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Understanding and preventing nocebo responses to medicines

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Understanding and Preventing Nocebo Responses to Medicines

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Abstract

A placebo effect is the experience of unpleasant symptoms in response to an inert exposure. The effect may explain many of the side effects that are attributed to medications. Preventing placebo effects should reduce costs to health services and improve patients' quality of life.

The mechanisms underlying placebo effects may include misattribution of symptoms, learning from past experiences, conditioning or social observation, and conscious expectation. In a systematic review of 89 studies testing predictors of symptom reporting following an inert exposure, I found considerable evidence supporting the role of expectations.

Using this evidence, I developed and piloted an intervention to reduce expectations by reframing the side effect information in patient information leaflets (PILs), reporting the chance of remaining side effect free rather than the risk of developing side effects. In a randomised controlled trial (RCT) of 203 healthy volunteers, this reframing significantly reduced the likelihood of participants attributing symptoms to a sham medicine.

To determine how the English population interpret the current side effect wording in PILs, I carried out a cross-sectional survey of a nationally representative sample of 1003 people. This showed that current wording results in unreasonably high side effect expectations, adding justification for the wording to be altered.

As part of the systematic review and RCT, I also examined associations between baseline characteristics and symptom reporting. The results showed little support for the importance of demographic or personality characteristics. However, medicine-related beliefs are important risk factors for placebo effects, and could be targeted in future interventions.

Overall, my works suggests that the way we currently communicate about side effect risks is ineffective, that reframing risk may be beneficial, and that assessing medicine-related beliefs may allow us to identify patients at risk of experiencing placebo effects. Future work is needed to test these findings in a patient sample.

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Abbreviations

Abbreviation	Meaning
ADR	Adverse drug reaction
APA	American Psychological Association
B	Between subjects design
BMQ	Belief about medicines questionnaire
BPS	British Psychological Society
CASP	Critical appraisal skills programme
CCK	Cholecystokinin
CO ₂	Carbon dioxide
COMT	Catechol-O-methyltransferase
DA	Dopamine activation
EC	European commission
EMF	Electro-magnetic fields
GASE	Generic assessment of side effects
HPA	Hypothalamic-pituitary-adrenal
IEI-EMF	Idiopathic environmental intolerance attributed to electromagnetic fields
KCL	King's College London
LOT-R	Revised life orientation test
MHRA	Medicine and Healthcare Products Regulatory Agency
MPI	Mass psychogenic illness
NHS	National Health Service
NIHR	National Institute of Health Research
ns	non-significant
O ₂	Oxygen

OR	Odds ratio
OTC	Over the counter
P	Prospective design
PHQ	Patient health questionnaire
PIL	Patient information leaflet
PS	Perceived sensitivity
PPI	Patient and public involvement
RCT	Randomised controlled trial
RR	Rate ratio
rTMS	Repetitive transcranial magnetic stimulation
SARS	Severe acute respiratory syndrome
tsp	teaspoon
U/K	Unknown
UPDRS	Unified Parkinson's disease rating scale
W	Within subjects design

Publication status

Several of the Chapters reported in this thesis have previously been published as peer-reviewed articles. These are:

Chapter 2: Webster, R. K., Weinman, J., & Rubin, G. J. (2016). A systematic review of factors that contribute to placebo effects. *Health Psychology*, 35(12), 1334-1355. doi: 10.1037/hea0000416

Chapter 7: Webster, R. K., Weinman, J., & Rubin, G. J. (2018). Positively Framed Risk Information in Patient Information Leaflets Reduces Side Effect Reporting: A Double-Blind Randomized Controlled Trial. *Annals of Behavioral Medicine*, kax064-kax064. doi: 10.1093/abm/kax064

Chapter 8: Webster, R. K., Weinman, J., & Rubin, G. J. (2018). Medicine-related beliefs predict attribution of symptoms to a sham medicine: A prospective study. *British Journal of Health Psychology*, n/a-n/a. doi: 10.1111/bjhp.12298

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Chapter 10: Webster, R. K., Weinman, J., & Rubin, G. J. (2017). How does the side effect information in patient information leaflets influence peoples' side effect expectations? A cross-sectional national survey of 18 to 65 year olds in England. *Health Expectations*, 00, 1-10, doi: 10.1111/hex.12584

Extra paper

In a survey undertaken by our wider team, I had the opportunity to add in a measure of interest that related to my PhD. This work is not reported in detail in this thesis, but is described in brief in Chapter 9:

Chapter 9: Smith, L. E., Webster, R. K., Weinman, J., Amlôt, R., Yiend, J., & Rubin, G.

J. (2017). Psychological factors associated with uptake of the childhood influenza vaccine and perception of post-vaccination side-effects: A cross-sectional survey in England. *Vaccine*, 35(15), 1936-1945. doi: 10.1016/j.vaccine.2017.02.031

Statement of Contribution

The original concept for this PhD was suggested by Dr Rubin. Upon starting the PhD, this was further developed by myself in terms of the studies that needed to be carried out (one of which I secured extra funding for [see Chapters 9 & 10]) and what exactly these would entail (e.g. the design). The design for each of the studies was developed by myself, with advice from my supervisors and a patient and public involvement group who advised on their appropriateness and feasibility.

I carried out the data collection for all the studies, apart from the survey in which Ipsos MORI were contracted to recruit a representative sample. I carried out the data analysis for all studies and interpreted the results which were subsequently discussed at meetings with both my supervisors.

To help with the statistical applications I took advice from the biostatistics advisory service offered to PhD students at King's in terms of sample size calculations and advanced analyses before carrying out the analyses myself.

I drafted the Chapters and manuscripts for publication and once completed I sent them to my supervisors for their comments. I then revised the Chapters and manuscripts accordingly. Peer-review comments from the manuscripts I submitted for publication were discussed with both my supervisors and a plan of action on how to address them was agreed. I gave final approval of the version of the manuscripts to be published.

Chapter 1 Introduction

In 2006, ‘Mr A,’ a patient enrolled in a clinical trial for depression, acted on impulse and swallowed 29 of the tablets that he had been prescribed. He immediately regretted his attempted overdose and attended his local emergency department, where he collapsed. Physicians reported him to be “pale and diaphoretic with a blood pressure of 80/40 and heart rate of 110. He was tremulous, and respirations were rapid.” Saline infusions were begun to stabilize his blood pressure. Only four hours and six litres of saline later did a physician from the clinical trial team arrive and clarify that Mr A had been in the placebo arm of the trial: there had been no overdose. Within minutes of hearing the news, a tearfully relieved Mr A “was fully alert, blood pressure was 126/80, heart rate was 80” (Reeves, Ladner, Hart, & Burke, 2007). The unfortunate Mr A had fallen victim to a ‘nocebo effect’.

1.1 What is the nocebo effect?

The nocebo effect has been described as the flip-side to the placebo effect, whereby an adverse reaction is experienced by someone who receives an inert exposure (Kennedy, 1961). The name ‘nocebo’ was created to distinguish between the desirable and undesirable effects of an inert exposure (Hauser, Hansen, & Enck, 2012). Just as positive expectations can lead to beneficial effects from an inert exposure (the placebo effect) so too can negative expectations lead to harmful effects (Hahn, 1997). An inert exposure in this context is a substance or procedure that has no active medicinal or physiological properties able to directly influence the symptom experience in the receiver. In the context of experimental trials, inactive substances are often called “sham” exposures and used as a control condition for the active exposure or medication that is under investigation (Barsky, Saintfort, Rogers, & Borus, 2002).

1.2 Nocebo effects in environmental exposures

Although originally defined in terms of inert exposures, more recently the nocebo effect has been used to describe the non-specific side effects experienced following exposure to very low intensity physical stimuli that are suspected to be unable to cause any specific physiological effect (Faasse & Petrie, 2013). For example, the advancement of many new technologies has been met with the development of symptomatic complaints. These include headache and fatigue attributed to electromagnetic fields (EMF) from mobile phones and Wi-Fi (e.g. Baliatsas et al. (2012); Rubin, Cleare, and Wessely (2008)), ear problems, dizziness and nausea attributed to infrasound from wind farms (Knopper & Ollson, 2011; Simonetti & Chapman, 2012), and similar symptom complaints reported in relation to the magnetic fields emitted from overhead power lines (Porsius, Claassen, Woudenberg, Smid, & Timmermans, 2016). There is little empirical support for a direct pathophysiological link between any of these stimuli and health complaints (Bolin, Bluhm, Eriksson, & Nilsson, 2011; Rubin, Nieto-Hernandez, & Wessely, 2010). Although these effects impact people's quality of life and can cause distress, multiple double-blind experiments have repeatedly shown that sham exposures are just as likely to trigger symptoms in affected patients as real ones.

Non-specific symptoms can also arise from suspected food intolerances. For example many people report being lactose intolerant, but show no signs of lactose malabsorption following objective testing (Suarez, Savaiano, & Levitt, 1995). Similar results have been seen for self-reported food allergies in the UK and Germany (Young, Stoneham, Petrukevitch, Barton, & Rona, 1994; Zuberbier et al., 2004), while feeding people with self-reported gluten intolerance a series of high-gluten meals has no apparent effect on symptom reporting when done under double-blind conditions (Biesiekierski et al., 2013). If the symptoms reported by these highly prevalent

conditions are not triggered by the food itself, where then do they come from? The nocebo effect is a likely culprit.

Demonstrations of these effects are not restricted to the laboratory. A clear example of a nocebo effect was seen in 2010 when the mobile network iBurst erected a mobile phone mast in a town near Johannesburg, South Africa. iBurst received complaints from local people of headaches, nausea, tinnitus, itchy skin and disrupted sleep as a result of the mast (Douglas, 2010). Although iBurst called a meeting to explain the mast was very low powered and that there was no scientific evidence to suggest that these symptoms were due to the signals from the mast, opposition persisted. In the end iBurst agreed to turn off the tower. In doing so they found out that a mistake had been made. The tower had already been turned off six weeks previously (Douglas, 2010). No signals were being emitted while symptoms were being reported.

Such nocebo responses are common for environmental exposures where the agent is invisible, making it harder for people to tell if they have been exposed. And when apparent environmental exposures are sudden and feared, symptom reporting can sometimes be dramatic. For example in 1995 immediately after the subway sarin nerve gas attack in Tokyo, hospitals in Tokyo were flooded with 4000 patients as a result of the attack. Roughly 85% of these patients, who were suffering from symptoms such as nausea and dizziness, had not been exposed to the sarin (Smithson & Levy, 2000). Similar effects are seen regularly following major disasters or terrorist incidents: from radiological disasters, to scud missile attacks in the Gulf War, to the SARS outbreak, most symptomatic patients seen by healthcare workers are found not to have been exposed to the hazard in question (Hyams, Murphy, & Wessely, 2002; Page, Petrie, & Wessely, 2006; Rubin & Dickmann, 2010).

1.3 Nocebo effects in medication

As well as explaining symptoms attributed to environmental exposures, some non-specific side effects experienced in relation to medications may arise also through a nocebo effect (Barsky et al., 2002).

It is widely acknowledged that drugs may generate adverse reactions, with studies showing that around 6.5% of patient admissions to hospitals are related to an adverse drug reaction (ADR) (Davies et al., 2009). An ADR is “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function” (World Health Organisation, 1972). These ADRs can have serious implications, for example medication side effects can significantly reduce patient adherence to their medication (Ammassari et al., 2001) leading to reduced therapeutic benefit for the patient. Not only do ADRs put physical and psychological strain on patients, they also lead to financial costs for health services as they are a major cause of hospital admissions, and emergency department and outpatient care visits (Monguio, Otero, & Rovira, 2003). Pirmohamed et al. (2004) have estimated that ADR hospital admissions cost the National Health Service (NHS) £466 million annually. Non-adherence as a result of ADRs creates a further substantial cost, estimated to cost the NHS up to £196 million annually and up to £4 billion per year wasted on prescribed medication that is not taken as directed (National Institute For Health and Clinical Excellence, 2009).

Less well-reported is that these ADRs are not always related to the physiological action of the medication (Faasse & Petrie, 2013). For example, de Frutos Hernansanz et al. (1994) noted that only 10.9% of reported ADRs to commonly prescribed drugs were clearly attributable to the medication, the remaining 89.1% were judged to be only probably or possibly related. Instead, many non-specific side effects that are attributed

to medication are thought to occur due to a placebo effect (Barsky et al., 2002). A dramatic example of this can be found in the Eltroxin health scare in New Zealand. Eltroxin is a thyroid hormone replacement tablet primarily used to treat an underactive thyroid. After a change in formulation of this tablet in 2007, reports of side effects began to rise dramatically in the country (Faasse & Petrie, 2013). The side effects included lethargy, joint pain and depression as well as symptoms not normally associated with the drug or disease such as itching and nausea. However the active ingredients in the drug had not changed. The only change was that the manufacturer, GlaxoSmithKline, had moved its manufacturing process from Canada to Germany and as a result the drug's inert qualities, size, colour and markings had been altered (Scudellari, 2013). It was noticed that there was a spike in symptom reporting to official agencies following each TV broadcast about the scare, and that symptom reports matched those that were specifically mentioned in the broadcast (Scudellari, 2013). As such, it appeared to be the media hype surrounding the health scare that triggered the increased rates of ADR reporting, rather than any pharmacological change (Faasse & Petrie, 2013).

High levels of apparent placebo effects associated with medication can also be observed during emergency responses to public health crises. For example, in the early stages of the 2009/10 swine flu pandemic, antivirals (primarily oseltamivir) were prescribed as a prophylactic measure to people who might have come into contact with infectious patients. Public health officials were surprised by the number of people who reported side effects to oseltamivir (around 50% in some settings (Kitching, Roche, Balasegaram, Heathcock, & Maguire, 2009)) which dramatically exceeded expectations based on clinical trial data (20%). Similarly surprising levels of side effects were reported during the US anthrax attacks in 2001 when ciprofloxacin was prescribed as a

precautionary measure to 10,000 postal workers (Stein et al., 2004), with 46% subsequently reporting non-specific symptoms (Brechner et al., 2001).

