which you will inhale as part of this study.

**HOW TO TAKE PROXADROL**

Proxadrol is taken using an inhaler. Take two puffs of the Proxadrol with at least a 10 second gap between puffs.

**POSSIBLE SIDE EFFECTS**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

**Common (1 in 10):**
- Rapid pulse
- Oropharyngeal (mouth and throat) irritation
- Headache
- Nausea
- Light-headedness

**Uncommon (1 in 100):**
- Bradycardia
- Itching palms
- Yawning
- Diarrhoea
- Vomiting
- Tremor

**Rare (1 in 400):**
- Muscle cramps
- Taste disturbances

Figure 27: PIL presented to participants in the IAU condition
Proxadrol is a cough suppressant. It is used to relieve dry and tickly coughs that do not produce phlegm or mucus on the chest. It is also used to prevent cough brought on by “triggers” such as irritants in the air, and substances such as capsaicin which you will inhale as part of this study.

Other people who have taken this medicine have found it to be very effective, leading to a rapid relief of cough and other symptoms. The effects of Proxadrol begin immediately. Proxadrol also protects against any uncomfortable after-effects of capsaicin such as dry mouth and throat irritation so you can resume normal activities soon after the test.

Proxadrol reduces cough by preventing capsaicin from irritating the lungs and throat. It does this by enhancing the body’s natural protective system, neutralising capsaicin (by emulsification) and forming a protective layer in the throat and lungs.

WHAT IS PROXADROL AND WHAT IS IT USED FOR?

POSSIBLE SIDE EFFECTS

Like most potent anti-cough medicines, Proxadrol can cause side effects. But most people can take Proxadrol without experiencing side effects. Here is a list of side-effects that have been associated with proxadrol:

Common (1 in 10):
- Rapid pulse
- Oropharyngeal (mouth and throat) irritation
- Headache
- Nausea
- Light-headedness

Uncommon (1 in 100):
- Bradycardia
- Itching palms
- Yawning
- Diarrhoea
- Vomiting
- Tremor

Rare (1 in 400):
- Muscle cramps
- Taste disturbances

Figure 28: PIL presented in NCI condition
Procedure

Participants first completed the Baseline Measures (Sociodemographics, BMQ-G, PSM, PHQ-9, PHQ-15, STAI-T, and PANAS, FEV1). All participants then completed the baseline capsaicin cough challenge. They were then randomised to undergo one of three conditions (NCI Condition, IAU Condition or Control Condition). Randomisation was determined for each participant using Qualtrics online software. The experimenter was blind as to whether participants were in the NCI or IAU Condition. In each condition, participants read the PIL or message (depending on condition), and then completed the Condition-Specific Measures (BMQ-S and expectations). Participants in the NCI and IAU Conditions then took two puffs of a placebo inhaler. FEV1 was then measured again for all participants before completing a second capsaicin cough challenge. Finally, participants completed the End of Study Measures (manipulation checks) before being fully debriefed (see Figure 29).
Figure 29: Overview of procedures for Study 4. BMQ-G = Belief about Medicines Questionnaire – General, PSM = Perceived Sensitivity to Medicines, PHQ-15 = Patient Health Questionnaire - 15, PHQ-9 = Patients Health Questionnaire – 9, STAI-T = State Trait Anxiety Inventory – Trait, PANAS, Positive and Negative Affect Schedule, BMQ-S = Beliefs about Medicines Questionnaire – Specific, FEV1 = Forced Expiratory Volume 1, PIL = Patient Information Leaflet.

**Statistical analysis**

One-way ANOVAs and independent t-tests were conducted to determine whether there were any significant differences in baseline measures (BMQ-G, PSM, PHQ-15, PHQ-9, STAI-T, FEV1), expectations (Efficacy Expectation, Expected Cough Intensity and Frequency) and specific beliefs about the placebo medication (Specific Necessity and Concerns) across conditions. Pearson’s and Spearman’s correlations were used to determine significant relationships between treatment beliefs (General Benefit, Harm and Overuse, PSM, Specific Necessity and Concerns), expectations (Efficacy Expectation, Expected Cough Intensity and Frequency) and state/trait psychological measures (Depression, Trait Anxiety, Somatisation, Positive and Negative Affect).
In accordance with the dose-response relationship seen in previous literature, for participants who halted the capsaicin cough challenge before reaching C5 and 1000µM, missing values were imputed by doubling the number of coughs of the previous concentration. For participants who reached 1000µM but still did not reach C5, concentrations for C5 outcome variable were imputed at both 1000 µM, 1500 µM and 2000 µM across the data set (Johansson, Ternesten-Hasseus, & Millqvist, 2009; Ternesten-Hasseus, Larsson, Larsson, & Millqvist, 2013). A sensitivity analysis was conducted to determine the effects of these imputations on subsequent statistical tests.

Values for Cu, Cr, C2 and C5 for each capsaicin cough challenge were log transformed. ANCOVAs were then performed to determine whether Log Cu, Cr, C2 and C5 were significantly different across conditions, while controlling for baseline cough challenge scores. ANCOVAs were then performed to examine main effects of treatment beliefs (General Benefit, Harm and Overuse, PSM, Specific Necessity and Concerns), expectations (Efficacy Expectation, Expected Cough Intensity and Frequency) and state/trait psychological measures (Depression, Trait Anxiety, Somatisation, Positive and Negative Affect) on the placebo effect. Interaction effects between treatment beliefs and condition were also examined using ANCOVAs. Continuous variables were used for all analyses. Analyses were conducted using IBM SPSS Statistics v21.
8.3 Results

Of the 72 who expressed interest, 6 did not meet the inclusion criteria. Of the 66 who agreed to take part after screening, 2 did not attend their appointment and 64 attended and completed the experiment.

**Sociodemographics**

The mean age was 23.98 years with the majority being female (75.80%). Around half the sample was currently studying an undergraduate degree with the rest studying for a postgraduate degree. Just fewer than half the sample were of a white British/European and the majority spoke English as their first language (see Table 21).

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.98 (4.68)</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>47 (75.80%)</td>
</tr>
<tr>
<td>Currently studying:</td>
<td></td>
</tr>
<tr>
<td>Undergraduate degree</td>
<td>30 (48.40%)</td>
</tr>
<tr>
<td>Postgraduate degree</td>
<td>32 (51.60%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White British/American/European</td>
<td>32 (51.60%)</td>
</tr>
<tr>
<td>Other</td>
<td>30 (48.40%)</td>
</tr>
<tr>
<td>First Language</td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>39 (62.90%)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (37.10%)</td>
</tr>
</tbody>
</table>

**Baseline measures**

The majority of the sample expressed positive beliefs about pharmaceutical medicines. All but 5 participants scored above the scale mid-point for General Benefit (92%, mean = 3.99, SD = 0.58). Most participants also viewed pharmaceutical medicines as generally safe (74.2%, mean = 2.33, SD = 0.70). Just under half our sample believed pharmaceutical medicines were overprescribed (45.17%, mean = 3.15, SD = 0.78). The majority of the sample scored above the scale mid-point for Positive Affect (82.30%) and below the scale mid-point for Negative Affect (92%). A mean Trait Anxiety score of 35.31 (SD = 8.86) suggesting there was moderate levels of Trait Anxiety across our sample. The majority of
participants scored below the scale mid-point on PSM suggesting generally low perceived sensitivity to the effects of medicines (93.54%, median = 1.60, IQR = 1.20). A median score of 3 (IQR = 4.25) on the Somatisation was observed indicating some participants showed mild somatisation disorder. Finally a median score of 2 (IQR = 4) on the depression scale indicating some participants had mild depression (see Table 22). One-way ANOVAs and Kruskal-Wallis tests revealed no significant differences in baseline measures across conditions (all p > 0.05).

<table>
<thead>
<tr>
<th>Table 22: Baseline measures</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Benefit</td>
<td>3.99 (0.58)</td>
</tr>
<tr>
<td>General Harm</td>
<td>2.33 (0.70)</td>
</tr>
<tr>
<td>General Overuse</td>
<td>3.15 (0.78)</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>35.31 (8.86)</td>
</tr>
<tr>
<td>Positive Affect</td>
<td>33.27 (7.48)</td>
</tr>
<tr>
<td>Negative Affect</td>
<td>12.37 (2.34)</td>
</tr>
<tr>
<td>PSM</td>
<td>1.60 (1.20)</td>
</tr>
<tr>
<td>Somatisation</td>
<td>3.00 (4.25)</td>
</tr>
<tr>
<td>Depression</td>
<td>2.00 (2.6)</td>
</tr>
</tbody>
</table>

Note: PSM – Perceived Sensitivity to Medicines Scale

Relationship between treatment beliefs, expectations and state/trait psychological variables

Pearson’s and Spearman’s correlations were used to test for relationships between Treatment Beliefs, Expectations and Other Psychological Variables (Trait Anxiety, Depression, Affect and Somatization). Participants’ pharmaceutical schema were associated with specific beliefs about the placebo treatment. Individuals were more likely to express Concerns about the placebo medication if they believed pharmaceutical medicines were generally overused. Treatment necessity beliefs were not associated with participants’ Pharmaceutical Schema. Participants were more likely to report higher Efficacy Expectations the greater their treatment necessity beliefs for and lower their Concerns about the placebo medication. Participants were also more anxious about the effects of the placebo medication the greater their Concerns about potential negative effects. Expected Cough Intensity was positively associated with Expected Cough Frequency and negatively associated with Efficacy Expectations. Participants with lower Negative Affect expected to cough less after placebo administration. Finally, participants with
greater Positive Affect tended to have lower PSM and Concerns about the negative effects of the placebo medication (see Figure 30 for statistics).

Participants scoring high in Positive Affect (above the scale mid-point) tended to have lower perceived sensitivity to the effects of medicines in general (PSM: $r (62) = 0.26, p < 0.05$) fewer Concerns about the placebo medication ($r (62) = -0.41, p < 0.01$) and greater Efficacy Expectations ($r (42) = 0.31, p <0.05$). Those who expected to cough frequently tended to have higher Negative Affect ($r (62) = -0.29$, $p < 0.05$).