Sudden, population-wide effects such as this are eye-catching, but thankfully rare. Individual reactions to medicines are more common and are a general problem across all types of medicines. Systematic reviews and meta-analyses of the side effects reported in the placebo-controlled arm of clinical trials have shown that 4-26% of patients in statin drug trials discontinue placebo use because of perceived side effects (Rief, Avorn, & Barsky, 2006); 64.7% of patients in trials of pharmacological treatments for Parkinson disease report at least one side effect (Stathis, Smpiliris, Konitsiotis, & Mitsikostas, 2013); 52.0% of patients in trials of pharmacological treatment for neuropathic pain report side effects (Papadopoulos & Mitsikostas, 2012); 74.4% of patients in trials investigating disease-modifying treatments for multiple sclerosis report side effects (Papadopoulos & Mitsikostas, 2010); and 66.7% of patients in trials investigating treatments for Alzheimer's disease report side effects (Amanzio, Benedetti, & Vase, 2012). The high prevalence of side effects reported in the placebo arm of clinical trials shows just how common these nocebo effects can be. In addition, the side effects in the placebo arms tend to corresponded to those of the active medication which the placebo is compared against, something which patients are warned about before the start of the trial (Amanzio, Corazzini, Vase, & Benedetti, 2009). Indeed evidence suggests that between 38% and 100% of medication side effects are caused by non-specific factors dependent on the treatment context such as finding out about the potential side effect and the doctor-patient interaction, rather than by the active ingredients in the medication itself (Mahr et al., 2017).

Regardless of their cause, the presence of non-specific medication side effects can have a substantial impact on people's willingness to adhere to their medication (Ammassari et al., 2001; Kardas, Lewek, & Matyjaszczyk, 2013; Stein et al., 2004).

Research to understand whether these side effects are triggered by a nocebo effect, and if so, how to reduce them, could improve adherence and save lives in such instances.

1.4 Theories of the nocebo effect

Due to the problems nocebo effects can cause in terms of the side effects attributed to medication and symptoms from suspected environmental exposures, there is an obvious need to understand the mechanisms for how they occur. Although several theories exist, our knowledge about the mechanisms underlying nocebo effects still falls behind the understanding we have of the placebo effect. Deliberately inducing negative symptoms in research participants using techniques that often involve deception is often poorly received by ethical review boards, reducing the amount of work that has been done. While early research focused on psychological accounts of the phenomenon, more recent work has begun to explore possible immunological, endocrine and genetic mechanisms.

1.4.1 Biological mechanisms

Research into the biological mechanisms of nocebo effects can be broadly grouped into three lines of research: neurochemical, neuroimaging and genetic studies.

1.4.1.1 *Neurochemical*

The role of neurochemicals in nocebo responses has been best shown in the field of pain. A series of studies have highlighted the role of the neurotransmitter cholecystokinin (CCK) in nocebo hyperalgesia responses (Benedetti, Amanzio, Viggetti, & Asteggiano, 2006). In the first of these studies, postoperative patients were given proglumide, a CCK antagonist, during nocebo hyperalgesia induced by administration of saline solution which they were told would produce a pain increase (Benedetti, Amanzio, Casadio, Oliaro, & Maggi, 1997). This study found that the administration of proglumide prevented nocebo hyperalgesia in a dose-dependent manner, therefore suggesting that nocebo hyperalgesia is mediated by the transmission

of CCK (Benedetti et al., 1997). As CCK is involved in anxiety mechanisms it was thought that proglumide could also affect placebo hyperalgesia by preventing the generation of anxiety about the impending pain (Benedetti et al., 1997). To test this, Benedetti et al. (2006) studied experimental ischemic arm pain in healthy volunteers and found that administration of an inert substance, along with verbal suggestions of hyperalgesia, induced hyperalgesia and activity of the hypothalamic-pituitary-adrenal (HPA) axis which is involved in the stress response. After administration of diazepam (an anti-anxiety drug), both HPA activity and placebo hyperalgesia were blocked. However when just the CCK antagonist, proglumide, was given only hyperalgesia was prevented, there was no effect on the HPA axis (Benedetti et al., 2006). This suggests that CCK does not act on placebo-induced anxiety but, rather, on the placebo/anxiety-induced hyperalgesia. Therefore proglumide does not block anticipatory anxiety of impending pain as previously thought, and instead must interrupt the link between anxiety and pain (Colloca & Benedetti, 2007).

As well as CCK, endogenous opioids and dopamine activity have been implicated in placebo research. Benedetti, Lanotte, Lopiano, and Colloca (2007) have found that verbal suggestions of a decrease in pain activates endogenous opioid neurotransmission, while suggestions of an increase in pain activates the CCK receptors. Supporting this, Scott et al. (2008) has shown that placebo responses to a pain challenge are associated with greater dopamine activation (DA) and opioid activity, whereas placebo responses are associated with deactivations of dopamine and a decrease in opioid release.

1.4.1.2 Neuroimaging

Neuroimaging techniques have added to our knowledge of which brain structures are active during the experience of placebo effects. Again studies in the pain field have tended to show that placebo effects are mediated by the hippocampus and

regions involved in anticipatory anxiety processing. Kong et al. (2008) compared functional magnetic resonance imaging responses following thermal stimuli of equal intensity delivered at control sites or at nocebo sites (where participants were conditioned or told to expect pain) on participants' right forearms. Increased pain reports for the nocebo sites were associated with increased activity in the medial pain matrix, which included the bilateral dorsal anterior cingulate cortex, insula, left frontal and parietal operculum, orbitofrontal cortex, and hippocampus. In a subsequent study that investigated the influence of expectancy on the analgesic effect of remifentanyl, Bingel et al. (2011) found that positive expectancy effects were associated with activity in the endogenous pain modulatory system, and negative expectancy effects with activity in the hippocampus, suggesting different mechanisms underlying placebo and nocebo effects. However Scott et al. (2008) found an overlapping network. In this study, placebo responding to a 20 minute pain challenge was associated with enhanced opioid neurotransmission in the anterior cingulate, orbitofrontal and insular cortex, nucleus accumbens, amygdala, and periaqueductal gray, as well as DA in the ventral basal ganglia, including the nucleus accumbens. Nocebo responding was associated with the opposite changes in brain activity: a decrease of DA, and decreased opioid release in those brain regions. Endogenous opioids and DA have also been identified as neurochemical systems involved in nocebo responses (Planès, Villier, & Mallaret, 2016), as highlighted previously.

Studies that directly compare the placebo and nocebo effects using the same cohort of subjects may help provide a general model of how different expectancies can modulate brain responses. Freeman et al. (2015) manipulated subjects' treatment expectation of the effectiveness of different inert creams administered before noxious stimuli and found that the expectation of an increase in pain induced significant activity in the insula, orbitofrontal cortex, and periaqueductal gray, whereas the expectation of

pain relief evoked significant activity in the striatum. There were no brain regions which were common to both positive and negative expectation conditions, suggesting they engage different brain networks, rather than acting in opposite directions within a common network.

However, considering the broad range of potential physiologic systems and symptoms, various exchanges between placebo and nocebo mechanisms may occur for each symptom and physiologic system (Enck, Benedetti, & Schedlowski, 2008). To further our understanding we need to directly compare placebo and nocebo responses in the absence of an active treatment in the same cohort of subjects for different symptoms. This has started to be done with recent studies looking at brain activity during nocebo responses in itch (Napadow et al., 2015) and neurochemical activity during hypobaric hypoxia headaches (Benedetti, Durando, & Vighetti, 2014). This work is still very much in its infancy, however, Napadow et al. (2015) found that patients with greater dorsolateral prefrontal cortex and caudate activation to a real allergen also had greater activation in these areas for nocebo-induced itch. This suggested that the prefrontal and striatal circuitry activated by the real allergen is also activated to support this nocebo-induced itch sensation. In addition, they found an association between patients reporting greater nocebo-induced itch and those reporting greater reduction of allergen itch ratings following a placebo intervention, suggesting increased capacity for generalised modulation of itch perception in these patients through the involvement of cortico-striatal brain activity (Napadow et al., 2015).

Benedetti et al. (2014) studied altitude induced headaches and the cyclooxygenase- prostaglandins pathway (involved in triggering high altitude headaches). They found a significant increase in headache and salivary prostaglandins and thromboxane in a nocebo group who received negative information by an individual who was informed of the risk of headache at high altitude compared to a control group,

suggesting that negative expectations enhance cyclooxygenase activity (Benedetti et al., 2014). Placebo administration to headache sufferers at high altitude reduced pain and prostaglandins synthesis, indicating that the cyclooxygenase- prostaglandins pathway (involved in triggering high altitude headaches) can be modulated by both nocebos and placebos (Benedetti et al., 2014).

1.4.1.3 Genes

A limited amount of research has started to point to the involvement of genes in predicting those who may be more susceptible to placebo responses. Wendt et al. (2014) focussed on the genetic polymorphisms in the catechol-O-methyltransferase (COMT) gene (Val158Met), which has previously been implicated in studies looking at genetic risk factors for patients' responsiveness to placebo analgesia in irritable bowel syndrome (Hall et al., 2012). They analysed side effects at baseline and after ingestion of a sham immunosuppressive medication in 62 healthy male subjects, and found significantly more side effects were reported from Val/Val homozygous carriers compared to the Val/Met or Met/Met genotype groups (Wendt et al., 2014). Schedlowski, Enck, Rief, and Bingel (2015) notes that this supports a link between the dopaminergic system and placebo effects, as the val genotype is associated with a 3-4 times higher breakdown of brain dopamine than the met variant of the COMT gene.

1.4.2 Psychological mechanisms

The placebo literature provides evidence for a range of different psychological mechanisms that could explain the occurrence of placebo effects. Research can be broken down into four main areas: misattribution, expectation, learning and predisposing factors.

1.4.2.1 Misattribution

It is possible that people may misattribute pre-existing or unrelated symptoms to the effects of a new exposure, with placebo effects being the simple product of such

misattribution. Symptoms are common throughout the world (Eriksen, Hellesnes, Staff, & Ursin, 2004; Petrie, Faasse, Critchon, & Grey, 2014), with very few people reporting no symptoms in the last 30 days (Ihlebaek, Eriksen, & Ursin, 2002). Although these symptoms are often short-lived and do not cause any particular alarm, when subjected to a new exposure those symptoms that were present before the exposure or which occur coincidentally after the exposure are available to be mistakenly attributed to it (Cocco, 2009). For example, Petrie et al. have shown one of the strongest predictors of whether people attribute symptoms to exposures such as pesticide spraying and travel vaccinations is the number of symptoms reported before such exposure occurred (Petrie et al., 2005; Petrie, Moss-Morris, Grey, & Shaw, 2004).

Despite representing a logical and relatively straightforward explanation for some symptoms attributed to medications and other exposures, there is disagreement about how to conceptualise misattribution in the literature. While many researchers label all cases of symptom reporting following sham administration as nocebo effects, others explicitly exclude misattributed symptoms, e.g. Enck, Bingel, Schedlowski, and Rief (2013), and Colloca and Miller (2011), preferring to categorise only those symptoms generated as a direct result of a perceived exposure as a ‘true nocebo effect.’

1.4.2.2 Expectations

Negative expectations have also been suggested as contributing to the nocebo effect (Hahn, 1997). These negative expectations are generated as the product of cognitive engagement involving the subjective likelihood of a future effect and are often induced by verbal suggestions (e.g. Jaen and Dalton (2014)), written information (e.g. Myers, Cairns, and Singer (1987)) or cultural beliefs (Hahn, 1997). According to this theory, the simple act of informing people about the possible side effects of an exposure can make it more likely that they will develop them, as negative expectations make the individual more likely to attend to new or changed sensations, and to attribute them to

the exposure (Barsky et al., 2002). For example, Benedetti et al. (1997) showed that post-operative patients given an injection of saline and told that it would increase pain, reported significantly more pain than patients given the same injection which was administered behind a screen through an intravenous line so they were unaware it had been administered. The increase in an unpleasant experience due to negative expectations may occur through perceptual biases, for example people may notice signs that they would not have noticed otherwise but that would have occurred anyway (Ross & Olson, 1981). Or it may occur through a response bias, for example, expectations might lower the criterion for labelling an experience as painful without actually altering the recipient's pain experience (Clark, 1969).

Negative expectations can also alter patients' experiences of actual medicine. For example, Bingel et al. (2011) exposed participants to heat pain and then gave them the analgesic remifentanyl under three different conditions. Participants were told to expect either analgesia, hyperalgesia or were given no expectations. Positive expectations of analgesia doubled the perceived strength of the drug, with participants showing twice as much pain relief in this condition compared to those who were given no expectations. Conversely, participants given negative expectations of hyperalgesia did not get any pain relief from the remifentanyl, the mere suggestion that it would increase pain was enough to abolish the pharmacological effect of the drug (Bingel et al., 2011). Expectations can also have a significant effect on patients' health outcomes after surgery. Recent reviews have shown that patients' pre-operative expectations are associated with acute post-surgical pain and their post-surgery quality of life (Auer et al., 2016; Sobol-Kwapinska, Babel, Plotek, & Stelcer, 2016).

1.4.2.3 Learning

Learning is another mechanism that has been reported to play a role in the nocebo effect. Through classical conditioning, a neutral stimulus can come to elicit

symptoms if it has been previously paired with a symptom-inducing stimulus (Barsky et al., 2002). For example, Ader and Cohen (1975) investigated classical conditioning in rats, and showed that pairing an unconditioned stimulus such as sweetened water with an immunosuppressant can lead to illness and death in rats when they are presented with only the sweetened water to drink. A similar mechanism has been shown in humans in a series of studies by Van den Bergh et al. These showed that pairing an odour with breathing in air high in carbon dioxide can elicit symptoms following subsequent exposure to the odour alone, especially if the odour is foul smelling (Van den Bergh, Kempynck, van de Woestijne, Baeyens, & Eelen, 1995; Van den Bergh, Stegen, & Van de Woestijne, 1997; Van den Bergh et al., 1999). The effect of classical conditioning on nocebo responses can also be seen in everyday life. For example, drinking decaffeinated coffee can be enough to induce caffeine-related symptoms due to the association of the taste of coffee with caffeine, which has developed through our previous experiences of drinking coffee (Mikalsen, Bertelsen, & Flaten, 2001).

As well as conditioning working through conscious mechanisms (e.g. recognising the taste of coffee and forming a conscious expectation of how the coffee will affect you), conditioning can also work through unconscious mechanisms. Jensen et al. (2012) assessed whether conditioned nocebo responses could be triggered in response to non-conscious cues. In this study, participants were exposed to a thermal pain stimulus using a conditioning paradigm, whereby clearly visible facial cues for high and low pain were presented in conjunction with high and low temperatures. After this conditioning, participants were presented with the test sequence where the faces were presented for 12ms followed by a visual mask for 84ms preventing them from consciously recognising the stimuli. The results revealed significantly higher pain ratings in response to the high pain face and lower ratings for the low pain face, despite identical moderate temperatures used in the thermal pain stimuli. This study, and others like it,

has challenged the role of awareness and conscious cognitions in nocebo responses, highlighting the limitations of expectancy theory which cannot explain how nocebo responses can be elicited from such non-conscious processes.

1.4.2.3.1 Social observation

Another route through which learned nocebo effects can arise is social observation. Observing others can influence people's own symptom reporting (Goubert, Vlaeyen, Crombez, & Craig, 2011). When an individual sees people developing symptoms from an exposure, it can impact their own symptom reporting to the same exposure through social modelling (Faasse & Petrie, 2013). This has been demonstrated by Vogtle, Barke, and Kroner-Herwig (2013) who showed that observing a person display more pain after application of an ointment on the skin, resulted in participants reporting significantly more pain during a pressure pain task after application of the same ointment. Faasse, Grey, Jordan, Garland, and Petrie (2015) have also shown the impact of social observation by giving participants a sham beta-blocker medication for pre-examination anxiety and randomising them to witness a female confederate report either side effects or no side effects after taking the same medication. They found that female participants who saw the confederate report side effects reported significantly more symptoms than those who saw the confederate report no side effects.

One of the most powerful examples of social observation contributing to nocebo effects is mass psychogenic illness (MPI). MPI is the outbreak of illness among a population which is thought to be attributable to a toxic agent but for which no organic source is found (Page et al., 2010). In essence this occurs when nocebo effects happen on a large scale. Incidents often begin with just an index case whose symptoms are then transmitted through a 'social contagion' in which the outbreak spreads along the 'line of sight' (Wessely, 1987). Those who do not witness the outbreak, tend to not become ill. After the trigger event is witnessed, e.g. someone fainting, this creates anxiety among

the group of observers as they do not know what the problem is or what caused it. This anxiety can be symptom-inducing in itself as anxiety is often experienced as muscle spasms, nausea and chest pain (Wessely, 1987).

1.4.2.4 Predisposing factors

Several predisposing factors are suspected to predict placebo reactivity. These include demographic characteristics such as being female (Liccardi et al., 2004) and personality characteristics such as pessimism (Geers, Helfer, Kosbab, Weiland, & Landry, 2005), neuroticism (Davis, Ralevski, Kennedy, & Neitzert, 1995), anxiety (Petrie et al., 2004) and Type A personality (Drici, Raybaud, De Lunardo, Iacono, & Gustovic, 1995). In addition, a tendency to amplify the symptoms experienced and have a heightened awareness of bodily sensations has also been associated with non-specific side effects (Barsky et al., 1999), along with a perceived sensitivity to medicines (Petrie et al., 2004) and modern health worries (Kaptein et al., 2005; Petrie et al., 2005; Petrie et al., 2001; Rief et al., 2012). More recently patients with negative medication beliefs have been shown to be more likely to misattribute symptoms to medications and subsequently to intend to stop medication (Heller, Chapman, & Horne, 2015). Apart from being female, many if not all of these factors may work by increasing negative expectations related to specific exposures. Demographic factors may influence placebo responding by affecting the strength of the relationship between the different factors identified and their corresponding mechanism. See Figure 1-1 for a model overview of the factors discussed and how they can trigger placebo effects.

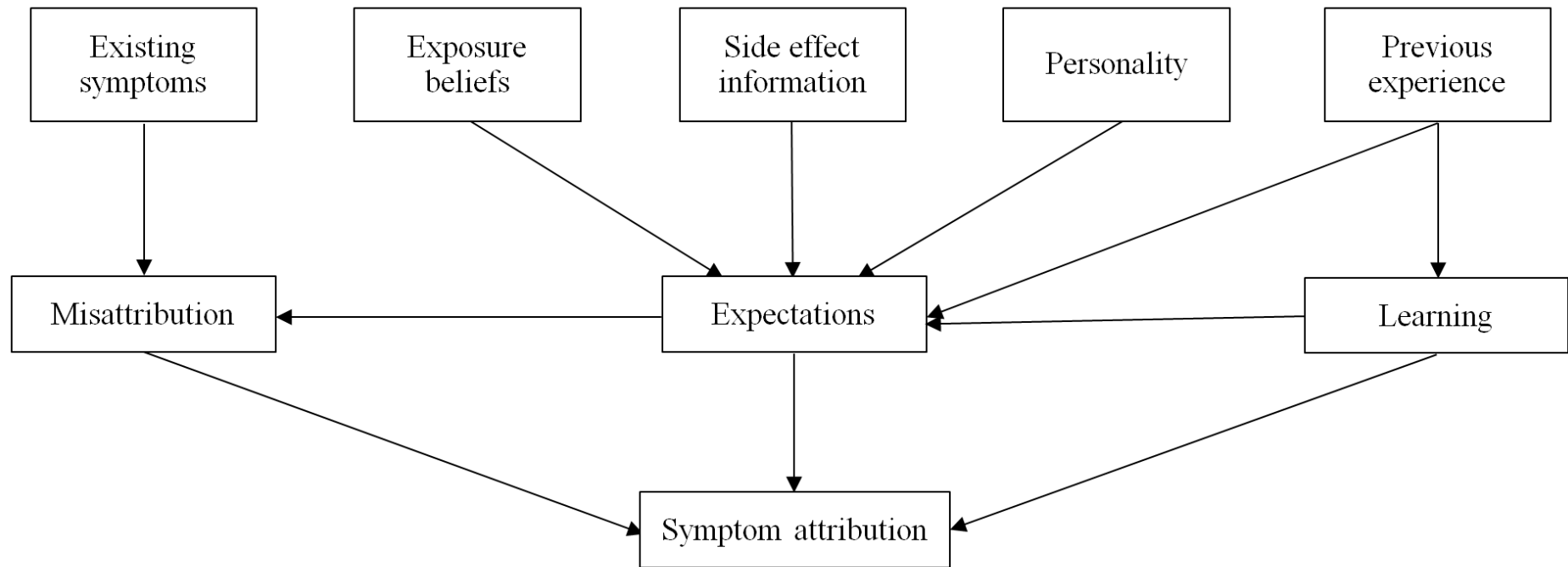


Figure 1-1 Factors that trigger placebo effects to a sham exposure.

1.4.3 Is there more than one type of nocebo effect?

The mechanisms discussed so far all appear to have merit. Indeed, some have suggested that the existence of multiple valid mechanisms may suggest that there isn't one "nocebo effect" at all, but several that have been inappropriately lumped together. This is something that has also been discussed in reference to the placebo literature. Stewart-Williams (2004) suggested that although the main theories of the placebo effect such as expectancy theory, emotional change, classical conditioning and biological approaches are often considered competing models, they may in fact just highlight the different aspects of placebo effects. As such there may be many different types of nocebo effects and perhaps we should not be confined to the term 'the nocebo effect.' Either way, the identification of the mechanisms may suggest important ways to intervene. One avenue in particular may be important in this regard: communication.

1.5 Side effect communication

If expectations play a role in nocebo effects, how we communicate with patients about the risk of side effects associated with their medications could have a substantial impact on the side effects they experience. For example, in a classic study involving a multicentre trial of aspirin or sulfinpyrazone in the treatment of angina, the consent form in two of the three centres included a statement outlining possible gastrointestinal side effects, which resulted in a six-fold increase in the number of patients in these centres withdrawing from the study because of subjective, minor gastrointestinal symptoms (Myers et al., 1987). The authors concluded that the inclusion of gastrointestinal side effects in the consent form may have increased the likelihood of patients attributing gastrointestinal symptoms to the drug, leading to subsequent withdrawal from the study. More recent research has also noted the importance of verbal risk communication. For example Varelmann, Pancaro, Cappiello, and Camann (2010) randomised one hundred forty women at term gestation requesting neuraxial

analgesia to receive either "placebo" ("We are going to give you a local anaesthetic that will numb the area and you will be comfortable during the procedure") or "nocebo" ("You are going to feel a big bee sting; this is the worst part of the procedure") suggestions. They found median pain scores were lower when reassuring words were used compared with the harsher words. Communication of the risk of side effects is important as poor communication can lead to negative expectations which facilitates the generation of nocebo induced nonspecific side effects.

Currently, the main way side effect information is communicated to patients is through patient information leaflets (PILs). According to the European Commission (EC, 1992), overseen by the European Medicines Agency, all medicines prescribed in each of the 27 member states must be distributed with a comprehensive PIL, supplied as a package insert. This leaflet is required to list all the potential side effects in a way that the patient can understand. Research has shown that around 35% of patients receiving a prescribed drug read at least some of the leaflet, but this rises to over 70% of those receiving a drug for the first time (Raynor, Silcock, Knapp, & Edmondson, 2007). This should be interpreted with caution as participants for this study were recruited from patients who were collecting their own medicine. Many medicines are taken by older, more frail patients who are likely to be taking multiple medications and not attending the pharmacy (Raynor et al., 2007). In these cases they may be less likely to read PILs, instead relying on family members or carers for this information. In addition, the relevant study only had a 67.5% consent rate. It seems possible that people who did not consent will also have been unlikely to read the PIL. This would result in an inflated estimate of the proportion of the population who do read their PIL.

Effectively communicating medical information involving risk and uncertainty in terms of side effects to a diverse audience is difficult, and the written information provided to patients has not always been of high quality (Knapp, Gardner, McMillan,

Raynor, & Woolf, 2013). Therefore the EC (1998) guideline suggested grouping adverse effects within a PIL according to five frequency bands, each described using one of five terms.

These five terms were:

- *Very common (More than 1 in 10 patients will be affected)*
- *Common (Up to 1 in 10 patients will be affected)*
- *Uncommon (Up to 1 in 100 patients will be affected)*
- *Rare (Up to 1 in 1000 patients will be affected)*
- *Very rare (Up to 1 in 10,000 patients will be affected)*

These recommended risk expressions were not based on any systematic empirical evidence demonstrating how readers would perceive them (Knapp, Gardner, & Woolf, 2015). Since these guidelines were published several studies have attempted to evaluate the usefulness of the descriptors. Most have found the terms to be problematic with participants overestimating the risk implied by the descriptors (Berry, Knapp, & Raynor, 2002; Berry, Raynor, & Knapp, 2003; Büchter, Fechtelpeter, Knelangen, Ehrlich, & Waltering, 2014; Knapp et al., 2013; Knapp, Raynor, et al., 2009). These studies are limited, however, as they tend to be based on small samples of students or specific patient populations. However, given that any overestimation could increase people's expectations of side effects, it is possible that the risk communication used in PILs could inadvertently be promoting the experience of the very side effects they are intended to warn about.

Research has looked at how different ways of communicating the potential risk of side effects to medications can alter people's risk perceptions of developing such side effects. A systematic review of 10 trials comparing the effects of words versus numbers in communicating the probability of adverse effects to consumers in written health information found that portraying the risk in numbers compared to verbal descriptors

(e.g. “10%” versus “common”) results in lower expectations of side effect occurrence (Büchter et al., 2014). Comparing different types of numerical communication, Knapp, Gardner, Carrigan, Raynor, and Woolf (2009) recruited 285 users of the Cancer Research UK website and randomly allocated them to receive hypothetical side effect risk information in the form of natural frequencies (e.g. 1 in 10) or percentages (e.g. 10%). They found that percentages lead to an overestimation of the risk of side effects compared to natural frequencies (Knapp, Gardner, et al., 2009). In addition, in a sample of 298 internet users, Peters, Hart, and Fraenkel (2011) carried out a randomised trial and found that positively framing a hypothetical side effect risk in terms of those who will not be affected (e.g. 9 in 10 people will not be affected) results in lower side effect risk perceptions than negatively framed numerical risk (e.g. 1 in 10 people will be affected).

Although it seems plausible that expectations and risk perceptions generated through side effect risk communication could be a factor influencing nocebo effects to medication, most studies have not looked at the effect of risk communication on actual side effect development. Only one study to date has specifically investigated side effect framing on symptom development. O'Connor, Pennie, and Dales (1996) randomly assigned unimmunised patients to receive benefit/risk information about the influenza vaccine that was framed either positively as the percentage of people who experience no vaccine side effects or negatively as the percentage who do experience vaccine side effects. They found that patients in the positive frame group experienced fewer side effects to the vaccine compared to those in the negative frame group (O'Connor et al., 1996). This study has never been replicated.

1.6 Research Questions

The aim of this PhD was to improve our understanding of nocebo responses to medications and what we can do to prevent them by answering the following research questions.

1. What predicts whether someone will experience a nocebo response?
2. Can altering communication about side effect risk reduce the occurrence of nocebo responses?
3. Do the English population misinterpret the current wording used to communicate side effect risk in PILs?

In order to answer these questions, this PhD set out to:

1. Carry out a systematic review of the factors that contribute to the development of nocebo effects, broadly defined to include both misattribution of existing symptoms and development of new symptoms. [See Chapter 2]
2. Consider the ethical issues involved in carrying out nocebo research involving information-based interventions and what can be done to limit these issues. [See Chapter 4]
3. Design an intervention intended to reduce nocebo effects based on reframing the likelihood of side effects occurring, as presented in PILs that accompany most medicines. [See Chapter 5]
4. Pilot test the intervention for its effect on the number of expected symptoms and the overall likelihood of expected symptoms [See Chapter 6]
5. Test whether the intervention reduces the number of people attributing symptoms to a tablet, the overall number of attributed symptoms and severity of attributed symptoms in comparison to current practice, using a

large scale randomised controlled trial (RCT) involving healthy volunteers who are asked to take a sham medicine. [See Chapter 7]

6. Investigate the associations between participants' baseline characteristics in the RCT and the odds of attributing one or more symptoms to a sham medication, and number of attributed symptoms. [See Chapter 8]
7. Carry out a cross-sectional survey of a representative sample of the English population to determine the distribution of various interpretations of the verbal side effect risk descriptors in PILs as currently used. [See Chapter 9]
8. In the same survey as above, determine how the English population interpret the current side effect risk information in PILs in terms of their own likelihood of getting side effects. [See Chapter 10]

Chapter 2 A Systematic Review of Factors that Contribute to Nocebo Effects

2.1 Introduction

As discussed in Chapter 1, nocebo effects in medication settings can result in significant costs to patients' quality of life, and to the National Health Service. So far, although many different risk factors have been implicated in the nocebo literature, no study has systematically reviewed these risk factors to identify those which appear to be the strongest predictors of nocebo effects and which may therefore be the most important targets for future interventions.