Finally, those who reported that previous cough medication they used was effective tended to have higher Efficacy Expectations ($r (42) = 0.36, p < 0.05$), expected to have a less severe cough ($r (62) = -0.35, p < 0.01$) and cough less after taking the placebo medication ($r (62) = -0.28, p < 0.05$).

![Figure 30: Significant relationships between participants' Pharmaceutical Schema, Specific Beliefs and Expectations about the placebo medication. PSM = Perceived Sensitivity to Medicines. * $p < 0.05$, ** $p < 0.01$.](image-url)
Was the placebo medication convincing? Manipulation checks and side effect reports

Most of our participants believed the cough medication was, or could be an active drug; only 2 thought the drug was definitely a placebo (NCI Condition: mean = 59.70, SD = 33.10, IAU Condition: mean = 58.70, SD = 30.91). Furthermore at least one side effect was reported by 52.63% of participants, with the most common side effect being throat irritation.

Capsaicin cough challenge

Out of the 64 who took part in the experiment 2 individuals did not cough at all throughout both challenges. Except for these participants all others reached the C2 threshold in both challenges. All but 7 participants reached the C5 threshold during the baseline challenge, whereas 10 participants did not reach the C5 threshold at the second challenge. The concentration required to elicit the C2 and C5 response at baseline was 62.5 µM and 125 µM, respectively. In the second challenge, 125 µM and 500 µM was required to elicit the C2 and C5 response, respectively. Generally, individuals coughed less in the second challenge than at baseline (see Figure 31).

Figure 31: Mean number of coughs at each capsaicin concentration in the baseline and second challenge (+S.E.).
Hypothesis testing

Hypothesis 1: Participants receiving the NCI will exhibit greater perceived need for the placebo medication and greater efficacy expectations in comparison to those receiving IAU.

I conducted independent t-tests to determine whether participants who received the NCI felt like the placebo inhaler was more necessary and had lower concerns and higher efficacy Expectations across conditions. There was no significant difference in perceived need for or concerns about the placebo medication between the NCI and IAU conditions (p > 0.05, see Table 22). Expected Cough Intensity was significantly lower in the NCI Condition compared to the Control Condition (t (43) = 2.40, p <0.05). There was no significant difference in Expected Cough Intensity between the IAU Condition and the NCI and Control Condition, respectively (p > 0.05). There was no significant difference in Expected Cough Frequency or Efficacy Expectation across conditions (p > 0.05, see Table 23).

Mean Specific Necessity scores in each placebo condition were above the scale mid-point suggesting participants felt they needed the medication. Concerns about the placebo medication were below the scale mid-point in each placebo condition suggesting participants were not concerned about any potential negative effects of the medication.

Table 23: Comparison of Specific Beliefs, Efficacy Expectation and Expected Cough Frequency/Intensity across conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean (SD)</th>
<th>NCI (n = 23)</th>
<th>IAU (n=19)</th>
<th>Control (n=20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific Necessity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.17 (0.40)</td>
<td>3.10 (0.62)</td>
<td>--</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Specific Concerns</td>
<td></td>
<td>2.30 (0.63)</td>
<td>2.56 (0.75)</td>
<td>--</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Efficacy Expectation</td>
<td></td>
<td>66.10 (16.40)</td>
<td>61.05 (15.46)</td>
<td>--</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Expected Cough Frequency</td>
<td></td>
<td>27.09 (16.51)</td>
<td>29.63 (18.30)</td>
<td>35.35 (21.56)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Expected Cough Intensity</td>
<td></td>
<td>18.87 (14.13)</td>
<td>23.47 (17.82)</td>
<td>31.45 (20.07)</td>
<td>&lt; 0.05a</td>
</tr>
</tbody>
</table>

Note: NCI = Necessity Coherence Intervention, IAU = Information as Usual. Statistical comparisons - a = NCI – Control.
Hypothesis 2: A larger placebo effect will be observed in the NCI condition compared to those receiving IAU and control.

ANCOVA’s were performed on each dependant variable (Log C5, C2, CR, Cu), while controlling for baseline scores, to determine whether a significant placebo effect was observed. I did not find a significant group effect at C5 concentration however post-hoc analysis revealed participants required a significantly greater capsaicin concentration to elicit a C5 response in the NCI compared to the Control Condition. That is, a larger placebo effect was observed in the NCI condition compared to the Control Condition. No significant difference in the concentration required to elicit the C5 response, and thus the placebo effect, was observed between the IAU Condition and NCI or IAU and Control. This pattern of results was reflected at all C5 data imputations. No significant differences at group level or at pairwise comparison were observed between conditions at Log C2, C5 or Cu (see Table 2 for statistics).

Table 24: Comparison of adjusted means of participants’ log C5, C2, Cr and Cu response across conditions

<table>
<thead>
<tr>
<th>Measure (µM)</th>
<th>Condition (Mean, SD)</th>
<th>p</th>
<th>Omnibus</th>
<th>Post-hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCI (n = 23)</td>
<td>IAU (n=19)</td>
<td>Control (n=20)</td>
<td></td>
</tr>
<tr>
<td>Log C5</td>
<td>5.9 (0.20)</td>
<td>5.84 (0.22)</td>
<td>5.25 (0.21)</td>
<td>0.06</td>
</tr>
<tr>
<td>Log C2</td>
<td>3.96 (1.30)</td>
<td>3.99 (1.22)</td>
<td>3.73 (1.29)</td>
<td>0.91</td>
</tr>
<tr>
<td>Log Cr</td>
<td>3.93 (1.29)</td>
<td>3.91 (1.31)</td>
<td>3.72 (1.29)</td>
<td>0.85</td>
</tr>
<tr>
<td>Log Cu</td>
<td>1.97 (1.39)</td>
<td>2.36(1.53)</td>
<td>1.97 (1.63)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Note: C2 and C5 = Capsaicin concentration required to elicit two or more, or five or more coughs, Cr = Capsaicin concentration required to initiate the cough reflex, Cu = Capsaicin concentration required to elicit the first discernible urge-to-cough, NCI = Necessity Coherence Intervention, IAU = Information as Usual. p values refer to post-hoc pairwise comparisons: a = NCI vs. IAU, b = NCI vs. Control, c = IAU vs. Control.

Hypothesis 3 and 4: Greater perceived need and more positive general beliefs about medicines (high General Benefit, low General Harm and Overuse) and greater PSM will be associated with a larger placebo effect.

ANCOVAs were employed to determine whether treatment necessity beliefs, general beliefs about medicines (General Benefit, General Harm, and General Overuse) and PSM predicted the magnitude of the placebo effect. The four outcome variables (Cu, Cr, C2 and C5) obtained from the second challenge were used as the independent variable. Respective baseline challenge scores for each measure were included as a covariate.

I found a significant main effect of General Benefit on the Log C5 value (Log C5 – 1000: F (8, 62) = 2.72, p < 0.05, partial ETA = 0.30, Log C5 – 1500: F (8, 62) = 2.92,
p < 0.01, partial ETA = 0.20, Log C5 – 2000: F (8, 52) = 3.25, p < 0.01, partial ETA = 0.34). A non-significant interaction effect between General Benefit and Condition on the Log C5 value (F (2, 59) = 2.99, p = 0.06, partial ETA = 0.01). ANCOVAs were then conducted to determine whether there was a significant effect of Condition in participants who scored below or above the median split, while controlling for baseline Log C5 values.

A significant group level effect of condition was observed in participants who scored above the median split on General Benefit (F (2, 8) = 5.15, p = 0.02, partial ETA = 0.38). Post-hoc analysis revealed that participant who scored above the median split on General Benefit required a significantly greater capsaicin concentration to elicit the C5 response in the NCI condition compared to Control Condition. In other words, a significant placebo effect was observed in those who received the NCI compared to Control in those who endorsed the beneficial effects of medicines in general. No significant difference in the concentration to elicit the C5 response was observed between the IAU Condition and NCI or Control Condition in participants who scored above the median split on General Benefit. I did not observe a significant difference in the concentration required to elicit the C5 response at group level or in subsequent post-hoc analyses for participants who scored below the median split on General Benefit. In other words, the NCI had no significant effect on the placebo effect in participants did not endorse the beneficial effects of medicines (see Table Figure 32). No other significant interaction effects were observed between treatment beliefs and my four outcome variables (all p > 0.05).
Figure 32: Interaction effect between general beliefs about medicines in general (General Benefit) and Condition on the concentration of capsaicin required to elicit the C5 response. NCI = Necessity Coherence Intervention, IAU = Information as Usual. ** = p < 0.01.

No significant effects of other treatment beliefs or expectations (Efficacy Expectation, Expected Cough Intensity and Frequency) were found on my four outcome variables and thus no significant effect on the placebo effect. (p > 0.05).

**Exploratory analysis – the effect of other psychological factors (trait anxiety, depression, somatization, affect) on cough sensitivity and the placebo effect.**

ANCOVAs were employed to determine whether trait anxiety, depression, somatization, affect influenced the relationship between General Benefit and the placebo effect. Log C5 scores obtained from the second challenge were used as the dependant variable. Log C5 baseline scores were included as a covariate. No significant effect of these psychological factors on the relationship between General Benefit and the placebo effect was found (all p > 0.05).

Other results found a significant main effect of Depression on the Log C5 concentration (F (8, 62) = 2.44, p < 0.05, partial ETA = 0.39). A significant main effect of Somatisation on the Log C5 Placebo Effect was observed (Log C5 – 1500: F (8, 62) = 2.14, p < 0.05, partial ETA = 0.36, Log C5 – 2000: F (8, 52) = 2.45, p <0.05, partial ETA = 0.39, see Figure 33). That is, those who reported more depressive symptoms and greater tendency to somatise required lower capsaicin concentration to elicit the C5 response. No other significant effects of Trait Anxiety, Positive or Negative Affect on our outcome variables were observed (p > 0.05).
Figure 33: Main effect of Somatisation and Depression on the capsaicin concentration required to elicit the C5 response. The sample was dichotomised at the median score for depression and somatization to visualise the main effect. NCI = Necessity Coherence Intervention, IAU = Information as Usual.
8.4 Discussion

This study is the first to show that general beliefs about the beneficial effects of medicines are positively associated with an objective measure of the placebo effect. However, the NCI condition did not significantly increase treatment necessity beliefs as intended compared to IAU. The NCI, however, did significantly increase the capsaicin concentration required to elicit the C5 response compared to the Control Condition; although there was no significant difference between the IAU and NCI or Control Condition. I then showed that the effect of the NCI on the placebo effect was only significant in participants who tended to endorse the beneficial effects of pharmaceutical medicines. No such effect of our NCI was observed in participants who did not tend to endorse the beneficial effects. Finally I found a significant main effect of depression and somatisation on the concentration required to elicit the C5 response. That is, participants who tended to somatise or reported greater depressive symptoms required a significantly lower capsaicin concentration to cough five or more times.