Instead, previous systematic reviews of the nocebo literature have tended to focus on the magnitude of nocebo effects on a specific symptom, e.g. pain (Petersen et al., 2014) or in clinical trials of experimental medical treatments (Hauser, Bartram, Bartram-Wunn, & Tolle, 2012). One review (Symon, Williams, Adelasoye, & Cheyne, 2015) has provided a preliminary assessment of some of the risk factors involved in nocebo effects. However this paper, described by the authors as a "scoping review" was not fully systematic and only identified 17 papers. This was probably due to the restrictive search strategy that is often used by reviews in this field. For example, Petersen et al. (2014) used only the single search term 'nocebo' for their search, although many relevant papers might not include this terminology. In addition, although Symon et al. (2015) attempted to better this, adding in the search term 'negative placebo effect' again this is still restrictive, neglecting studies that may refer to nocebo effects as 'adverse placebo effects,' 'placebo side effects' and so on.

Previous reviews have also tended to include studies that have investigated both active and inert exposures. By including the active exposure literature it could be argued they are not reviewing the true nocebo effect, described as the undesirable effects experienced from an inert exposure (Kennedy, 1961). Using an active exposure such as

a painful stimulus runs the risk that any direct physiological effects of the exposure interact with, or obscure placebo effects (Neukirch & Colagiuri, 2014).

2.2 Aim

To address the current issues and gaps in the literature this systematic review set out to identify the risk factors for symptom reporting in response to an inert exposure using a broad search strategy in an attempt to capture relevant studies that do not necessarily use the term ‘placebo.’ Such risk factors could include experimental manipulations such as verbal suggestions, or naturally occurring baseline factors such as personality.

2.3 Method

2.3.1 Identification of studies

The following electronic databases were searched for potentially relevant studies: Web of Science, Scopus, Medline, PsychINFO (1806-2014), Journals @ Ovid full text, and Global health. These databases were searched using the terms “placebo” or “placebo effect.” Where available, the searches were limited to studies that only used a human population and review articles were restricted. The reference sections of included studies were also examined as well as papers suggested through personal contacts. No temporal constraints were used. The review followed a previously designed protocol that was developed in conjunction with both supervisors. Searches were carried out on 11th December 2014.

2.3.2 Selection criteria

Studies were eligible for inclusion in the review if they met the following criteria:

- Studied a human population (healthy volunteers, patients or children were allowed).
- Used an experimental or prospective design.

- Used an inert exposure, i.e. containing no pharmacological or physiological active ingredient.
- Assessed factors on their ability to predict symptom reporting. These factors could be baseline characteristics or experimentally induced.
- Included an outcome of symptom reporting after participants received an inert exposure. Reported symptoms must not have been due to an active exposure (e.g. studies where an inert exposure was applied after an active exposure such as heat stimulation were excluded, as in this case the symptoms might have resulted from the heat stimulation).
- Measured symptoms via self-report or inferred their presence through objective measures (e.g. scratching behaviour). Such symptoms could be somatic, a measure of arousal or mood. Because of the difficulty in defining when an outcome is aversive or beneficial I took an inclusive approach. For example measures of alertness (where an increase could be aversive in some instances) or contentedness (where decreases might be possible) were both included.
- Published in any language.

2.3.3 Data extraction

Any non-English articles were translated. For each study included in the review, details relating to 20 methodological issues were extracted using a standardised spreadsheet. In summary these variables related to: the sample size; demographic details of the participants; the inclusion criteria; the number of participant withdrawals; the study design; specific details of the method (e.g. whether the study was double or single-blind; whether condition order was randomised or counterbalanced); the type of inert exposure; the experimental condition(s) manipulated; the control condition; which baseline risk factors were assessed, how they were assessed and when; and how

symptoms were assessed and when; the statistical analysis used to assess the effect of baseline risk factors and/or experimental conditions on symptoms and the results relating to these outcomes. In addition, details regarding ethical approval and informed consent were extracted. I differentiated between studies that used an experimental or a prospective design in order to easily identify factors implicated in placebo effects that can be manipulated and those that naturally occur at baseline.

2.3.4 Quality assessment

Eligible studies using an experimental design were assessed using the Cochrane Collaboration's Risk of Bias tool (Higgins et al., 2011). This two part tool addresses sequence generation, allocation concealment, blinding of participants and outcome assessor, incomplete outcome data, and selective reporting. For prospective studies, the CASPin (1998) critical appraisal tool was used. This addresses the focus of the study, recruitment process, exposure and outcome measurement, confounding factors, appropriateness of the follow-up, applicability of the results, and implications for practice. The CASP is usually scored with yes/no answers but this was re-scored to low risk (yes) and high risk (no) as well as including an unclear risk response for when enough information was not provided, bringing it more into line with the Cochrane Risk of Bias tool. As these tools had no criteria assessing sample size I also rated this separately for each study.

2.3.5 Review process

I conducted the database searches and performed the initial screening of the titles and abstracts of articles found via these searches to assess their potential relevance. During this time guidance was obtained from my first supervisor if there was any uncertainty as to whether to include an article to the full text review stage. I then obtained the full articles for those citations that appeared potentially relevant and checked them against the inclusion criteria. If it was unclear whether an article met the

inclusion criteria or not, consensus was sought from my supervisors. I then independently extracted data for each included study and carried out the quality assessment with guidance from my first supervisor as to what criteria needed to be met for a low, unclear or high risk outcome. Due to the expected heterogeneity in the studies I did not plan for any meta-analyses and instead I used a narrative synthesis. There is no general consensus on the best way to carry out a narrative synthesis for systematic reviews (Popay et al., 2006). Because of this I decided to use a weight of evidence approach. To do this, I identified the strength of evidence for each risk factor based on the number of studies investigating each risk factor and their respective quality.

2.4 Results

2.4.1 Search results

The database search retrieved 12582 citations. After removing duplicates 6585 citations remained. After screening titles and abstracts, I reviewed the full text of 88 articles relating to 96 studies. Of these, 13 studies were excluded for not investigating any risk factors for the development of symptoms, nine were excluded for using an active exposure and seven were excluded for not measuring symptoms. Sixty-six articles met the inclusion criteria. Twenty-one additional articles were identified by reference checks of included articles and through personal contacts, resulting in a total of 87 articles. Two articles reported results on two separate studies each (Walach & Schneider, 2009; Winters et al., 2001) and are referred to as 'Exp 1' or 'Exp 2' where necessary, leaving 87 articles reporting on 89 studies. Of these, 70 were experimental and 19 prospective. Figure 2-1 provides a flow diagram of the study selection according to the Preferred Reporting for Systematic Reviews and Meta-analyses statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

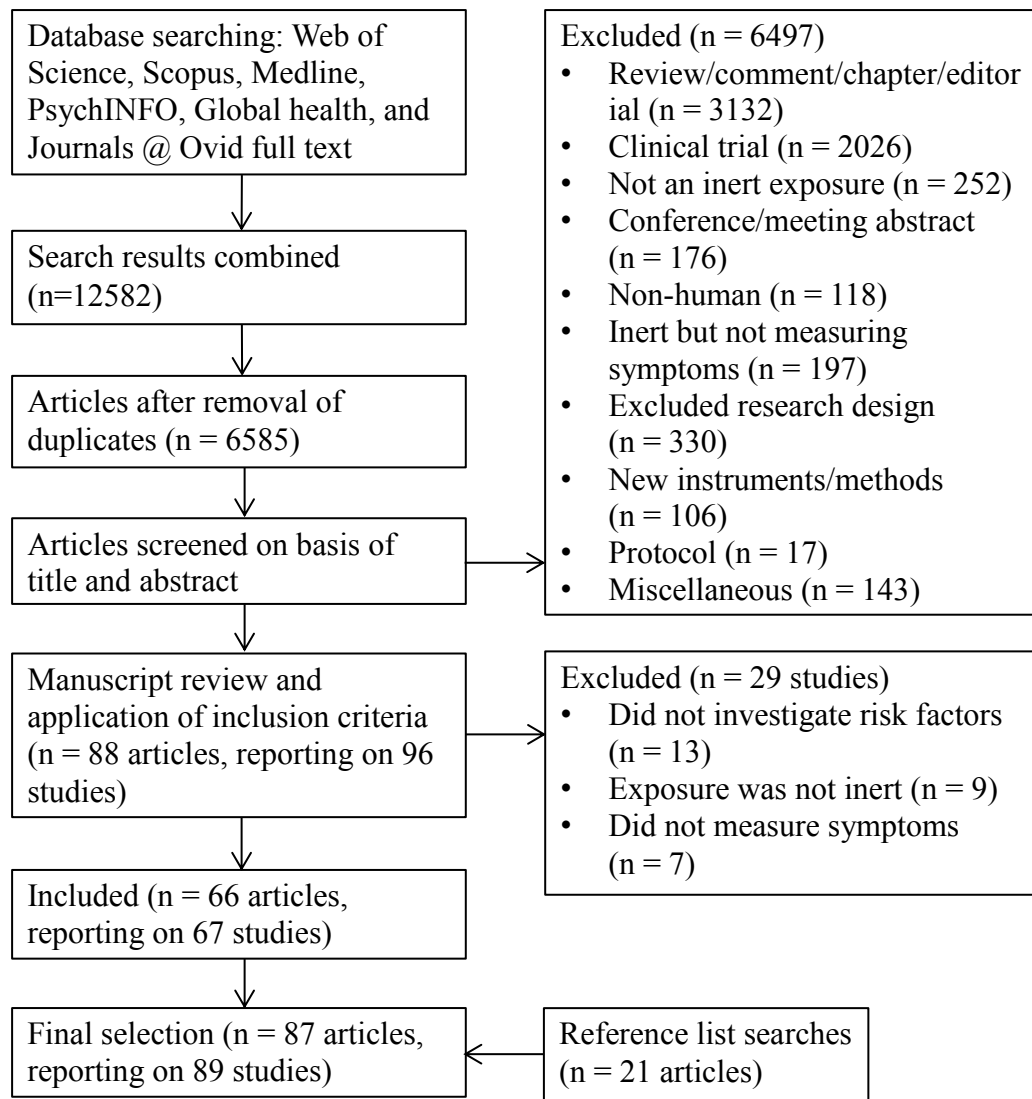


Figure 2-1 Flow diagram of the selection process of studies including the number of events and reasons for exclusion.

2.4.2 Quality assessment

2.4.2.1 Experimental studies

The quality of experimental studies was poor (see Figure 2-2), with the main problem being a lack of clear reporting. Thirty-six studies neglected to mention how they carried out randomisation while 22 studies were at high risk of bias for failing to mention if participants were randomised or for not using randomisation at all. Due to the unclear reporting of random sequence generation, the risk for allocation concealment bias followed a similar pattern. For blinding of participants and personnel, studies often failed to state if the experimenters were blind to the manipulation that

accompanied the exposure, leaving the risk of bias unclear. Only six studies used adequate blinding procedures, with 12 not using blinding at all. Sixty-five studies used self-report measures, therefore blinding of the outcome assessment was judged to be unlikely to influence these results. For 52 studies, drop outs were not addressed, or if they were, they typically failed to explain how this affected the results, leaving the risk of bias unclear. Only one study had lodged a protocol in a publically accessible registry prior to the start of recruitment leaving me unable to assess the risk for selective reporting for the remaining studies. Justification of sample size was typically poorly addressed, with only 9 out of the 70 studies mentioning that they carried out an a priori sample size calculation.

2.4.2.2 Prospective studies

The prospective studies performed well against the quality check (see Figure 2-2). All studies addressed a clearly focused issue with a standardised exposure across all participants. Studies often lacked information about how participants were recruited. However, self-report measures were widely used to minimise bias from experimenters. The identification and control of confounding factors was only deemed an issue for six studies that neglected to control for demographic factors such as gender or age and past symptom reporting. The follow up of participants was judged to be appropriate in 16 studies. Regarding the generalisability of the findings, it was often difficult to know if the results could be applied to the population being studied due to the insufficient information about how participants were recruited. In addition, similarly to the experimental studies, justification for sample size was limited with only one study providing an a priori sample size calculation.