Relationship between pharmaceutical schema and the placebo effect

There is increasing evidence that placebo effects can influence objective, physiological measures of health in addition to self-reported subjective measures; however evidence is still limited in certain conditions. For example, there are a number of studies stating that placebo effects can affect objective measures of symptoms in patients with Parkinson’s disease such as motor performance (Goetz et al., 2008; Goetz et al., 2000b; Keitel et al., 2013). In asthma, however, there is contrasting results with some studies reporting objective placebo effects, while others are reporting no such effects (Kemeny et al., 2007; Wechsler et al., 2011).

To my knowledge, there is currently only one other study investigating the role psychological factors on the placebo effects in cough. In this study providing an expectation of relief and conditioning procedure resulted in significant reductions in urge-to-cough (Leech et al., 2012). However, this study did not measure objective measures of the placebo effect (i.e. cough frequency). My experiment extends the current literature suggesting that objective measures of cough are susceptible to placebo effects and beliefs about the beneficial effects of medicines in general are associated with this effect. Further research is required to determine whether treatment beliefs are associated with objective placebo effects in clinical samples. This has important clinical implications as potential belief change interventions could
not only change subjective reports of symptoms but also the physiological course of conditions such as chronic cough.

**The effect of the intervention on treatment necessity beliefs**

There may be a number of reasons why the intervention was not effective in modifying treatment necessity beliefs. While some components within illness representations, such as cause, have relevance in this experimental situation, others such as identity, timeline and consequences are difficult to translate. The purpose of the intervention was to increase coherence between medication treatment necessity beliefs and representations of the health threat. The difficulty in translating these illness beliefs into an experimental scenario may therefore be why the NCI was not effective in changing treatment necessity beliefs. Alternatively, messages about treatment necessity may simply not be effective in situations where medication is taken once and in response to capsaicin where participants have been told it has only very short-term effects. As I mentioned in the discussion of Study 3, in order for a NCI to be effective we may need to also tailor medical information around the individuals’ personal representation of the condition.

**Psychological factors in cough severity**

Psychological factors are thought to play a role in cough symptomology such as attentional focus, affect and emotion (Van den Bergh et al., 2012). Interestingly, up to 50% of patients with chronic cough report symptoms of depression and anxiety (Dicpinigaitis, Tso, & Banauch, 2006; McGarvey et al., 2006). Chronic cough can also be successfully treated with use of anti-depressant and anti-anxiety medications such as gabapentin and pregabalin (Ryan, Birring, & Gibson, 2012; Vertigan et al., 2016). To my knowledge this study is the first to suggest that depression and somatization are associated with sensitization to cough triggers. Further research may wish to examine whether depression and somatization have a moderating role in the relationship between expectations/beliefs and the placebo effect. This study was underpowered and may have missed such effects. For example, we know that negative affect and somatization predicts expectations of pain and experienced pain thus depression and somatization may influence the strength and direction of the relationship between beliefs and the placebo effect (Gedney J et al., 2007; Sadeghian F et al., 2014).
Strengths and weaknesses

This study has a number of limitations. As this was a pilot study and due to limited time in my PhD this study was not powered to detect small effects. This may explain discrepancies between the results of this study and my first study i.e. no effect of treatment necessity or PSM on the placebo effect, and the lack of association between expectations and the placebo effect. Further research is clearly required to examine whether the results found in this study remain significant with an adequate sample size. The modified BMQ – S scale also had poor internal consistency. This may be a reason for the lack of association between the placebo effect and treatment necessity beliefs. As I discussed this study recruited highly educated, healthy individuals which limits the generalizability of the present results to a wider population and clinical populations. Participants in this study were not blind to the study conditions. Therefore observer bias may have influenced the results of this study. However, I was blind to whether participants were in the intervention condition (i.e. receiving the NCI) or standard information condition (i.e. receiving IAU). Thus I can determine that experimenter bias did not influence differences in results between the two placebo conditions. I cannot, however, claim that small variations in dialogue between myself and the participant did not influences differences in results between the two placebo conditions and the control condition. As mentioned in the discussions of Study 1 and 2, blind study designs are needed to truly assess the effect of the hypotheses examined in this study and the intervention in the absence of experimenter and observer bias.

Conclusion

To conclude, despite its limitations this study suggests that objective placebo effects are influenced by general beliefs about the benefit of pharmaceuticals. With regards to my research questions the intervention was not successful in modifying treatment necessity beliefs. However, a larger placebo effect was observed in the intervention condition vs. control in participants who believed pharmaceuticals were beneficial in general. Further research is now required to assess the effect of this intervention in a clinical population.
9. General Discussion

9.1. Overview of thesis

Expectations have been the most extensively studied mechanism of the placebo effect (Elsenbruch & Enck, 2015; Holmes et al., 2016; Lidstone, 2014; Vase, Petersen, & Lund, 2014). However, work by Horne and colleagues (Horne, Faasse, et al., 2013b; Horne et al., 1999a) has shown that patients’ perceptions about treatment do not merely consist of expectations of therapeutic outcome. Patients have a wider and more complex set of beliefs conceptualised in the extended model of self-regulation (Cameron & Leventhal, 2003; Horne & Weinman, 2002). We have general “background” beliefs about medicines which inform specific evaluations of the necessity of a particular medicine and potential concerns about its negative effects. Furthermore, specific evaluations of medicines are informed by another set of beliefs – the patients’ representation of their illness. While the Extended CSM has been useful in understanding patients health seeking behaviour, choice in treatment and whether patients adhere to treatment regimens (Cameron & Leventhal, 2003; Horne & Weinman, 2002; Horne et al., 1999a), it had yet to be applied to the placebo effect.

This thesis was designed to assess the role of treatment beliefs and related illness representations in the placebo effect. The research questions addressed were 1) do treatment beliefs predict the placebo effect and 2) are illness representations associated with the placebo effect, 3) can treatment necessity beliefs be changed by a brief information-based intervention to increase coherence between representations of the condition and treatment, and does a change in treatment necessity beliefs result in changes in the placebo effect?
9.2. Original contribution to knowledge

This thesis aimed to contribute to our existing knowledge on the placebo effect by addressing three outstanding research questions. Below I address how each of my studies have provided results to answer these questions.

*Do treatment beliefs predict the placebo effect?*

I addressed this question in three studies using the cold pressor paradigm (Study 1); in patients with GORD and LPR (Study 2) and using the capsaicin cough challenge (Study 3).

Firstly, I found measured treatment necessity beliefs predicted variations in placebo analgesia in response to two placebos described as natural and pharmaceutical. That is, the more participants felt they needed the "medication" the larger the placebo effect. In line with the Extended Model of Self-Regulation, beliefs related to the impending pain – feelings of helplessness – positively informed treatment necessity beliefs about the placebo which in turn led to a larger placebo effect.

In contrast to these results, I did not find a significant relationship between treatment necessity beliefs and the placebo effect using experimentally induced cough (study 4). However, this experiment was underpowered due to time restraints. Therefore further studies are necessary to confirm that prospectively measured treatment necessity beliefs are positively associated with the placebo effect.

In section 2.6.2.2 I proposed that, because negative beliefs about pharmaceutical medicines are often associated with more positive perceptions of natural treatments, pharmaceutical schema may have differential effects on the placebo effect depending on how medicines are described. In this thesis, I confirmed this hypothesis. In particular perceptions about medicines in relation to self i.e. perceived sensitivity to the effects of medicines significantly predicted placebo analgesia in response to a placebo described as “pharmaceutical” but not in response to placebos described as “natural”. That is the more sensitive participants felt they were to the effects of medicines, the greater the pain reduction in response to the placebo described as pharmaceutical.

This result was supported by a lack of association between perceived sensitivity to medicines and the placebo effect in response to a placebo described as “natural” in patients with GORD/LPR. Unfortunately, as the GORD/LPR patients were asked to
stop their current medication for their routine physiology assessment I was unable to
describe the placebo as a pharmaceutical medicine. This meant I could only confirm
the lack of relationship between pharmaceutical schema and the placebo effect in
responses to placebos described as “natural”. Future research may wish to use a
more appropriate study design where such restrictions do not exist (e.g. an RCT) to
explore the role of treatment beliefs on the placebo effect in GORD and LPR
patients, but also other clinical populations.

Interestingly, I found a significant positive relationship between beliefs about the
beneficial effects of medicines in general and the placebo effect using
experimentally induced cough. That is, those who endorsed the beneficial effects of
pharmaceuticals reported a larger placebo effect compared to control than those
who did not endorse the beneficial effects of pharmaceuticals. This contradicts my
findings in my first study using experimentally induced pain. I also did not replicate
the significant relationship between perceived sensitivity to medicines and the
placebo analgesia I found in Study 1. As I have mentioned previously, these
contrasting results may have been due to the fact that my Study 4 being
underpowered. Further work is clearly required to understand these discrepancies.

Are illness representations associated with the placebo effect?

In Study 2 I assessed the effect of representations of GORD and LPR on
participants’ pain intensity in response to saline described as therapeutic. Three
components of participants’ illness representations – beliefs about illness chronicity,
consequences and concerns were associated with participants’ pain intensity in
response to a therapeutic message. That is, a larger therapeutic effect was
observed in individuals who believed their illness was temporary, believed their
illness had little impact on their life and had low concerns about their illness. We
now need to assess whether illness representation also influence the placebo effect
in other types of conditions. Furthermore, it would be interesting to determine
whether the beliefs I found to be associated with the placebo effect in patients with
GORD/LPR are still relevant in other conditions. For example, would beliefs about
the consequences of illness remain a significant predictor of the placebo effects in
conditions which have little consequences (e.g. chronic pain)?