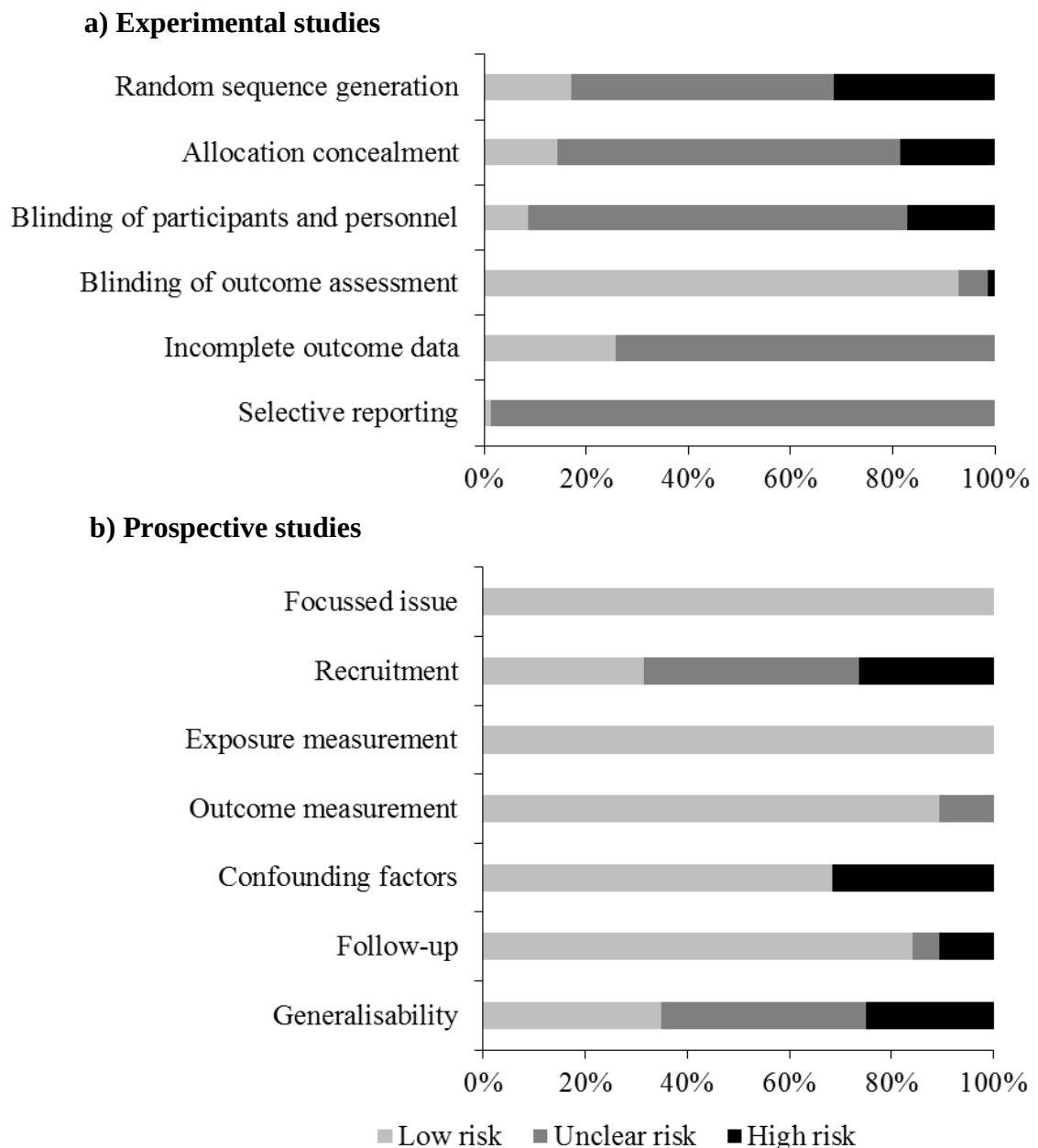


Figure 2-2 Quality assessment of experimental and prospective studies.

2.4.3 Experimentally induced risk factor categories

Seventy experimental studies were included that investigated risk factors which fell into 9 different categories as discussed below.

2.4.3.1 Learning

Twenty three studies manipulated different types of learning on symptom reporting finding some evidence for its role in placebo effects (see Table 2-1). Four of these investigated prior experience of which two lower quality studies found no

significant effects (Bayer, Coverdale, Chiang, & Bangs, 1998; Dinnerstein & Halm, 1970). However, Andre-Obadia, Magnin, and Garcia-Larrea (2011) showed that sham repetitive transcranial magnetic stimulation (rTMS) tended to worsen patients' pain when following an active yet unsuccessful rTMS treatment (however caution is required as no statistical test accompanied this finding), and a high quality study by Stegen et al. (1998) found that participants reported significantly more arousal and respiratory symptoms when completing a breathing trial with room air before a breathing trial with carbon dioxide rather than afterwards. As such there is some evidence that prior experience is involved in the development of placebo effects. Two studies of mixed quality explored the impact of implicit association supporting its role in placebo effects, finding that drinking sham caffeine in a coffee solution resulted in significantly more alertness, contentedness, and arousal, than drinking sham caffeine in an orange juice solution (Flaten & Blumenthal, 1999; Mikalsen et al., 2001). Three studies of high quality investigated learning through the manipulation of social observation, with two finding a significant effect, broadly supporting its role in placebo effects. Lorber, Mazzoni, and Kirsch (2007) failed to show any main effects of observing a confederate display symptom behaviours after inhaling a sham environmental toxin which they were also exposed to. However, in a similar study, participants who observed a confederate display symptoms had significantly higher symptom ratings after inhalation than participants who did not (Mazzoni, Foan, Hyland, & Kirsch, 2010). Similarly, patients who watched a video of people scratching compared to those who saw a video of people sitting idle had higher itch and scratching behaviour rating after administration of sham histamine (Papoiu, Wang, Coghill, Chan, & Yosipovitch, 2011), no results were reported for the healthy volunteers in this study.

Of the remaining 14 studies, 13 investigated learning by using classical conditioning to pair inert exposures such as odours with CO₂ inhalation before

presenting the inert exposures on their own (De Peuter et al., 2005; Devriese, De Peuter, Van Diest, Van de Woestijne, & Van den Bergh, 2006; Devriese et al., 2000; Devriese et al., 2004; Meulders et al., 2010; Van den Bergh et al., 1995; Van den Bergh et al., 1997; Van den Bergh, Stegen, & Van de Woestijne, 1998; Van den Bergh et al., 1999; Van Diest et al., 2006; Winters et al., 2003) including Winters et al. (2001) exp 1 and 2. Six studies of mixed quality found significant effects of classical conditioning and although seven found no main effect of conditioning on symptom reporting, six of these were of lower quality. As such there is some evidence for the role of classical conditioning in placebo effects, and that this learning effect can be generalised to new odours (Devriese et al., 2000; Van den Bergh et al., 1997, 1998). However odour type alone, without classical conditioning is not enough to elicit symptoms as demonstrated in this group of studies and the remaining study in this category (Dalton, 1999).

2.4.3.2 Perceived dose

Six studies manipulated participant perceptions of the dose of the exposure that they received (see Table 2-2). Four of these found significant effects with three being of higher quality, broadly supporting a link between higher perceived dose and placebo effects. Only two studies found no significant effects of dose related to decaffeinated coffee consumption (Flaten, Aasli, & Blumenthal, 2003) or taking a sham sedative pill (Jensen & Karoly, 1991). The remaining four all demonstrated significant main effects: Increasing the setting on a sham shock generator increased pain intensity ratings in two studies (Bayer, Baer, & Early, 1991; Bayer et al., 1998), tension scores increased as a function of perceived dose following decaffeinated coffee consumption in one study (Kirsch & Weixel, 1988), and in a final study being told that a sham EMF exposure would be strong resulted in a higher overall symptom scores compared to being told the exposure would be weak (Szemerszky, Koteles, Lihi, & Bardos, 2010).

2.4.3.3 Self-awareness

Four studies manipulated self-awareness during exposure (see Table 2-3). Three higher quality studies found no significant effects with only one lower quality study reporting an effect, showing little evidence that self-awareness increases the likelihood of a placebo effect. Both Geers, Helfer, et al. (2005) and Geers, Helfer, Weiland, and Kosbab (2006) showed no significant main effects of instructing participants to attend to any symptoms or sensations they experienced. Using a distraction task also did not have a significant effect on symptom reporting (Van den Bergh et al., 1998). Gibbons, Carver, Scheier, and Hormuth (1979) however, did find a significant main effect, with participants facing a mirror reporting less perceived arousal than participants not facing a mirror following ingestion of a sham drug.

Table 2-1 The effect of learning on symptom reporting in response to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Experimental conditions (n)	Main effect on symptoms measured	Interaction(s) with other risk factors
Andre-Obadia et al. (2011) b,e	RCT (W)	Chronic neuropathic pain patients (45, 55.0, 37.8)	Sham rTMS	1. Prior experience: a. Sham rTMS before active rTMS (20); b. Sham rTMS after successful active rTMS (12); c. Sham rTMS after ineffective active rTMS (13)	i. Mean pain intensity (c>a>b) "placebo sessions tended to worsen pain when following an unsuccessful rTMS" – no statistics given ii. Combined pain assessment "Comparable results obtained" – no statistics given	No significant interactions with baseline pain ratings
Bayer et al. (1998) a,e	RCT (B)	Job seekers (62, U/K, 82.0)	Sham electrical shock	1. Prior experience: a. Exposed to two physical pain induction procedures prior to sham stimulation (32); b. Warned of pain and received sham stimulation. They were not exposed to any prior pain induction (30)	i. Subjects reporting pain (ns) ii. Mean maximal pain rating (ns) iii. Subjects reporting pain over analgesic threshold (ns) iv. Pain intensity over time (ns)	Prior experience x Dose i-iii. Not assessed iv. Increased with increasing stimulator settings for those in condition a (p<.01), ns for those in condition b
Dalton (1999) e	RCT (B)	Healthy volunteers (180, 31.7, 49.4)	Odours	1. Odours: a. Pleasant smelling methyl salicylate (60); b. neutral smelling isobornyl acetate (60); c. Foul smelling butanol (60)	i. Symptom reports (ns)	Odours x Verbal symptom suggestions i. "Highest for those exposed to butanol following negative suggestions, lowest for those exposed to methyl salicylate following positive suggestions" No other interactions assessed

De Peuter et al. (2005) e	RCT (W)	Asthma patients and healthy controls (40, 23.9, 52.5)	Sham inhaler	1. Conditioning: a. One sham inhaler previously paired with CO2 challenge; b. One sham inhaler previously paired with O2	i. Total symptom score (a>b, p<.01) ii. Obstruction (ns) iii. Dyspnoea (a>b, p<.01) iv. Fatigue (ns) v. Hyperventilation (ns) vi. Anxiety (ns) vii. Irritation (ns)	No significant interaction with clinical condition No other interactions assessed
Devriese et al. (2000) a,e	Non RCT (B+W)	Healthy students (56, U/K, 41.1)	Odours	1. Odour: Within each group participants were exposed to foul smelling ammonia and pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (28); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (28) 3. Generalisation: Within each group participants were exposed to a. a new foul smelling odour butyric acid; b. a new foul smelling odour acetic acid; and c. a new pleasant smelling odour citric aroma	i. Total symptom score (1 ns; 2 ns; 3 a>b+c, p<.001, b vs c ns) ii. Arousal (1 ns; 2 ns; 3 ns) iii. Respiratory (1 ns; 2 ns; 3 ns) iv. Cardiac (1 ns; 2 ns; 3ns) v. Tingling (1 ns; 2 ns; 3 ns) vi. Unclassified (1 ns; 2 ns; 3 ns) vii. Dummy (1 ns; 2 ns; 3 ns)	Conditioning x Odour i+iii. Higher in response to odour paired with CO2 but only when the odour was ammonia (p<.05) ii, iv-vii. ns Conditioning x Odour x Negative affect i+iii. Higher in response to odour paired with CO2 but only when the odour was ammonia and participants had high negative affect (p<.05) ii, iv-vii. ns Odour x Negative affect x Generalisation i+iii. Higher in response to butyric and acetic acid than citric aroma when ammonia was paired with CO2 and participants had high negative affect (p<.05)

						iv. Higher in response to butyric acid than acetic acid or citric aroma when ammonia was paired with CO2 and participants had high negative affect ($p<.05$) ii+ v-vii. Ns No other interactions assessed
Devriese et al. (2004) a,e	Non RCT (B+W)	Healthy students (53, U/K, U/K)	Odours	1. Odour: Within each group participants were exposed to foul smelling ammonia and foul smelling butyric acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, butyric acid paired with room air breathing task (28); b. Ammonia paired with room air breathing task, butyric acid paired with CO2 breathing task (25)	i. Total symptom score (1 ns; 2 ns) ii. Arousal (1 ns; 2 ns) iii. Respiratory (1 ns; 2 ns) iv. Cardiac (1 ns; 2 ns) v. Tingling (1 ns; 2 ns) vi. Unclassified (1 ns; 2 ns) vii. Dummy (1 ns; 2 ns)	Odour x Conditioning i. Higher in response to butyric acid than ammonia when butyric acid paired with room air ($p<.01$) ii-vii. ns Perceived cue odour x Odour i. Higher to butyric acid than ammonia when butyric acid was thought to have been paired with CO2 ($p<.05$) ii-vii. ns No other interactions assessed
Devriese et al. (2006)	RCT (B+W)	Psychology students (40, U/K, 0.0)	Odour	1. Odour: Within each group participants were exposed to foul smelling ammonia and foul smelling acetic acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, acetic acid paired with room air breathing task (20); b. Ammonia paired with	i. Total symptom score (1 ns; 2 higher for the odour paired with CO2 than the odour paired with room air, $p<.05$) ii. Arousal (1 ns; 2 ns) iii. Respiratory (1 ns; 2 ns) iv. Cardiac (1 ns; 2 ns) v. Tingling (1 ns; 2 ns) vi. Unclassified (1 ns; 2 ns)	Not assessed

				room air breathing task, acetic acid paired with CO2 breathing task (20)	vii. Dummy (1 ns; 2 ns)	
Dinnerstein and Halm (1970) c,e	RCT (B)	Male students (80, U/K, 100.0)	Sham arousal liquid	1. Prior experience: a. Received aspirin prior to sham (40); b. Received lactose prior to sham (40)	i. Friendly (ns) ii. Aggressive (ns) iii. Sleepy (ns) iv. Dizzy (ns) v. Unhappy (ns) vi. Clear thinking (ns)	Prior experience x Arousal suggestion i. Lower in condition a than condition b under energiser suggestion, reverse under tranquiliser suggestion (p<.05) ii-iv. ns v+vi. Higher in condition a than condition b under energiser suggestion, reverse under tranquiliser suggestion (ps<.05)
Flaten and Blumenthal (1999) e	RCT (W)	Healthy coffee drinkers (21, 24.8, 61.9)	Decaffeinated solution	1. Association: a. Given in an orange juice solution; b. Given in a coffee solution	i. Stress score (ns) ii. Arousal score (b>a, p<.05) iii. Alertness score (b>a, p<.05)	N/A
Lorber et al. (2007) e	RCT (B)	Students without upper respiratory conditions (86, U/K, 40.7)	Sham environm ental toxin	1. Social observation: a. Told inhaled substance has been reported to produce symptoms and observed a female confederate inhale and display symptoms (U/K) b. As above but no observation of confederate (U/K)	i. Specified verbal symptom ratings: headache, nausea, itchy skin, drowsiness (ns) ii. Other verbal symptom ratings: watery eyes, scratchy throat, chest tightness, and breathing difficulty (ns)	Observation x Gender i. Higher in observation compared to no observation conditions when participants are female (p<.05) ii. ns