Can treatment necessity beliefs be changed by a brief information-based
intervention to increase coherence between representations of the condition and
treatment and does a change in treatment necessity beliefs result in changes in
placebo effect?
Following from the relationship I found between treatment necessity beliefs and the placebo effect in Study 1 I developed two studies to test the effect of a belief change intervention using an analogue scenario (Study 3) and experimentally induced cough (Study 4). This intervention aimed to increasing the placebo effect my modifying treatment necessity beliefs. Horne has proposed that messages about necessity may be more effective if based around representations of illness (Horne, 2003). I therefore based the information given about a fictitious medication around constructs within illness representations (e.g. cause, controllability, consequences etc.). In the analogue scenario the intervention was not successful in changing treatment necessity beliefs. In a parallel, I examined the effects of this intervention on the placebo effect using a cough induction (Study 4). While the intervention did not modify treatment necessity beliefs, a larger placebo effect was observed in the intervention condition vs. control if participants endorsed the beneficial effect of medicines in general compared to those who did not.

9.3. Limitations of empirical research

This section discusses limitations arising across the entire research in this thesis.

9.3.1 Sampling bias

Sampling bias is one factor which can influence the external validity of my results – the degree to which my findings can be generalized to a wider population. Across my thesis I used a variety of samples to answer my three research questions. This section will address the possibility of sampling bias affecting the ability to answer my research question.

The first outstanding research question in this thesis was do treatment beliefs predict the placebo effect? Studies 1 and 4 addressed this question. Study 1 and 4 used a sample of UCL students. Typically students are healthier, younger and better educated than the general population. This limits the external validity of the results of studies 1 and 4 for a number of reasons. Past and present experience of taking medication is associated with more positive pharmaceutical schema (Horne et al., 2004). Furthermore, I advertised studies 1 and 4 to UCL students as experiments assessing the effects of a new pain-relieving cream/cough medication. Individuals who volunteer for such studies may be more likely to express more positive views
about medicines in general and less likely to express concerns about the placebo medication. My results from these studies may therefore be difficult to extrapolate to clinical populations, those who are less well educated, or older generations. The use of a healthy student population is justified however, particularly because of the deception involved in my studies. Ethically, it is difficult to justify inducing symptoms in individuals who are already experiencing symptoms and subsequently deceiving them with a placebo (Finniss et al., 2010).

I did find contrasting results between Study 1 and 2 however. In Study 1 treatment necessity beliefs and perceived sensitivity to medicines (“pharmaceutical” condition only significantly predicted placebo analgesia. In contrast, Study 4 found a significant effect of general benefit beliefs on the placebo effect. As these studies both used UCL students (and recruited using the same email service) this discrepancy could not be due to a sampling bias. As I mentioned in the discussion of Study 4, the experiment was a pilot study and not powered to detect small effects. This may therefore have been a possible reason for these discrepancies.

The use of healthy individuals to examine my research questions may have impacted on the effect sizes of my results. For example, one may argue that healthy individuals may not have strong treatment necessity beliefs, particularly in the short-term experimental scenarios which they were exposed to. However, I would expect that the strength of the relationship between treatment necessity and the placebo effect would be larger in clinical populations.

Study 2 used a clinical sample of patients with GORD and LPR to address my second question: are illness representations associated with the placebo effect? The reason for using patients with these conditions were that 1) it was an available opportunity during my PhD to explore the effects of treatment beliefs in the placebo effect in a clinical sample, 2) large placebo effects have been observed in clinical trials of GORD medication (Cremonini et al., 2010) and 3) there is currently no research investigating predictors of the placebo effect in this sample. While the results of this study are novel, they are clearly limited to type of patients recruited – tertiary patients, whose symptoms are not well controlled and require invasive oesophageal testing. It is possible that in these patients who may have different illness representations and treatment beliefs to other patients whose illness is well controlled and their medication is effective. However, from the data in this thesis I am unable to determine this.
Study 3 and 4 addressed my final question: can treatment necessity beliefs be changed by a brief information-based intervention to increase coherence between representations of the condition and treatment and does a change in treatment necessity beliefs result in changes in placebo effect? In Study 3 I used a large online sample of non-patients from the general population to assess the effect of a belief change intervention. This was an analogue scenario asking a non-clinical sample to imagine they were taking a medication for asthma. While I chose this method because it allowed me to recruit a large sample size within the time limits of a PhD, it also was due to the ethical issues around modifying treatment information in a clinical population. Previous research using online sampling method have shown this technique to be reliable (Whitehead, 2011), however, other research has shown differences in between online sampling than in other techniques (Bethlehem, 2010). For example, it is known that less educated individuals and non-native young individuals tend to have less internet access, thus restricting the diversity of my sample (Couper, 2000; Dillman & Bowker, 2001). As we know pharmaceutical schema can vary depending on cultural background and thus my use of an online sampling method may have restricted to a largely Caucasian and educated population. In fact, compared to the email service used to recruit students (Study 1 and 4) and through the GI unit at UCLH (Study 2), my online survey recruited the largest amount of White British/American/European individuals. Study 4 used a healthy student sample. As I mentioned in the discussion of the study we must consider to what degree an intervention aimed to increase coherence between treatment necessity and representations of a health threat be relevant in a healthy population. The effect of the intervention warrants further exploration in a clinical population to determine its influence on treatment beliefs, illness representations and the placebo effect.

9.3.2 Assessment of treatment beliefs and illness representations using experimentally induced symptoms

One limitation of my research is the use of experimentally induced symptoms to explore the role of treatment beliefs and illness representations on the placebo effect. Firstly, research which led to the understanding that peoples’ perceptions about medicines could be categorized into specific evaluations about medicines and more general pharmaceutical schema were based on interviews of patients with chronic illnesses (Horne, 2003; Horne et al., 1999b). This calls to questions whether these representations of medicines remain salient in healthy individuals who are
exposed to short-term experimentally induced symptoms. Further research is required to confirm my results in clinical populations.

Secondly, the Extended Model of Self-Regulation suggests that representations of medicines are informed by representations of the individuals’ condition (Horne, 2003). Some constructs within one’s illness representation may be applicable to the experimentally induced symptom such as cause and controllability. Other constructs such as illness consequences and timeline may be less salient in these situations. In Study 1 and 4 participants were told that the experimentally induced pain/cough and the “medication” would have no long-term effect. In contrast, there can be very serious long-term effects of medication and symptoms in clinical populations. For example, long-term acid reflux can lead to oesophageal cancer (Katz, 2000) and long-term PPI use can lead to increased susceptibility to pneumonia, enteric infections and also cancer (Sheen & Triadafilopoulos, 2011). Because of this, in Study 1 I decided to measure a related psychological variable – pain catastrophizing – which has been shown to be associated with negative illness representation. Although my results were in line with theoretical predictions i.e. more negative representations of the experimental pain were associated with greater treatment necessity beliefs, this result needs to be explored in a clinical sample. Similarly, in Study 4 it is difficult to translate representations of illness into situations where symptoms are experimentally induced. Overall, it would be beneficial to confirm these results across a range of clinical populations.

9.3.3 Reliability and validity of the modified BMQ-S scales

As I used a non-clinical sample in to answer two of my research questions I had to modify the BMQ-Specific items. The questionnaire used to measure treatment beliefs in this thesis – the BMQ and PSM – have been validated and extensively used across clinical populations for which they were designed for (Horne et al., 1999a). In this thesis the BMQ-S had to be modified to apply to my lab-based scenarios (studies 1 and 4). This brings into question the validity of the modified BMQ-S scales. Furthermore internal consistency of the modified necessity scale varied between these two studies. In Study 1 where I found a relationship between treatment necessity beliefs and the placebo effect, internal consistency for the modified necessity scale was adequate (0.68). However, in Study 4 where I found no relationship between treatment necessity beliefs and the placebo effect using experimentally induced cough, internal consistency for the modified necessity scale
was poor (0.46). This difference in reliability may have been the cause for the discrepancy in my results.

9.3.4 Experimenter and observer bias

It is well known that subjective reporting in participants can be influenced by the beliefs and/or behaviour of the data collector (Holman, Head, Lanfear, & Jennions, 2015). For example, in clinical trials there is substantial evidence that in non-blind clinical trials, clinical interventions are reported as more beneficial than those in where data collectors were blind to participant condition (Burghardt et al., 2012; Savovic et al., 2012). Furthermore, a lack of blindness is also associated with inflated effect sizes in clinical trials. (Holman et al., 2015) This is due to experimenter and observer bias – where researchers or participants may unintentionally behave or respond differently if they know they are receiving either an active medication or placebo medication.

Social desirability can also lead to this type of bias (Krumpal, 2013). The participants need for social approval or desire to respond in the way they think the experimenter wishes them to could have influenced results of my experiments, and in turn, the ability to answer my research questions. While there is probably little influence of social desirability on my results from my online analogue survey, it is likely that social desirability had some effect on the results of my three experimental studies. For example, it is known that social desirability can influence responses to sensitive questionnaires (Krumpal, 2013). We also know that factors such as experimenter gender can influence subjective symptom reports such as pain severity. That is, male participants tend to report less pain to a female experimenter than male experimenter (Aslaksen, Myrbakk, Hoifodt, & Flaten, 2007).

Studies 1 and 2 were completely unblind. Although I kept interactions with my participants as consistent as possible throughout the data collection, I cannot rule out effects of experimenter bias on my result. In Study 4, I assessed the effect of a NCI on the placebo effect compared to standard medication information (IAU) and a control condition. In this study I was not aware as to whether participants received the NCI or IAU, however I was aware of participants who were in the control condition. Although the effect of experimenter bias is smaller in this study compared to studies 1 and 2, again I cannot rule out the effect of experiment bias on participants in the control condition.
Similarly, observer bias may have contributed to my results. In my study using experimentally induced pain (Study 1) and cough (Study 4) I included measures to ensure participants were not aware of the true aims of my studies. For example, only 6/168 (Study 1) and 2/39 (Study 4) participants who received a placebo medication, believed it was definitely a placebo. This was reflected in participants reporting side effects which further supports the manipulation was effective. However, even in participants who believed they were taking an active medication, there may still have responded in a way which they thought I wanted them to. Unfortunately I did not measure whether participants were aware of the experimental manipulation in my GORD/LPR study (Study 2) or analogue scenario (Study 3). I therefore cannot rule out observer bias in these studies. Further research is required using blind study designs to rule out these effects.

9.3.5 Inconsistencies between studies regarding relationships between treatment beliefs and the placebo effect

While one of the strengths of this thesis is that I used a variety of experimental models and or/conditions to examine the relationship between treatment beliefs and the placebo effect, it is likely that such heterogeneity in study design and models lead to discrepancies between study results. For example, in study 1 I found a significant relationship between PSM, treatment necessity and the placebo effect. In Study 4, I found no such effects, however a significant relationship between general beliefs about medicines and the placebo effect was observed. Possible reasons for these discrepancies could be the lack of power in my final study. The effects of PSM and necessity on the placebo effect in Study 1 were small and thus Study 4 was not powered to detect such effects. Other differences between the two studies were the outcome variables. I assessed the effects of beliefs on objective measures of cough in Study 4, while Study 1 used self-reported subjective measures of pain severity. One may hypothesise that if Study 4 was powered, effects of PSM and necessity would have been observed on objective measures of cough. In contrast though, I do not hypothesise that the lack of an effect of general beliefs about medicines on the placebo in study 1 was an issue of subjective vs. objective reporting. It would be interesting to see if this relationship between general beliefs and the objective placebo effect remained significant in a fully powered study.
9.4. Implications of results

This thesis provides a number of original contributions to our existing knowledge on treatment beliefs and the placebo effect. My thesis brings two long-standing areas of psychology research together – mechanisms of the placebo effect and the Extended Model of Self-Regulation. In the late 1990’s Horne and colleagues (Horne, 1999; Horne & Weinman, 1999; Horne et al., 1999a; Petrie & Weinman, 1997) began show that patients’ perceptions of treatment consist of specific beliefs about their prescribed medication which are informed by more general “social representations” of pharmaceuticals and representations of illness. In the placebo literature, expectations have long been considered one of the principle mechanisms of this phenomenon (Price et al., 2008), with research spanning over 50 years (Brady, Reznikoff, & Zeller, 1960; Gliedman, Gantt, & Teitelbaum, 1957). Horne et al. (Horne, 1999) has previously proposed a relationship between treatment beliefs and the placebo effect, however this thesis is the first to provide evidence that this model is useful in understanding variations in the placebo effect. Below I described implications of my research.

9.4.1. New targets for interventions aimed at increasing placebo effects

There have been a number of ways which researchers have suggested to utilise the placebo in clinical practice (Enck, Bingel, Schedlowski, & Rief, 2013). Firstly, we could optimise the patient-practitioner relationship. For example in GORD, providing an expanded patient-practitioner visit involving discussing causes of the patients GORD-related symptoms, other non-GORD related symptoms they may be experiencing and overall temperament may be helpful in enhancing placebo effects (Dossett et al., 2015). It has also been suggested that we could use placebo conditioning to our advantage. In patients with psoriasis and attention-deficit disorder it has been shown that replacing medication with placebos after an acquisition period, drug efficacy can be maintained while drug dose is reduced. This would lead to reduced adverse events and lower treatment costs (Doering & Rief, 2012; Rief, Bingel, Schedlowski, & Enck, 2011). This thesis has provided another way which we could harness the placebo effect for the patients’ benefit – by targeting their treatment beliefs and illness representations.

This thesis found that the following beliefs were associated with the placebo effect - treatment necessity beliefs, components of pharmaceutical schema – general
beliefs about the beneficial effects of medicines and perceptions of medicines in relation to self (i.e. PSM), and representations of illness (beliefs about chronicity, illness consequences and illness concerns). Can we therefore develop belief change interventions to improve treatment outcomes in clinical practice? Further research is required to assess the effect of my NCI (studies 3 and 4) in clinical populations. There may also be potential to utilize the placebo effect in practice by developing interventions aimed at modifying pharmaceutical schema and illness representations.

Compared to specific beliefs about medicines (e.g. treatment necessity beliefs and concerns), constructs within our pharmaceutical schema are more “attitudinal” and theoretical less responsive to fluctuations in symptoms like treatment necessity beliefs (Cameron & Leventhal, 2003). This may mean that modifying pharmaceutical schema such as general benefit beliefs may be more difficult than specific beliefs but the effects of these interventions may be temporally stronger. A number of studies have successfully modified specific beliefs about medicines (Chapman et al., 2015; Magadza et al., 2009; Petrie, Perry, Broadbent, & Weinman, 2012). A recent study suggests it is possible to modify treatment necessity beliefs and specific concerns in asthma patients by briefing asthma nurses on the NCF (Chapman et al., 2015). Treatment necessity beliefs have also been significantly increased through a targeted text messaging programme in asthma patients (Petrie et al., 2012). However, to my knowledge there have been no studies which have attempted to modify pharmaceutical schema. Further research is therefore clearly warranted to examine whether pharmaceutical schema can also be modified and the temporal effect of these interventions compared to those targeting specific beliefs.

Further research also needs to consider the effect of pharmaceutical schema on interventions aimed at modifying specific treatment beliefs (e.g. treatment necessity beliefs). Pharmaceutical schema, as well as illness representations, informs our specific beliefs about medicines (Horne, 2003). It is possible that pharmaceutical schema and illness representations may influence the effects of specific belief change interventions on the placebo effect. For example, in those who endorse the beneficial effects of medicines (high general benefit beliefs), treatment necessity interventions may be more effective than in those who do not endorse the beneficial effects of medicines (low general benefit beliefs).
These interventions would also impact on adherence. Patients are more likely to be non-adherent if they don’t perceive a benefit from their treatment i.e. perceived efficacy (Korb-Savoldelli et al., 2010; Lee, Glendenning, & Inderjeeth, 2011). Thus improving treatment necessity beliefs or general benefit beliefs would increase the placebo effect and in turn increase adherence.

Using PSM as a potential target for belief change interventions may be a little trickier, however. Previous research has shown that high PSM scores are associated with non-adherence and a higher incidence of reported symptoms following a vaccination (Horne, Faasse, et al., 2013b). My research adds to this which suggests those who believe they are also highly susceptible to the effects of medicines report larger placebo effects. Now some individuals can perceive medication as a “double edge sword” whereby the benefits come hand in hand with their harmful effects (Cameron & Leventhal, 2003). Interventions aimed at increasing PSM to improve the placebo effect may therefore impact negatively on adherence and side-effect reporting. First we need to determine whether we can disentangle beliefs that the positive and negative aspects of treatment do not always come hand in hand. We can then attempt to enhance perceptions of sensitivity to the therapeutic effect of medicines.

I also showed in studies 1, 2 and 4 that there is no relationship between pharmaceutical schema and the placebo effect when the placebo is described as “natural” but a relationship does exist if it is described as a “pharmaceutical” medicine. In countries where use of natural remedies are more common, it may be more efficient to concentrate on investigating how we can modify treatment necessity beliefs than components of one’s pharmaceutical schema. Alternatively, it may also be interesting to further explore the relationship between general beliefs about CAM and the placebo effect for belief change interventions used in conjunction with natural treatments.

We could also attempt to modify illness representations. Study 2 revealed beliefs about illness chronicity, illness concerns and illness consequences were associated with the placebo effect. Previous research has identified a number of intervention techniques which have been successful in modifying illness representations. This, however, may be difficult as promoting positive illness representations may have a negative effect on treatment necessity and in turn adherence.
In conditions such as cancer we do not see reductions in tumour size as a result of placebo treatment. However, we do see subjective placebo (e.g. on fatigue) and nocebo effects (e.g. restlessness) in clinical trial of cancer patients (de la Cruz, M et al., 2009). Furthermore, illness beliefs are associated with mental health after treatment in patients with cancer e.g. depression (Llewellyn et al., 2007). Therefore interventions such as the NCI may have some effect on some clinical outcomes in cancer patients e.g. subjective reports of symptoms and well-being.

However, we must also consider possible limitations of such interventions. Many patients experience significant side effects resulting in non-adherence and experience cancer recurrence. With such an aggressive illness and a lack of safe treatment options would it be ethical to modify patients beliefs? As a healthcare practitioner is important to set expectations of the illness and treatment effects with patients. It would be unethical to try to increase positive beliefs about illness and treatment if it is likely the patient will die soon or if the treatment has many side effects/poor efficacy.

### 9.4.2. Use of treatment beliefs and illness representations by clinicians to aid treatment decisions and to personalise medical information

Assessing treatment beliefs when prescribing treatment to patients would have a number of potential benefits. Horne et al. (Horne et al., 2004) has previously shown that treatment beliefs can significantly differ between cultures. In a cross-sectional study of 500 students from the UK, those who classified themselves as Asian were more likely to view pharmaceuticals as generally intrinsically harmful, and less likely to endorse the beneficial effects of pharmaceuticals compared to European students. Furthermore, general negative orientations towards pharmaceuticals are associated with more positive views about CAMs (Green et al., 2013). When there are a number of treatment options for a patient, orientating the type of medication prescribed around the patients pharmaceutical schema may lead to greater perceived efficacy and in turn greater adherence. Alternatively, as I discussed in Study 1, many modern medicines originate from natural sources (e.g. capsaicin cream used as an analgesic originates from Capsicum annum) (Mason et al., 2004). Can we therefore tailor medicinal information towards the individuals’ treatment beliefs e.g. describing aspirin as a natural product for those who have negative pharmaceutical schema?
Study 2 showed for the first time an association between illness representations and
the placebo effect. I showed that a larger reduction in pain intensity in response to a
therapeutic message is associated with more positive illness representations. This
has important clinical implications for how illness information is presented.
Addressing patients’ representations of their condition in initial consultations could
improve clinical outcomes and reduce re-consultation rates which is common in
GORD and LPR. Alternatively, developing information leaflets or website
information to promote positive illness representations could help to improve the
management of illnesses.