				c. Did not inhale the substance and observed a female confederate inhale and display symptoms (U/K) d. As above but no observation of confederate (U/K)		
Mazzoni et al. (2010) e	RCT (B)	Healthy students (120, 20.7, 50.0)	Sham environmental toxin	1. Social observation: a. Observed a male/female confederate inhale the substance and display symptoms (60) b. Did not observe a male/female confederate inhale the substance and display symptoms (60)	i. Specified verbal symptom ratings: headache, nausea, itchy skin, drowsiness (a>b, p<.001) ii. Other verbal symptom ratings: watery eyes, scratchy throat, chest tightness, and breathing difficulty (ns)	Not assessed
Meulders et al. (2010) a,e	Non RCT (B+W)	Healthy adults (58, 22.0, 48.3)	Odours	1. Odour: Within each group participants were exposed to foul smelling ammonia and foul smelling butyric acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, butyric acid paired with room air breathing task (29); b. Ammonia paired with room air breathing task, butyric acid paired with CO2 breathing task (29)	i. Total symptom score (1 ns; 2 ns) ii. Arousal (1 ns; 2 ns) iii. Respiratory (1 ns; 2 ns) iv. Cardiac (1 ns; 2 ns) v. Tingling (1 ns; 2 ns) vi. Unclassified (1 ns; 2 ns) vii. Dummy (1 ns; 2 ns)	Conditioning x Ability to predict i. Higher in response to odours which had been paired with CO2 compared to room air when participants were able to predict which odour had caused the most symptoms (p<.05) ii-vii. ns Conditioning x Ability to predict x Odour i-iv+vii. Higher in response to butyric acid which had been

						paired with CO2 compared to room air when participants were able to predict which odour had caused the most symptoms (i-iv, $p<.01$; vii, $p<.05$) v+vi. ns No other interactions assessed
Mikalsen et al. (2001) a,b,e	RCT (W)	Student coffee drinkers (21, 25.9, 66.7)	Sham coffee	1. Association: a. Given in a juice solution (U/K); b. Given in a coffee solution (U/K)	i. Alertness VAS score ($b>a$, $p<.05$) ii. Contentedness VAS score ($b>a$, $p=.02$) iii. Calmness VAS score (ns)	Not assessed
Papoiu et al. (2011) e	RCT (W)	Healthy volunteers and patients with atopic dermatitis (25, U/K, 44.0)	Sham histamine	1. Social Observation: a. Watched a 5 minute video of people scratching their left forearm b. Watched a 5 minute video of the same persons in the scratching video but sitting idle.	i. Average itch intensity rating ($a>b$ for patients $p=.027$; ns for healthy volunteers) ii. Scratching behaviour ($a>b$ for patients $p=.002$; ns for healthy volunteers)	No significant interactions with gender
Stegen et al. (1998) e	RCT (W)	Healthy psychology students (72, U/K, 48.6)	Breathing trial with room air	1. Prior experience: a. Room air breathing trial before 7.5% CO2 challenge; b. Room air breathing trial after 7.5% CO2 challenge	i. Total symptom score (ns) ii. General arousal ($a>b$, $p<.001$) iii. Respiration ($a>b$, $p<.001$) iv. Cardiac (ns) v. Tingling (ns) vi. Unclassified (ns) vii. Gastrointestinal (ns) viii. Dizziness (ns)	Prior experience x Negative affect i+ii. Participants scoring high on negative affect reported more complaints than participants with low negative affect in condition a (i, $p<.001$; ii, $p<.005$) iii-viii. ns

Van den Bergh et al. (1995) a,e	Non RCT (B+W)	Healthy students (28, U/K, 50.0)	Odours	1. Odour: Within each group participants were exposed to foul smelling ammonia and pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (14); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (14)	i. Total symptom score (1 ns; 2 ns) ii. Arousal (1 ns; 2 ns) iii. Respiratory (1 ns; 2 ns) iv. Cardiac (1 ns; 2 ns) v. Tingling (1 ns; 2 ns) vi. Unclassified (1 ns; 2 ns)	Conditioning x Odour i-iii+vi. Higher in response to odour paired with CO2 but only when that odour was ammonia (i, p<.05; ii, p<.001; iii, p<.02; vi, p<.05) iv+v. ns No other interactions assessed
Van den Bergh et al. (1997) a,e	Non RCT (B+W)	Psychosomatic patients (28, 36.0, 50.0)	Odours	1. Odour: Within each group participants were exposed to foul smelling ammonia and pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (14); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (14) 3. Generalisation: Within each group participants were exposed to a new foul smelling odour Ichtyol and new pleasant smelling odour Rose	i. Total symptom score (1 ns; 2 higher for odours that had been paired with CO2 compared to room air; 3 ns) ii. Arousal (1 ns; 2 ns; 3 ns) iii. Respiratory (1 ns; 2 ns; 3 ns) iv. Cardiac (1 ns; 2 ns; 3 ns) v. Tingling (1 ns; 2 ns; 3 ns) vi. Unclassified (1 ns; 2 ns; 3 ns) vii. Dummy (1 ns; 2 ns; 3 ns)	Conditioning x Odour i+iii+vi. Higher for odour paired with CO2 but only when that odour was ammonia (i+iii, p<.001; vi, p<.005) ii+iv+v+vii. Ns No other interactions assessed

Van den Bergh et al. (1998) e	RCT (B+W)	Healthy adults (56, 42.5, 50.0)	Odours	1. Odour: Within each group participants were exposed to foul smelling ammonia and pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (28); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (28) 3. Generalisation: Within each group participants were exposed to a new foul smelling odour Ichtyol and new pleasant smelling odour Rose	i. Total symptom score (1 ns; 2 ns; 3 higher in response to ichtyol than rose odour, $p<.005$) ii. Arousal (1 ns; 2 ns; 3 ns) iii. Respiratory (1 ns; 2 ns; 3 ns) iv. Cardiac (1 ns; 2 ns; 3 ns) v. Tingling (1 ns; 2 ns; 3 ns) vi. Unclassified (1 ns; 2 ns; 3 ns) vii. Dummy (1 ns; 2 ns; 3 ns)	Conditioning x Odour x Self-awareness i+ii+iv+vi+vii. Higher in response to the odour paired with CO2 when this was ammonia and participants had not been distracted (i+ii, $p<.001$, iv+vi+vii, $p<.002$) ii+v. ns No other interactions assessed
Van den Bergh et al. (1999) a,e	Non RCT (B+W)	Healthy students (64, U/K, 25.0)	Odours	1. Odour: Within each group participants were exposed to foul smelling ammonia and foul smelling butyric acid 2. Conditioning: a. Ammonia paired with CO2 breathing task, butyric acid paired with room air breathing task (32); b. Ammonia paired with room air breathing task, butyric acid paired with CO2 breathing task (32)	i. Total symptom score (1 ns; 2 higher in response to odour paired with CO2 compared to room air, $p<.001$) ii. Arousal (1 ns; 2 ns) iii. Respiratory (1 ns; 2 higher in response to odour paired with CO2 compared to room air, $p<.001$) iv. Cardiac (1 ns; 2 ns) v. Tingling (1 ns; 2 ns) vi. Unclassified (1 ns; 2 ns)	Not assessed

					higher in response to odour paired with CO2 compared to room air, $p < .001$) vii. Dummy (1 ns; 2 ns)	
Van Diest et al. (2006) e	RCT (B+W)	Students (28, U/K, 21.4)	Odours	1. Odour: Within each group participants were exposed to foul smelling ammonia and foul smelling acetic acid 2. Conditioning: a. Ammonia paired with hypocapnic over breathing trial, acetic acid paired with normocapnic over breathing trial (13); b. Ammonia paired with normocapnic over breathing trial, acetic acid paired with hypocapnic over breathing trial (15)	i. Paresthesia (1 ns; 2 ns) ii. Cerebral (1 ns; 2 ns) iii. Cardiac (1 ns; 2 ns) iv. Gastrointestinal (1 ns; 2 ns) v. Respiratory (1 ns; 2 ns) vi. Anxiety (1 ns; 2 ns) vii. Neuropsychological (1 ns; 2 ns) viii. Unclassified (1 ns; 2 ns) ix. Dummy (1 ns; 2 ns) x. Feeling unreal (1 ns; 2 ns) higher for odour paired with hypocapnic compared to normocapnic over breathing)	Not assessed
Winters et al. (2001) Exp 1 a,e	Non RCT (B)	Psychology students (50, U/K, U/K)	Ammonia	1. Conditioning: a. Odour + CO2 trials and room air trials (10); b. Odour trials and CO2 trials (10); c. Odour trials, CO2 trials, odour + CO2 trials, room air trials (10); d. odour trials, room air trials (10); e. CO2 trials, room air trials (10)	i. Symptom reports (ns)	N/A
Winters et al. (2001)	Non RCT	18-30 year olds	Odour	1. Odour: a. Foul smelling ammonia (20); b. Pleasant	i. Symptom reports (1 ns; 2 ns)	Not assessed

Exp 2 a,e	(B)	(40, U/K,U/K)		smelling niaouli (20) 2. Conditioning: a. Odour + CO2 trials and room air trials (20); b. Odour trials and CO2 trials (20)		
Winters et al. (2003) a,e	Non RCT (B+W)	18-30 year olds (32, U/K,15.6)	Odour	1. Odour: Within each group participants were exposed to foul smelling ammonia and pleasant smelling niaouli 2. Conditioning: a. Ammonia paired with CO2 breathing task, Niaouli paired with room air breathing task (16); b. Ammonia paired with room air breathing task, Niaouli paired with CO2 breathing task (16)	i. Total symptom score (1 ns; 2 higher in response to odour paired with CO2 compared to room air, p<.05) ii. Arousal (1 ns; 2 ns) iii. Respiratory (1 ns; 2 ns) iv. Cardiac (1 ns; 2 ns) v. Tingling (1 ns; 2 ns) vi. Unclassified (1 ns; 2 ns) vii. Dummy (1 ns; 2 ns)	Conditioning x Odour i. Higher in response to the odour paired with CO2 when this was ammonia (p<.05) ii-vii. ns Conditioning x Verbal symptom suggestions i+iii+iv+vi. Higher following odour which was paired with CO2 when given symptom suggestions (i, p<.01; iii+iv+vi, p<.05) ii+v+vii. ns No other interactions assessed

Note: RCT = Randomised Controlled Trial, B = Between subjects design, W = Within subjects design, U/K= Unknown, ns = non-significant, italicised = not directly given but has been extrapolated from the available data, rTMS = Repetitive Transcranial Magnetic Stimulation, CO2 = Carbon dioxide, O2 = Oxygen, **a** = high risk random sequence generation bias, **b** = high risk allocation concealment bias, **c** = high risk blinding of participants and personnel bias, **e** = did not mention an a priori sample size calculation, Not assessed = did not assess interactions with another risk factor

Table 2-2 The effect of perceived dose manipulation on symptom development in response to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Experimental conditions (n)	Main effect on symptoms measured	Interaction(s) with other risk factors
Bayer et al. (1991) e	RCT (B+W)	Unemployed Men (100, U/K, 100.0)	Sham electrical shock	a. Within each group the stimulator setting increased from 0 to 80 mA	i. Mean pain ratings (increased with greater sham stimulation, $p<.001$)	No significant interactions with symptom suggestion
Bayer et al. (1998) a,e	RCT (B+W)	Job seekers (62, U/K, 82.0)	Sham electrical shock	a. Within each group the stimulator setting increased in steps of 10 every 5 minutes till it reached 50	i. Number of subjects reporting pain (ns) ii. Mean maximal pain rating (ns) iii. Subjects reporting pain over analgesic threshold (ns) iv. Pain intensity rating over time (Increased, difference between stimulator settings, $p<.01$)	Perceived dose x Prior experience i-iii. Not assessed iv. Increased with increasing stimulator settings for those who experienced prior pain ($p<.01$), ns for those with no prior pain
Flaten et al. (2003) a,b,e	W	Coffee drinkers (20, U/K, 50.0)	Sham coffee	a. Participants were first given one cup and then a second	i. Alertness, contentedness, calmness, arousal, and stress VAS scores (ns)	Not assessed
Jensen and Karoly (1991) e	RCT (B+W)	Students (86, U/K, 45.3)	Sham sedative pill	a. Suggestions of a high dose or low dose were counterbalanced across each group	i. General placebo response rating (ns) ii. Adjective symptom checklist score (ns)	No significant interactions with social desirability or gender
Kirsch and Weixel (1988) e	RCT (B)	Student coffee drinkers (U/K, 19.3, 31.0)	Sham coffee	a. 1 tsp (U/K) b. 2 tsps (U/K) c. 3 tsps (U/K) d. 5 tsps (U/K) e. 8 tsps (U/K)	i. Mean change in alertness (ns) ii. Mean change in relaxation (ns) iii. Mean change in tension ("significant linear increase in tension as a function of dose", $p<.03$)	Perceived dose x Likelihood suggestion i+iii. Increased with increasing dose in the deceptive group, decreased in the double-blind group (i, $p<.02$; iii, $p<.04$) ii. ns

Szemerszky et al. (2010)	W	Healthy students (40, 22.8, 27.5)	Sham EMF	a. Told it would be weak b. Told it would be strong	i. Overall symptom score (b>a, p<.001)	Not assessed

Note: RCT = Randomised Controlled Trial, B = Between subjects design, W = Within subjects design, U/K= Unknown, ns = non-significant, EMF = Electromagnetic Field, tsp = teaspoon, italicised = not directly given but has been extrapolated from the available data, **a** = high risk random sequence generation bias, **b** = high risk allocation concealment bias, **c** = high risk blinding of participants and personnel bias, **e** = did not mention an a priori sample size calculation, Not assessed = did not assess interactions with another risk factor

Table 2-3 The effect of self-awareness manipulation on symptom development in response to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Experimental conditions (n)	Main effect on symptoms measured	Interaction(s) with other risk factors
Geers, Helfer, et al. (2005) e	RCT (B)	Healthy students (54, 21.0, 29.6)	Sham over-the-counter pill	a. Told to attend to any symptoms experienced (27) b. Not given any such instructions (27)	i. Affect questionnaire - Anxiety, restlessness, relaxed, irritable, and perspiration (ns)	No significant interactions with age, gender, likelihood suggestion or optimism
Geers et al. (2006) e	RCT (B)	Healthy students (54, U/K, 31.5)	Sham over-the-counter pill	a. Told to closely monitor feelings/bodily sensations (27) b. Not given any such instructions (27)	i. Overall placebo symptom index: anxiety, nausea, pleasant feelings, perspiration, and perceived pill effect (ns)	Self-awareness x Likelihood suggestion i. Higher in condition a participants with deceptive suggestions than condition a participants with control suggestions ($p<.01$) and condition a participants with double-blind suggestions ($p=.02$). In addition it is higher in condition a participants with deceptive suggestions than condition b participants with deceptive suggestions ($p=.02$)
Gibbons et al. (1979) a,e	RCT (B)	Female students (38, U/K, 0.0)	Sham drug	a. Mirror was facing participants (19) b. Mirror was not facing participants (19)	i. Perceived arousal ($b>a$, $p<.01$) ii. Salient symptom checklist (ns) iii. Non salient symptom checklist (ns)	Self-awareness x Symptom suggestion i +iii. ns ii. Lower in condition a than condition b when participants were misinformed ($p<.03$)

Van den Bergh et al. (1998) e	RCT (B+W)	Healthy adults (56, 42.5, 50.0)	Odours	a. Told to count lower tones and disregard higher tones (28) b. Told to ignore tones (28)	i. Total symptom score (ns) ii. Arousal (ns) iii. Respiratory (ns) iv. Cardiac (ns) v. Tingling (ns) vi. Unclassified (ns) vii. Dummy (ns)	Self-awareness x Conditioning i+ii+iv+vi+vii. Higher in response to the odour paired with CO2 when this was ammonia and participants were in condition b (i+ii, $p < .001$, iv+vi+vii, $p < .002$) ii+v. ns No other interactions assessed

Note: RCT = Randomised Controlled Trial, B = Between subjects design, U/K= Unknown, ns = non-significant, CO2 = Carbon dioxide, **a** = high risk random sequence generation bias, **e** = did not mention an a priori sample size calculation

2.4.3.4 Type of administration

Two studies of mixed quality tested whether type of administration affects symptom reporting, finding no evidence for a link with placebo effects (see Table 2-4). There was no difference in symptom reporting between a sham pill and either a saline injection (Goldman, Witton, & Scherer, 1965) or sham acupuncture (Kaptchuk et al., 2006).