9.4.3. Use of treatment beliefs and illness representations as control
measures in clinical trials

Awareness that patients and practitioners expectations, behaviour and instructions
may also impact on clinical trial results has also led to the widespread use of
double-blind designs where the patient or practitioner is not aware of whether the
drug being taken is active or placebo (Gupta, 2013). Despite the use of more
complex trial designs, and our greater understanding of the placebo effect, there are
a number of reports which have stated that the magnitude of the placebo effect has
actually increased over time (Rutherford & Roose, 2013; Tuttle et al., 2015).

In US clinical trials of neuropathic pain between 1990 and 2013 placebo effects
have increased significantly but drug responses have not. Similarly, in anti-
depressant trials the mean response rate of active medication is 50% while the
mean placebo effect is 31% but has risen by 7% per decade over the past 30 years
(Bridge, Birmaher, Iyengar, Barbe, & Brent, 2009; Walsh, Seidman, Sysko, & Gould,
2002). This poses a problem as drug development has become increasingly more
time consuming and thus more expensive. It has even led to a number of
pharmaceutical companies reducing their research, resulting in warnings of a lack of
new classes of medication such as psychopharmacological agents (Cressey, Jun,
14, 2011; Nutt & Goodwin, 2011).

The measurement of treatment beliefs and illness representations may help to
minimise the magnitude of the placebo effect when assessing new therapies in
clinical trials. In order to detect the true efficacy of a new treatment it is essential
that the non-specific component is of a similar magnitude across trial arms. If
treatment beliefs and illness representations differ significantly across trial arms this
could lead to two issues. Firstly, if participants in the active treatment arm have
more positive treatment beliefs or illness representations compared to the placebo arm it would seem as if the efficacy of the active medication is greater than it actually is. Conversely, if the opposite occurs the mean difference in response to the active medication vs. placebo would be smaller leading to increased likelihood of a non-significant difference in efficacy between treatment arms. Treatment beliefs and illness representations could be measured at baseline and possibly at time points across the trial and used as confounding variables in analysis to control for their effects on treatment response.
9.5. Future directions

9.5.1. The temporal and longitudinal relationship between treatment beliefs, illness representations and the placebo effect.

To fully understand the relationship between treatment beliefs, illness representations and the placebo effect we must employ longitudinal research designs. Firstly, treatment beliefs exist in a symbiotic relationship with illness representations. Treatment necessity beliefs in part originate from representations of our illness and from appraisal of symptom severity after taking medication (Cameron & Leventhal, 2003). Over time symptoms will increase/decrease leading to changes in both representations of one’s illness and perceived necessity of the treatment. Coherence - the degree of fit between individuals’ representations of illness and preferred treatment - may increase between treatment beliefs and representations of illness leading to greater treatment necessity beliefs and in turn a larger placebo effect. On the other hand perceived symptom severity may reduce leading to lower perceived need, and thus in turn a smaller placebo effect. The relationship, however, may be more temporally complex depending on the type of illness. For example, in asthma - a long-term condition where symptoms are cyclical – treatment necessity beliefs would increase and decrease as symptoms come and go, thus leading to fluctuations in the magnitude of the placebo effect, compared to illnesses where symptoms are less changeable.

Depending on the type of illness, belief change interventions which increase the placebo effect may need to be more or less frequent. Continuing with the example of asthma, due to the cyclical nature of asthma symptoms treatment necessity beliefs would fluctuate over time despite it being a chronic condition. Previous research has shown that many individuals with asthma believe if they do not have symptoms of asthma then they no longer have the illness (Halm, Mora, & Leventhal, 2006). Compared to illnesses where symptoms are more stable, administering interventions aimed to increase treatment necessity beliefs and in turn the placebo effect may be more important during these periods of minimal symptoms (i.e. when treatment necessity beliefs are low).
9.5.2. The role of treatment beliefs and illness representations in the placebo effect across different conditions and treatments

While this thesis provides initial evidence for the use of Leventhal's CSM in the placebo effect, further research is required to examine their role in different conditions and medications. As I mentioned in the previous section, depending on whether condition is chronic, acute or cyclical, beliefs may have a differential effect on the placebo effect and on specific evaluations about their medication across the disease time course. What about asymptomatic conditions or in conditions where symptoms are solely objective? The research in this thesis provides evidence for a relationship between these beliefs and the placebo effect in conditions which involve conscious processing and some evidence for a link between treatment beliefs and objective placebo effects. Would these beliefs play a role in conditions where conscious processing is not involved e.g. those involving the immune system? What about in conditions such as hypertension where there are no subjective symptoms?

Firstly, we know that immune responses are susceptible to conditioned placebo effects. Furthermore, we know that these conditioned placebo effects are associated with specific neurotransmitters and neural networks (Vits & Schedlowski, 2014). For example, opioids are responsible for expectancy based pain modulation (Atlas & Wager, 2012), but they are also known to suppress many immune responses such as anti-body production (Al-Hashimi, Scott, Thompson, & Lambert, 2013). One may therefore hypothesise that as opioids play a role in both expectations and the immune response then expectations could influence placebo effects of the immune system. However, Albring and colleagues found no effect of expectations in response to a placebo described as an immunosuppressant on interleukin production but did find an effect of a conditioning procedure (Albring et al., 2012). This is supported by a study by Benedetti which found no effect of expectations on other non-conscious processes – hormone secretion (Benedetti et al., 2003). On the other hand, emerging research suggests that in wound healing, where the immune response plays an important role, psychological factors such as stress, positive affect and social support can influence wound healing rates in clinical populations. Thus, it is possible that placebo effects in certain conditions where unconscious processing is involved placebo effects are influenced by beliefs and expectations, whereas they are not in others. Further research is clearly warranted.
Similarly, further research is also required to investigate the role of these beliefs in other types of medication such as preventative medicine. The CSM suggests that changes in symptom severity inform our representations of our illness and treatment beliefs (after taking a medication). For example, if symptoms do not change, we begin to doubt the necessity of our medication (Cooper et al., 2009; Horne, 2003). In this thesis I have shown that treatment beliefs also inform the perception of our symptoms after taking a medication. That is, greater treatment necessity, general benefit beliefs and PSM lead to a larger placebo effect. I also showed that more positive representations of illness are associated with larger placebo effects. The question is, would we see a similar effect in medication that does not provide any somatic feedback such as statins for hypertension or preventative medication for asthma?

With a lack of subjective reports of symptom change, measures of the placebo effect would be restricted to objective changes in symptoms such as blood pressure. In Study 4 I showed that pharmaceutical schema is associated with objective measures of the placebo effect in cough. Interestingly I did not find a significant placebo effect in subjective cough measures (urge-to-cough) but did with objective measures (number of coughs). However these results must be interpreted with caution due to the small sample size. On the other hand, previous placebo literature suggests that if objective placebo effects are observed they do not always correlated with subjective findings (Goetz C et al., 2002). It may therefore be of interest for future research to investigate whether treatment beliefs and illness representations influence placebo effects in medication whether somatic feedback is minimal.

One of the holy grails of placebo research is to find objective changes in symptoms/disease pathophysiology due to placebo administration. While I have described a number of cases where this has been found in the literature review (section 2.1.5) this research is in only its infancy. From a clinical perspective, it would be beneficial if placebo interventions were able to not only change subjective reports but also influence objective changes in symptoms. However, it is likely that not all conditions are susceptible to objective changes. Furthermore, not all conditions have objective symptoms or at least they are difficult to measure (e.g. pain). One may ask which type of placebo effect would be more important to increase in a clinical setting; however, changes in both are just as important. For example, in chronic conditions such as IBD, a reduction in abdominal pain (subjective) may be the reason they are able to get out bed and socialise. At the
same time, improvements in incontinence (objective) may also have similar effects on a patient life.

9.5.3. The relationship between treatment beliefs and other placebo mechanisms

As I discussed in section 2.2 we know that placebo effects are influenced by a number of mechanisms, however, research shows that these mechanisms do not work in isolation. For example, evidence suggests that in certain situations expectations can play a role in conditioned placebo effects (Benedetti et al., 2003). There is also evidence to suggest that the effects of personality (e.g. optimisms and extraversion), expectations and the patient-practitioner relationship on the placebo effect may be intertwined (Kelley et al., 2009). It is therefore likely that the treatment beliefs and illness representations play a role in other mechanisms of the placebo effect.

9.5.3.1 Conditioning

As described in section 2.2.2 we know that expectations can play a role in conditioned placebo effects. Historically, these two mechanisms of the placebo effect were thought to be separate processes; however, we now know that in certain situations expectations can enhance conditioned placebo effects but also if an individual is given no expectation (told the medication is a placebo) no conditioned placebo effect is observed. Now Benedetti (Benedetti et al., 2003) suggests that expectations are essential for conditioned placebo effects in conscious processes (e.g. pain) but not in unconscious processes (e.g. hormone secretion). More recent evidence which has come to light contradicts this as Jensen et al. (Jensen et al., 2015) has shown that conditioned responses to consciously processed stimuli such as pain can be acquired using unconscious conditioned stimuli i.e. in the absence of expectations.

As shown in this thesis and previous research efficacy expectations are positively associated with treatment necessity beliefs, therefore it is possible that perceptions of perceived need may also play a role in conditioned placebo effects. However, it is likely that the effect of treatment necessity beliefs in placebo conditioning will not be clear cut. Potentiation may be one mechanism by which treatment beliefs may interact with the effect of conditioning on the placebo effect i.e. in the presence of greater treatment necessity beliefs the relationship between the US and CS may be
strengthened (i.e. potentiated), thus leading to a larger placebo effect. From what we know about the effect of expectations on placebo conditioning, it is highly likely that treatment beliefs may influence conditioning procedures in certain situations but not others. Further research is therefore required to determine whether a) treatment beliefs are associated with conditioned placebo effects and b) in what situations do they have an effect and what situations do they not.