2.4.3.5 Verbal suggestions on performance

Three studies manipulated verbal suggestions about the effect an inert exposure would have on performance (see Table 2-5). Two higher quality studies found no significant effects with only one lower quality study reporting an effect, demonstrating little evidence that suggesting an exposure impairs performance increases the likelihood of a placebo effect. Both Harrell and Juliano (2009) and Nevelsteen, Legros, and Crasson (2007) found no significant main effects of suggesting sham coffee or sham EMF would enhance or impair performance on a task on any of their symptom measures, respectively. However, smokers told that a sham cigarette would impair performance had significantly more craving symptoms than those who were told it would enhance performance (Harrell & Juliano, 2012).

2.4.3.6 Verbal suggestions on likelihood of substance taken

Nine studies manipulated suggestions about the likelihood that an exposure would occur (see Table 2-6). All studies were of higher quality with four finding significant effects and five finding non-significant effects. In other words, there was mixed evidence for the role of likelihood suggestions in placebo effects. The studies used a mixture of conditions in which participants were either told they would receive an active exposure (deception), might receive an active or inactive exposure (double-blind), would receive an inactive exposure (open) or nothing (control). Five of the studies found no significant main effects (Geers, Helfer, et al., 2005; Geers et al., 2006;

Ossege et al., 2005; Walach, Schmidt, Dirhold, & Nosch, 2002) including Walach and Schneider (2009) exp 1. Geers, Wellman, Fowler, Rasinski, and Helfer (2011) however found that participants reported significantly more side effects in response to a sham pill when given deceptive information, compared to double-blind or control information. In addition, participants given deceptive or double-blind suggestions had a significantly higher increase in alertness following ingestion of sham coffee (Kirsch & Weixel, 1988) and a significantly higher number of adverse events following a sham weight loss supplement (Tippens et al., 2014) than participants in the control condition. For Walach, Schmidt, Bihr, and Wiesch (2001) participants told they would receive an inactive exposure scored higher on general wellbeing than those who received no substance or instruction.

Table 2-4 The effect of type of administration manipulation on symptom development in response to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Experimental conditions (n)	Main effect on symptoms measured	Interaction(s) with other risk factors
Goldman et al. (1965) a,b,e	Non RCT (B)	Male veterans with schizophrenia (64, 44.0, 100.0)	Sham arousal treatment	a. Received sugar pill (32) b. Received saline injection (32)	i. Reported symptoms identified through interviews (ns) ii. Reported drug effect identified through interviews (ns) iii. Ward activity (ns)	Not assessed
Kaptchuk et al. (2006)	RCT (B)	Adults with distal pain in the arms (266, 36.7, 45.9)	Sham treatment	a. Received sham acupuncture (133) b. Received placebo pill (133)	i. Frequency of one or more side effects reported (ns)	N/A

Note: RCT = Randomised Controlled Trial, Non RCT = Non-randomised controlled trial B = Between subjects design, ns = non-significant, **a** = high risk random sequence generation bias, **b** = high risk allocation concealment bias, **e** = did not mention an a priori sample size calculation, Not assessed = did not assess interactions with another risk factor, N/A = no other risk factors assessed

Table 2-5 The effect of verbal suggestions on performance on symptom development in response to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Experimental conditions (n)	Main effect on symptoms measured	Interaction(s) with other risk factors
Harrell and Juliano (2009) c	RCT (B)	Adult non-smoking coffee consumers (30, 22.6, 22.0)	Sham coffee	a. Told caffeine enhances performance (15) b. Told caffeine impairs performance (15)	i. Sum of ten self-reported symptoms (ns) ii. Profile of mood states score (ns)	N/A
Harrell and Juliano (2012) c,e	RCT (B)	Adult smokers (43, 28.7, 67.4)	Sham cigarette	a. Told cigarette enhances performance (20) b. Told cigarette impairs performance (23)	i. Cigarette evaluation scale - cravings score (b>a, p=.02)	No significant interaction with gender
Nevelsteen et al. (2007) e	RCT (B)	Healthy males (59, 48.4, 100.0)	Sham magnetic field	a. Told magnetic fields enhance cognitive performance (15) b. Told magnetic fields impair cognitive performance (15) c. Told magnetic fields have no effect on cognitive performance (14) d. Not exposed to sham magnetic field and received no information (15)	i. Subjective vigilance feelings (ns) ii. Profile of mood states score (ns) iii. 24 Physical symptoms scale (ns)	Not assessed

Note: RCT = Randomised Controlled Trial, B = Between subjects design, ns = non-significant, italicised = not directly given but has been extrapolated from the available data, **c** = high risk blinding of participants and personnel bias, **e** = did not mention an a priori sample size calculation, Not assessed = did not assess interactions with another risk factor, N/A = no other risk factors assessed

Table 2-6 The effect of verbal suggestions of likelihood on symptom development in response to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Experimental conditions (n)	Main effect on symptoms measured	Interaction(s) with other risk factors
Geers et al. (2006) e	RCT (B)	Healthy students (54, U/K, 31.5)	Sham over-the-counter pill	a. Told the pill had unpleasant side effects (18) b. Told they may or may not receive the active drug (19) c. Told they would ingest an inactive drug (17)	i. Overall placebo symptom index: anxiety, nausea, pleasant feelings, perspiration, and perceived pill effect (ns)	Likelihood suggestion x Self-awareness i. Higher in condition a than condition c ($p<.01$) or condition b participants ($p=.02$) when participants told to attend to sensations. Higher in participants told to attend to sensations than those not given such instructions when in condition a ($p=.02$)
Geers et al. (2011) e	RCT (B)	Healthy students (102, 20.5, 21.6)	Sham caffeine capsule	a. Told it contained 250mg of caffeine (34) b. Told they may or may not be ingesting 250mg of caffeine (34) c. Not given the capsule and received no caffeine expectation (34)	i. Placebo response index- anxious, sluggish, energized, calm, irritated, lazy, relaxed, and excited ($a>b$, $p<.05$; $a>c$, $p<.01$; b vs c , ns)	No significant interactions with gender
Geers, Helfer, et al. (2005) e	RCT (B)	Healthy students (54, 21.0, 29.6)	Sham over-the-counter pill	a. Told the pill had unpleasant side effects (18) b. Told the pill would make them feel either unpleasant or was an inactive substance (18) c. Told they would ingest an inactive pill (18)	i. Affect questionnaire - Anxiety, restlessness, relaxed, irritable, and perspiration (ns)	Likelihood suggestion x Optimism i. Higher in pessimists than optimists when in condition a than condition c ($p<.05$), condition a vs b, b vs c (ns) No significant interaction

						with age, gender or self-awareness
Kirsch and Weixel (1988) e	RCT (B)	Student coffee drinkers (100, 19.3, 31.0)	Sham coffee	a. Told they would receive coffee (U/K) b. Told they may or may not receive caffeinated coffee (U/K) c. No beverage, waited for 20 minutes (U/K)	i. Mean change in alertness (a+b>c, p<.003; a>b, U/K) ii. Mean change in relaxation (ns) iii. Mean change in tension (ns)	Likelihood suggestion x Perceived dose i+iii. Increased with increasing dose in condition a, decreased in condition b (i, p<.02; iii, p<.04) ii. ns
Ossege et al. (2005)	RCT (B)	Healthy volunteers (60, 27.6, 40.0)	Sham drug	a. Told it was an active medication (30) b. Told there was a 50% chance that it was a placebo or active medication (30)	i. Number of adverse events (ns) ii. Severity of adverse events (ns)	N/A
Tippens et al. (2014) e	RCT (B)	Obese adults (79, 49.4, 10.4)	Sham weight loss supplement	a. Told they would be given an active weight loss supplement (27) b. Told they would be randomly assigned to either the active or placebo supplement (28) c. Only received lifestyle education (24)	i. Number of recorded adverse events (a+b>c, p<.001; a vs b, ns)	N/A
Walach and Schneider (2009) Exp 1	RCT (B)	Healthy adult coffee drinkers (60, 32.3, 23.3)	Sham coffee	a. Told it was caffeine (15) b. Told it could be placebo or caffeine (15) c. Told it could be placebo or caffeine (15) d. Received no beverage (15)	i. Mean change in mood (ns) ii. Mean change in calmness (ns) iii. Mean change in alertness (ns)	Not assessed

Walach et al. (2001)	RCT (B)	Coffee drinkers (157, 28.1, 34.0)	Sham coffee	a. Told they would receive a placebo (41) b. Told they would receive coffee (39) c. Told they may receive real coffee or decaffeinated coffee (39) d. No substance or instruction given (38)	i. General wellbeing score (a>d, p<.0004; all other comparisons, ns)	No significant interaction with experimenter expectations
Walach et al. (2002)	RCT (B)	Coffee drinkers (159, 25.5, 58.0)	Sham coffee	a. Told they would receive a placebo (39) b. Told they would receive coffee (40) c. Told they may receive real coffee or decaffeinated coffee (40) d. No substance or instruction given (40)	i. General wellbeing score (ns)	No significant interaction with Symptom suggestion

Note: RCT = Randomised Controlled Trial, B = Between subjects design, U/K= Unknown, ns = non-significant, italicised = not directly given but has been extrapolated from the available data, e = did not mention an a priori sample size calculation, N/A = no other risk factors assessed

2.4.3.7 Verbal suggestions of arousal

Sixteen studies manipulated suggestions about the effect an inert exposure would have on arousal (see Table 2-7). Thirteen studies showed a significant effect, with 10 of these being of higher quality. This strongly supports a link with placebo effects. Only three studies revealed no main effects (Brondeur, 1965; Kuenzel, Blanchette, Zandstra, Thomas, & El-Dereby, 2012; Penick & Fisher, 1965). The remaining 13 all demonstrated significant effects. Participants given stimulant suggestions compared to sedative suggestions had higher tension scores and were more lively after administration of a sham drug (Flaten, Simonsen, & Olsen, 1999; Mrna & Skrivaneck, 1985), and had higher scores of stress, arousal, alertness, friendliness and aggressiveness, and lower fatigue scores after ingestion of an inert drink (Dinnerstein & Halm, 1970; Flaten, 1998; Slanska, Tikal, Hvizdosova, & Benesova, 1974). Higuchi, Shoji, and Hatayama (2002) demonstrated lower stress and stimulant symptoms for participants given relaxing suggestions compared to no information for lavender and jasmine fragrances respectively. Goldman et al. (1965) found that more patients reported suggested drug effects in a sedative condition than in a stimulant condition. The remaining studies found a significant increase in caffeine related symptoms (Geers, Weiland, Kosbab, Landry, & Helfer, 2005; Lotshaw, Bradley, & Brooks, 1996), and alertness (Schneider et al., 2006) including Walach and Schneider (2009) exp 2 and a significant decrease in calmness (Mikalsen et al., 2001) for participants told they would receive caffeine compared to participants who were told they would not receive caffeine or who received no beverage. Finally Angelucci and Pena (1997) found that participants given coffee with low arousal expectations had significantly lower alertness compared to participants given coffee with no expectations, high arousal expectations or no coffee at all.

2.4.3.8 Verbal suggestions of symptoms

Twenty one studies manipulated suggestions about what symptoms to expect from an inert exposure (see Table 2-8). Thirteen found a significant effect, with 11 of these being of higher quality, broadly supporting a link with nocebo effects. Out of the 21 studies, eight reported no significant main effects (Devriese et al., 2006; Devriese et al., 2004; Heatherton, Polivy, & Herman, 1989; Jaen & Dalton, 2014; Schweiger & Parducci, 1981; Walach et al., 2002; Winters et al., 2003; Witthöft & Rubin, 2013). For the remaining 13 studies, Benedetti et al. (1997), Wise et al. (2009), Crichton, Dodd, Schmid, Gamble, and Petrie (2014) and Pennebaker and Skelton (1981) found significantly higher symptoms scores for those warned about side effects compared to those not warned after administration of sham treatment, infrasound and ultrasonic noise respectively. Dalton (1999), Neukirch and Colagiuri (2014) and Put et al. (2004) found that participants' symptoms were significantly consistent with the warning they received about an odour, sham sleep medication and sham inhaler respectively. Three studies demonstrated that participants experienced significantly more symptoms when informed about side effects to a sham drug (Gibbons et al., 1979; Zimmermann-Viehoff et al., 2013) or saline eye drops (Gavrylyuk, Ehrt, & Meissner, 2010) compared to being informed it was a placebo. Similarly both Bayer et al. (1991) and Read and Bohr (2014) established significantly higher symptoms scores for those informed they would receive an active compared to an inactive exposure. Colagiuri, McGuinness, Boakes, and Butow (2012) however found the opposite, participants not warned about the side effects experienced more and a greater severity of side effects than those warned about one or four side effects.