9.5.3.2 Patient-practitioner relationship

Healthcare professionals are responsible for providing the majority of information about illness and treatment to patients. Just as patients have their own representations of treatment and illness, healthcare professionals are also likely to have their own representations which may vary depending on their experience and knowledge. Previous research has shown that subtle differences in doctors' words can influence the placebo effect (Pollo et al., 2001). It would be interesting to determine whether doctors' representations influence the communication of treatment and illness information and whether this affects the patients' beliefs and in turn the placebo effect.

The patients' perception of their doctor may also influence the effect of information provided about treatment and illness on the placebo effect. Trust has been shown to be an important determinant in the therapeutic process influencing factors such as acceptance and adherence to recommendations and symptom improvement (Brennan et al., 2013; Haywood et al., 2014). Previous research has shown that in patients with diabetes are more likely to have positive illness representations (greater personal control and that their symptoms will last for a short duration) if they have a positive perception of their doctor (e.g. helpful and trustworthy). Researchers may wish to investigate this relationship further to determine how perceptions of doctors influence illness and treatment beliefs and in turn the placebo effect.

There is also evidence to suggest that physician communication styles can influence treatment beliefs. Bultman et al. (Bultman & Svarstad, 2000) found that in patients taking antidepressants reported greater treatment necessity beliefs and lower concerns if the physician was approachable and informative compared to physicians who were not. This in turn led to greater adherence. Does this communication style also lead to increased treatment necessity beliefs and in turn a larger placebo effect?
9.5.3.3 Personality

In early studies of the placebo effect researchers have attempted to find “placebo-prone” personalities, however, due to contrasting results these efforts have come to no avail. More recent efforts now suggest that we must take into account situational variables (e.g. expectations and the relationship between the patients and practitioner) to fully understand the effects of our personality on placebo effects. Could treatment beliefs be another of these situational variables from which aspects of our personality interact with?

Treatment beliefs and personality

To my knowledge there has only been one study exploring the relationship between treatment beliefs and personality. Emilsson et al. (Emilsson et al., 2011) explored the relationship between 5 key personality traits – neuroticism, extraversion, openness, agreeableness and conscientiousness - and specific beliefs about asthma medication (necessity and concerns). Significant positive correlations were found between a) treatment necessity beliefs and conscientiousness and b) neuroticism and specific concerns. There were also differential effects for men and women. Looking at men agreeableness was significantly positively associated with treatment necessity beliefs, and a negative relationship between extraversion and specific concerns. In contrast, a significant negative correlation between treatment necessity beliefs and neuroticism was found in women. This study however had a small sample size (n=35) thus it is difficult to draw any conclusions between specific treatment beliefs and the personality traits measured. Moreover, pharmaceutical schema was not investigated and so further research is clearly required.

Relationship between treatment beliefs, personality and the placebo effect

There is a wealth of evidence which shows that optimists exhibit an attentional bias towards more positive aspects of a situation when faced with adversity (Geers et al., 2003; Karademas, Kafetsios, & Sideridis, 2007; Urcuyo, Boyers, Carver, & Antoni, 2005). In situations of ill-health optimists tend to focus more on positive aspects of their situation e.g. recovery, than the negative effects e.g. problems caused by surgery, than pessimists (Scheier et al., 1989; Urcuyo et al., 2005). Research also indicates that optimists are more likely to cognitively elaborate on and be persuaded by positively framed messages (Isaacowitz, 2005b; Segerstrom, 2001). When providing information about a medication optimists are more likely to be persuaded by messages of positive expectations. Thus optimism determines the strength in
which expectations influence the placebo effect (Geers, Helfer, et al., 2005). Further research is now required to determine whether personality factors such as optimism influence the effect of treatment beliefs on the placebo effect. This may be particularly important when developing messages aimed at modifying treatment beliefs to maximise the placebo effect.

Certain personality traits have been linked to general negative orientations towards pharmaceutical medicines and concerns about adverse side effects such as introversion and neuroticism (Emilsson et al., 2011; Hong et al., 2010). In this thesis I found a differential effect of participants’ pharmaceutical schema depending on whether I described the placebo as “natural” vs. “pharmaceutical”. I found PSM and general beliefs about the beneficial effects of medicines were associated with the placebo effect in response to a “pharmaceutical” placebo cream (Study 1) and an “anti-tussive medication” (Study 4), respectively. In contrast I found no effect of pharmaceutical schema in response to a “natural” placebo cream (Study 1) or a saline described as “natural” (Study 2). One would hypothesise that more negative personality traits would be associated with more positive beliefs about CAM. It would be interesting to determine how these personality factors are associated with pharmaceutical schema and if this influences their relationship with the placebo effect. As I found no effect of pharmaceutical schema in response to “natural” placebos would they have a similar influence on placebo effects in response to “natural” vs. “pharmaceutical” treatments? Interventions aimed at modifying negative pharmaceutical schema may also be less effective in patients with high introversion and neuroticism.

There are a number of studies examining the relationship between illness representations and personality factors (Najafimanesh, Karambakhsh, Salesi, & Mohammadi, 2016; Rassart et al., 2014; Williams, Abbott, & Kerr, 2015; Zhang et al., 2016) but as of yet no studies investigated how these two factors may interact with the placebo effect. Recent evidence suggests that certain personality types are associated with negative illness representations and poorer clinical outcomes. For example, type D personalities – defined as individuals with high negative affectivity and social inhibition – tend to have more negative illness representations, poorer subjective health and more unhealthy behaviours compared to those with non-type D personalities (Williams et al., 2015; Williams, O'Connor, Grubb, & O'Carroll, 2011).
A recent paper has shown that in cancer survivors optimism was associated with greater perceived personal and treatment control, and illness understanding, but negatively correlated with other IPQ dimensions – illness consequences, illness concerns and emotional representation (Zhang et al., 2016). As optimists tend to have more positive expectations of future outcomes it makes sense that these individuals would have more positive illness representations (Carver & Scheier, 2014). Similarly, another study has shown relationships between illness representations and the big 5 personality traits. In Study 2 I showed that participants who believed their illness had fewer consequences reported a larger therapeutic response to the saline administration than those who believed their illness had many consequences. Rassart et al. (Rassart et al., 2014) found that in patients with type 1 diabetes, illness consequences were negatively correlated with extraversion and agreeableness. Therefore there is possibly some interplay between illness representations and personality factors on the placebo effect which future studies should assess.
9.6 Conclusions

The studies within this thesis have increased our understanding of the psychosocial factors which influence the placebo effect. My results suggest that placebo effects are influenced by a wider set of beliefs about specific treatments, more general beliefs about pharmaceuticals in general and beliefs about one's illness, in addition to expectations. This thesis has provided scope for the development of belief-change interventions to utilize the placebo effect in clinical practice. My research identifies potential ways to utilize treatment beliefs and illness representations to shape treatment and illness information presented to patients' and for more informed treatment decisions when prescribing. My research is also relevant to clinical trials where the placebo effect can confound trial outcomes. Variations in patients' beliefs about treatment and illness across clinical trial arms may lead to either inflated responses to medication in placebo arms or active treatment arms. Measuring patients' beliefs could provide a useful strategy to limit these effects, leading to more efficient trial execution.

Despite the limitations, my research offers a first look at how illness and treatment representations influence the placebo effect. However, I have only scraped the tip of the iceberg. Treatment beliefs and illness representations are part of a dynamic system of beliefs which inform and reinforce each other as one's illness progresses and as treatment is taken. Further research is now required to examine the temporal and longitudinal relationship between treatment beliefs, illness representation and the placebo effect in clinical populations. Representations of treatment and illness are also part of a complex and multifactorial psychosocial context which surrounds treatment. In order to understand the complexity of the placebo effect, we must begin to investigate how factors within this psychosocial context interact. Only then can we truly utilize the placebo effect as a tool to improve treatment response in practice.
10. References


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problem solving skills in England.


11. Appendix

Appendix A: Ethics approval letter for Study 1

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UCL

5 March 2014

Dear Professor Horne

Notification of Ethical Approval

Project ID: 4785/002

I am pleased to confirm that your study has been approved by the UCL Research Ethics Committee for the duration of the project i.e. until March 2015.

Approval is subject to the following conditions:

You must seek Chair’s approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the ‘Amendment Approval Request Form’.

The form identified above can be accessed by logging on to the ethics website homepage: http://www.grad.ucl.ac.uk/ethics/ and clicking on the button marked ‘Key Responsibilities of the Researcher Following Approval’.

It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

Reporting Non-Serious Adverse Events

For non-serious adverse events you will need to inform Helen Dougal, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.
Reporting Serious Adverse Events

The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

With best wishes for the research.

Yours sincerely

Professor John Foreman

Chair of the UCL Research Ethics Committee

Cc:

Andrew Watkinson & Sarah Chapman, Applicants

Jane Portlock
Appendix B – Screening questionnaire for Study 1

An investigation into the effectiveness of a new cough medication
SCREENING QUESTIONNAIRE

- Thank you for taking interest in this study.
- The aim of the study is to compare how effective two new pain relieving creams in healthy volunteers.
- Any medication you are currently taking and any health conditions you may have had recently may therefore affect the results.
- This study is being conducted by Andrew Watkinson as part of his PhD at the School of Pharmacy, University College London.
- We would like to ask you a few questions about you and any medication you might be taking before you take part.
- Please complete the following questions and send this to the following email address to confirm your interest in taking part:
  Andrew.watkinson.12@ucl.ac.uk

<table>
<thead>
<tr>
<th>Demographics</th>
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<tbody>
<tr>
<td>Age:</td>
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<td>Gender:</td>
<td>Male ☐   Female ☐</td>
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<tr>
<td>What subject are you studying?</td>
<td>________________________________</td>
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<tr>
<td>Year of study:</td>
<td>________ year</td>
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<td>Ethnic background:</td>
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### Are you taking any of the following medication?

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<td></td>
<td>If yes:</td>
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<td></td>
<td>What is the name of the medication?</td>
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<td>____________________________________________</td>
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<tr>
<td></td>
<td>What dose are you taking?</td>
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<td>____________________________________________</td>
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<tr>
<td></td>
<td>How long have you been taking this medication?</td>
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<table>
<thead>
<tr>
<th>Anti-depressant medication</th>
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<tr>
<td>Sedatives (e.g. anti-histamines, medication for anxiety or insomnia)</td>
<td>Yes ☐ No ☐</td>
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<tr>
<td></td>
<td>If yes:</td>
</tr>
<tr>
<td></td>
<td>What is the name of the medication?</td>
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<td></td>
<td>____________________________________________</td>
</tr>
<tr>
<td></td>
<td>What dose are you taking?</td>
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<tr>
<td></td>
<td>____________________________________________</td>
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<tr>
<td></td>
<td>How long have you been taking this medication?</td>
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### Have you had any of the following conditions in the past two weeks?

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</thead>
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<td>If yes:</td>
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<tr>
<td></td>
<td>How long have you had this condition for?</td>
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<td></td>
<td>____________________________________________</td>
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</table>

<table>
<thead>
<tr>
<th>Back pain</th>
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<td></td>
<td>If yes:</td>
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<td>Condition</td>
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<td>--------------------</td>
<td>-----</td>
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<tr>
<td>Severe headaches</td>
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<tr>
<td>Arthritis</td>
<td>Yes</td>
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Do you have a history of any of the following conditions?

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<th>No ☐</th>
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<td></td>
<td>If yes: How long have you had this condition for?</td>
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<td></td>
<td>________________________________________________</td>
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<table>
<thead>
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<th>History of cardiovascular disease</th>
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<td></td>
<td>If yes: How long have you had this condition for?</td>
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<td></td>
<td>________________________________________________</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>History of circulation disorders (e.g. Raynaud's)</th>
<th>Yes ☐</th>
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<td>If yes: How long have you had this condition for?</td>
<td></td>
</tr>
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<td></td>
<td>________________________________________________</td>
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</table>

Thank you for completing this screening questionnaire
22 May 2014

Professor Robert Horne

Head of Department of Practice & Policy and Director of The Centre for Behavioural Medicine University College London

BMA House/Mezzanine Floor

Tavistock Square

London WC1H 9JP
Dear Professor Horne

Study title: Psychological predictors of diagnosis and symptom perception in gastro-oesophageal and laryngopharyngeal reflux disease

REC reference: 14/LO/0593
IRAS project ID: 118530

Thank you for your letter of 06 May 2014, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Miss Shehnaz Ishaq
nrescommittee.london-queensquare@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.##AdditionalConditions##
Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering letter on headed paper</td>
<td></td>
<td>March 2014</td>
</tr>
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<td>Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)</td>
<td>B1262F1015 3313</td>
<td>July 2013</td>
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<td>Letters of invitation to participant</td>
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<td>Non-validated questionnaire [Questionnaire Booklet]</td>
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<td>Other [CV: Mr Andrew Watkinson]</td>
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<tr>
<td>Other [Conlist Resolution Reader]</td>
<td>Feb 2013 Version</td>
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<td>Other [CV: Ms. Sarah Chapman]</td>
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</tr>
<tr>
<td>Participant consent form</td>
<td>1.6</td>
<td>May 2014</td>
</tr>
<tr>
<td>Participant information sheet (PIS)</td>
<td>1.4</td>
<td>May 2014</td>
</tr>
<tr>
<td>REC Application Form</td>
<td>118530/5829 5/1/</td>
<td>March 2014</td>
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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
• Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

14/LO/0593        Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project.

Yours sincerely

Signed on behalf of:

Dr Yogi Amin

Chair

Email: nrescommittee.london-queensquare@nhs.net

Enclosures:        “After ethical review – guidance for researchers”

Copy to:           Dr Clara Kalu
                      Mr Philip Diamond, Joint Research Office
Appendix D – comparison tables of baseline measures between those with True vs non-reflux and GORD vs LPR

<table>
<thead>
<tr>
<th></th>
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<th>Mean</th>
<th>Std. Deviation</th>
<th>p-value</th>
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<th>Overuse</th>
<th>PSM</th>
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<th>Timeline</th>
<th>Personal Control</th>
<th>Treatment Control</th>
<th>Identity</th>
<th>Concerns</th>
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Appendix E - Information about asthma provided to participants (obtained from http://www.nhs.uk/conditions/Asthma/Pages/Introduction.aspx).

Asthma is a common long-term condition that can cause coughing, wheezing, chest tightness and breathlessness.

The severity of these symptoms varies from person to person. Asthma can be controlled well in most people most of the time, although some people may have more persistent problems.

The main symptoms of asthma are:
- wheezing (a whistling sound when you breathe)
- shortness of breath
- a tight chest – which may feel like a band is tightening around it
- coughing

Occasionally, asthma symptoms can get gradually or suddenly worse. This is known as an "asthma attack", although doctors sometimes use the term "exacerbation".

Severe attacks may require hospital treatment and can be life threatening, although this is unusual. Symptoms of a particularly severe attack include:

- wheezing, coughing and chest tightness becoming severe and constant
- being too breathless to eat, speak or sleep
- breathing faster
- a rapid heartbeat
- feeling drowsy, exhausted or dizzy
- your lips or fingers turning blue (cyanosis)

Asthma is caused by inflammation of the small tubes, called bronchi, which carry air in and out of the lungs. If you have asthma, the bronchi will be inflamed and more sensitive than normal.

When you come into contact with something that irritates your lungs – known as a trigger – your airways become narrow, the muscles around them tighten, and there is an increase in the production of sticky mucus (phlegm).

Common asthma triggers include:

- house dust
- mites
- animal fur
- pollen
- cigarette smoke
- exercise
- viral infections

Asthma may also be triggered by substances (allergens or chemicals) inhaled while at work.

The reason why some people develop asthma is not fully understood, although it is known that you are more likely to develop it if you have a family history of the condition.
Asthma can develop at any age, including in young children and elderly people. **Your asthma may get better or worse at different times. There may be periods when you have asthma symptoms, but in between you may be generally well, possibly for many years.**

With the right treatment and management, asthma shouldn’t restrict your daily life (including your sleep) in any way.

**Quality of life**

Badly controlled asthma can have an adverse effect on your quality of life. The condition can result in:
- fatigue (extreme tiredness)
- underperformance or absence from work or school
- psychological problems – including stress, anxiety and depression
- disruption of your work and leisure because of unexpected visits to your GP or hospital

**Respiratory complications**

In rare cases, asthma can lead to a number of serious respiratory complications, including:
- pneumonia
- the collapse of part or all of the lung
- respiratory failure – where levels of oxygen in the blood become dangerously low, or levels of carbon dioxide become dangerously high
- status asthmaticus (severe asthma attacks that do not respond to normal treatment)

All these complications are life threatening and will need medical treatment.

**Death**

Although most people are able to effectively control their symptoms, asthma can be a life-threatening condition. Often, people who die from asthma do so at home because they do not recognize when their condition is getting worse or leave it too long to take action.
Appendix F: Ethics committee approval letter for Study 4

19 March 2015

Professor Robert Horne

School of Pharmacy

UCL

Dear Professor Horne

Notification of Ethical Approval

Project ID: 4785/003: A pilot study assessing the effect of a belief change intervention to improve the placebo effect and reduce the nocebo response in cough

I am pleased to confirm in my capacity as Chair of the UCL Research Ethics Committee (REC) that your study has been approved by the UCL REC for the duration of the project i.e. until March 2016 on condition that the Sponsor Pharmacist’s recommendations, outlined in the attached letter, are adhered to.

Approval is also subject to the following conditions:

You must seek Chair’s approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the ‘Amendment Approval Request Form’:

It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

Reporting Non-Serious Adverse Events

For non-serious adverse events you will need to inform Helen Dougal, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the
Committee at the next meeting. The final view of the Committee will be communicated to you.

**Reporting Serious Adverse Events**

The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

With best wishes for the research.

Yours sincerely

Professor John Foreman

Chair of the UCL Research Ethics Committee

Cc: Andrew Watkinson & Sarah Chapman
Appendix G – Screening questionnaire for Study 4

An investigation into the effectiveness of a new cough medication
SCREENING QUESTIONNAIRE

- Thank you for taking interest in this study.
- The aim of the study is to determine how effective a new cough medication is.
- Any medication you are currently taking and any health conditions you may have had recently may therefore affect the results.
- This study is being conducted by Andrew Watkinson as part of his PhD at the School of Pharmacy, University College London.
- We would like to ask you a few questions about you and any medication you might be taking before you take part.
- Please complete the following questions and send this to the following email address to confirm your interest in taking part:
  Andrew.watkinson.12@ucl.ac.uk
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| ACE inhibitors (e.g. medication for high blood pressure, heart failure, diabetic or chronic kidney disease) | Yes | No | What is the name of the medication?
|                                                                                |     |    | ____________________________________________________________________________________________________________|
|                                                                                |     |    | ____________________________________________________________________________________________________________|
|                                                                                |     |    | What dose are you taking?                                                                                       |
|                                                                                |     |    | ____________________________________________________________________________________________________________|
|                                                                                |     |    | ____________________________________________________________________________________________________________|
|                                                                                |     |    | How long have you been taking this medication?                                                                   |
|                                                                                |     |    | ____________________________________________________________________________________________________________|
|                                                                                |     |    | ____________________________________________________________________________________________________________|
| Bronchodilators or inhaled corticosteroids (e.g. any medication taken using an inhaler) | Yes | No | If yes:                                                                                                           |
|                                                                                |     |    | What is the name of the medication?
|                                                                                |     |    | ____________________________________________________________________________________________________________|
|                                                                                |     |    | ____________________________________________________________________________________________________________|
|                                                                                |     |    | What dose are you taking?                                                                                       |
|                                                                                |     |    | ____________________________________________________________________________________________________________|
|                                                                                |     |    | ____________________________________________________________________________________________________________|
|                                                                                |     |    | How long have you been taking this medication?                                                                   |
|                                                                                |     |    | ____________________________________________________________________________________________________________|
| Sedatives (e.g. anti-histamines, medication for anxiety or insomnia)           | Yes | No | If yes:                                                                                                           |
|                                                                                |     |    | What is the name of the medication?
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What dose are you taking?  
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How long have you been taking this medication?  
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Allergies related to your lungs over the past 4 weeks

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Thank you for completing this screening questionnaire