2.4.3.9 Miscellaneous

Six studies looked at factors that did not fit into the above categories (see Table 2-9). There was no significant effect of manipulating participants to cooperate (Geers,

Weiland, et al., 2005) or the experimenters' expectations of participants' symptoms (Walach et al., 2001). However, Faasse, Cundy, Gamble, and Petrie (2013) found that manipulating tablet brand to make participants think they had changed to a generic version resulted in a significantly higher number of symptoms compared to participants told that they were still taking the original branded tablet, although this study was of lower quality than the others in this group. Jensen and Karoly (1991) have shown that manipulating social desirability so that participants think responding to the pill is more socially desirable results in significantly higher symptom scores. Type of breathing has also been shown to affect symptom reporting with normocapnic overbreathing resulting in higher respiratory symptoms compared to spontaneous breathing (Van Diest et al., 2006). Lastly, a conditioned odour results in more symptoms if the odour is presented immediately rather than a week after conditioning trials (Devriese et al., 2000).

Table 2-7 The effect of verbal suggestions of arousal on symptom reporting in response to an inert exposure.

Reference and quality	Study design	Population (N, Mean Age, %Male)	Inert exposure	Experimental conditions (n)	Main effect on symptoms measured	Interaction(s) with other risk factors
Angelucci and Pena (1997) e	RCT (B)	Student caffeine consumers (148, U/K, 23.0)	Sham coffee	a. Given coffee with no expectations (37) b. Given coffee with low arousal expectations (37) c. Given coffee with high arousal expectations (37) d. no coffee and no expectations (37)	I. Stimulation/alertness (b<a+c+d, p<.001; all other comparisons, ns) ii. Anxiety/irritability (ns) iii. Subjective symptoms (ns)	Not assessed
Brodeur (1965) e	RCT (B)	Healthy senior students (45, U/K, 91.1)	Sham arousal capsule	a. Told it was a stimulant (15) b. Told it was a tranquilizer (15) c. No suggestion (15)	i. Arousal score (ns)	N/A
Dinnerstein and Halm (1970) e	RCT (B)	Male students (80, U/K, 100.0)	Sham arousal liquid	a. Told it was an energizer (40) b. Told it was a tranquilizer (40)	i. Friendly (b<a, p<.025) ii. Aggressive (b<a, p<.025) iii. Sleepy (b>a, p<.001) iv. Dizzy (ns) v. Unhappy (ns) vi. Clear thinking (ns)	Arousal suggestion x Prior experience i. Lower after aspirin than lactose under condition a, reverse under condition b (p<.05) ii-iv. ns v+vi. Higher after aspirin than lactose under condition a, reverse under condition b (ps<.05)
Flaten (1998) e	RCT (B)	Healthy students (48, U/K, 35.4)	Sham arousal drink	a. Told you will feel relaxed and sleepy (16) b. Told you will feel alert and a little	i. Subjective stress score (a<b, p<.05; a<c, p<.05; b vs c, ns)	N/A

				stress (16) c. Told you will take an inactive drug (16)	ii. Subjective arousal score (a<b, p<.05; all other comparisons, ns)	
Flaten et al. (1999) e	RCT (B)	Healthy volunteers in non-health professions (34, U/K, 54.5)	Sham arousal capsule	a. The drug will make you feel relaxed (11) b. The drug will make you feel alert (12) c. You will receive capsules that contain a prescription drug (11)	i. Sleep-wake dimension score (ns) ii. Relaxed-tense dimension score (tense score b>a, p=.041; all other comparisons, ns)	N/A
Geers, Weiland, et al. (2005) e	RCT (B)	Healthy student (57, U/K, 35.1)	Sham caffeine pill	a. Told they were given caffeine (U/K) b. No mention of caffeine (U/K)	i. Number of caffeine symptoms reported (a>b, p=.03)	Arousal suggestion x Cooperation prime i. Higher in condition a than b when primed for cooperation (p=.02), when not primed for cooperation there is no significant difference between condition a+b No significant interaction with caffeine consumption
Goldman et al. (1965) e	Non RCT (B)	Male veterans with Schizophrenia (64, 44.0, 100.0)	Sham arousal treatment	a. Told it would heighten their ward activity (32) b. Told it would lower their ward activity (32)	i. Reported symptoms identified through interviews (U/K) ii. Reported drug effect identified through interviews (b>a, p<.001) ii. Ward activity (ns)	Not assessed
Higuchi et al. (2002)	RCT (B)	Healthy volunteers	Fragrance	a. Told it was relaxing (10) b. Told it was stimulating (10)	i. Relaxed scores (ns) ii. Stimulant scores	N/A

e		(30, 21.2, 40.0)	(Lavender or Jasmine)	c. No information given (10)	(Lavender, ns; Jasmine, $c > a$, $p < .05$; other comparisons U/K) iii. Stress reduced scores (Lavender, $a > c$, $p < .05$, a vs b , ns, b vs c , U/K; Jasmine, ns)	
Kuenzel et al. (2012) e	RCT (B)	English speaking students (148, 21.7, 18.2)	Herbal infusion tea	a. Told it would make them feel relaxed (45) b. Told it would make them feel active (53) c. No information given (50)	i. Symptom ratings (ns)	N/A
Lotshaw et al. (1996) e	RCT (B)	Male student coffee drinkers (50, U/K, 100.0)	Sham coffee	a. Told coffee received decaffeinated (25) b. Told decaffeinated received decaffeinated (25)	i. Profile of mood states score (ns) ii. Effects of coffee received score ($a > b$, "subjects who were told they were receiving caffeine rated the effects to be significantly greater than subjects who were told they were receiving decaffeinated")	N/A
Mikalsen et al. (2001) e	RCT (W)	Student coffee drinkers (21, 25.9, 66.7)	Sham coffee	a. Told it was caffeine b. Told it was not caffeine	i. Alertness VAS score (ns) ii. Contentedness VAS score (ns) iii. Calmness VAS score ($a < b$, $p < .05$)	Not assessed

Mrna and Skrivanek (1985) a,b,e	W	Healthy volunteers (21, 17.0, 47.6)	Sham arousal drug	a. Told it was a new doping drug undetectable by anti-doping tests b. Told it was to relax pre-restart states	i. Observed behaviour ("after the doping drug students were lively and talkative whereas after the sedative they sat quietly and some fell asleep")	Not assessed
Penick and Fisher (1965) a,b,c,e	W	Healthy medical students (14, U/K, U/K)	Sham arousal drug	a. Told they would receive a stimulant drug b. Told they would receive a sedative drug	i. Overall arousal score (ns)	N/A
Schneider et al. (2006) c,e	RCT (B)	Healthy Adults (45, 31.0, 22.2)	Sham coffee	a. Told they were to consume decaffeinated coffee (15) b. Told they were to consume regular coffee (15). c. Informed they would receive no beverage and no instructions (15)	i. Mood (ns) ii. Alertness (b>c, p=.04; all other comparisons, ns) iii. Calmness (ns)	N/A
Slanska et al. (1974) a,e	Non RCT (B)	Medical students (33, U/K, U/K)	Salt solution	a. Told it was a stimulant (17) b. Told it was a sedative (16)	i. Perceived effect ("stimulation suggestion was effective in 12% of placebo reactors, sedation suggestion was effective in 25%") ii. Vigilance ("Sedative suggestion decreased alertness") iii. Fatigue ("b>a, statistically significant increase in fatigue") iv. Tension v. Relaxation	Not assessed

Walach and Schneider (2009) Exp 2	RCT (B)	Healthy adults coffee drinkers (30, 29.9, 33.3)	Sham coffee	a. Told it was caffeine (15) b. Received no beverage (15)	i. Mean change in mood (ns) ii. Mean change in calmness (ns) iii. Mean change in alertness (a>b, d=0.64)	Not assessed

Note: RCT = Randomised Controlled Trial, Non RCT = Non randomised controlled trial, B = Between subjects design, W = Within subjects design, U/K= Unknown, ns = non-significant, italicised = not directly given but has been extrapolated from the available data, **a** = high risk random sequence generation bias, **b** = high risk allocation concealment bias, **c** = high risk blinding of participants and personnel bias, **e** = did not mention an a priori sample size calculation, Not assessed = did not assess interactions with another risk factor, N/A = no other risk factors assessed

Table 2-8 The effect of verbal suggestions of symptoms on symptom development in response to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Experimental conditions (n)	Main effect on symptoms measured	Interaction(s) with other risk factors
Bayer et al. (1991) e	RCT (B)	Unemployed Men (100, U/K, 100.0)	Sham electrical shock	a. Told they would receive a safe but often painful undetectable current (60) b. Were assured there would be no shocks (40)	i. Mean pain rating ($a > b$, $p < .01$) ii. Frequency of pain reports ($a > b$, $p < .05$)	No significant interactions with dose
Benedetti et al. (1997) e	RCT (B)	Video assisted thoracoscopy patients (36, 53.7, 66.1)	Sham treatment	a. Open injection that it would increase pain (18) b. Hidden injection (18)	i. Pain intensity rating ($a > b$, $p < .005$)	N/A
Colagiuri et al. (2012) e	RCT (B)	Students experiencing sleep difficulty (82, 20.2, 22.0)	Sham sleeping pill	a. Treatment might cause one side effect (29) b. Treatment might cause four side effects (23) c. No warning about side effects (30)	i. Free side effect report (ns) ii. Change in appetite report (ns) iii. Severity of change in appetite (ns) iv. Cued report side effect ($c > a + b$, restlessness $p = .04$, poor concentration, $p = .001$; a vs b , ns) v. Severity of cued side effects ("trend" for $c > a + b$; a vs b , ns)	N/A
Crichton et al. (2014) e	RCT (B)	Students (54, U/K, 37.0)	Sham infrasound	a. TV footage detailing symptomatic experiences attributed to wind farms (27) b. TV footage with experts stating wind farms would not cause symptoms (27)	i. Total symptom change score ($a > b$, $p < .01$) ii. Total symptom change severity score ($a > b$, $p < .001$)	N/A
Dalton	RCT	Healthy	Odours	a. Told they would have relaxing	i. Symptom reports ($b > a + c$, $p < .05$)	Symptom

(1999) e	(B)	volunteers (180, 31.7, 49.4)		effects (60) b. Told they were industrial solvents (60) c. Told they were approved for olfactory research (60)		suggestions x Odour i. “Highest for those exposed to butanol following negative suggestions, lowest for those exposed to methyl salicylate following positive suggestions” No other interactions assessed
Devriese et al. (2004) a,e	Non RCT (B+W)	Healthy students (53, U/K, U/K)	Odours	a. Given information about possible health damaging effects of chemical pollution (U/K) b. No information (U/K)	i. Total symptom score (ns) ii. Arousal symptom score (ns) iii. Respiratory symptom score (ns) iv. Cardiac symptom score (ns) v. Tingling symptom score (ns) vi. Unclassified symptom score (ns) vii. Dummy symptom score (ns)	Non assessed
Devriese et al. (2006)	RCT (B+W)	Psychology students (40, U/K, 0.0)	Odour	a. Given information about possible health damaging effects of chemical pollution (20) b. No information (20)	i. Total symptom score (ns) ii. Arousal symptom score (ns) iii. Respiratory symptom score (ns) iv. Cardiac symptom score (ns) v. Tingling symptom score (ns) vi. Unclassified symptom score (ns) vii. Dummy symptom score (ns)	Non assessed

Gavrylyuk et al. (2010) e	RCT (B)	Healthy volunteers (30, 24.9, 32.0)	Saline eye drops	a. Informed of pupil dilation effects (10) b. Informed of pupil constriction effects (10) c. Informed of saline eye drops (10)	i. Frequency of symptoms (a+b>c, "Subjective symptoms, were more frequently reported by participants in the experimental placebo groups than by controls"; a vs b, ns)	N/A
Gibbons et al. (1979) a,e	RCT (B)	Female students (38, U/K, 0.0)	Sham drug	a. Told they were taking Cavanol which would produce some noticeable side effects (19) b. Told they were taking baking soda (19)	i. Perceived arousal (ns) ii. Salient Symptom score (a>b, p<.001) iii. Non salient symptom score (a>b, p<.01)	Symptom suggestion x Self-awareness i. ns ii. Condition a reported less symptoms than condition b when mirror was facing them, (p<.03) iii. ns
Heatherton et al. (1989) e	RCT (B)	Female students (59, U/K, 0.0)	Sham vitamin pill	a. Told vitamin has been reported to make people feel hungry (19) b. Told vitamin has been reported to make people feel full (20) c. Told no further information (20)	i. Hunger ratings (ns)	No significant interactions with participant restraint
Jaen and Dalton (2014) a,b,e	Non RCT (B)	Asthmatics (17, 38.5, 52.9)	Sham active odour	a. Labelled the odour as therapeutic (9) b. Labelled the odour as asthmogenic (8)	i. Asthma symptom checklist (ns)	N/A

Neukirch and Colagiuri (2014) a,e	RCT (B)	Students with sleep difficulty (91, 21.3, 33.0)	Sham sleep medication	a. Warned about an increase/decrease in appetite and received placebo treatment (24) b. Warned about the side effect but received no treatment (23) c. Not warned about the side effects and received placebo treatment (22) d. Not warned about the side effects and received no treatment (22)	i. Free reporting of side effects (ns) ii. Change in appetite (ns) iii. Change in appetite consistent with warning (a, $p=.008$) iv. Severity of changes in appetite (lower for those warned about a decrease compared to those warned of an increase, $p=.02$, or those not warned, $p=.012$) v. c vs d (change in appetite, ns; direction of change, ns; severity of change, ns)	N/A
Pennebaker and Skelton (1981) e	RCT (B)	Students (38, U/K, 31.6)	Ultrasonic noise	a. Told it would increase skin temperature (13) b. Told it would decrease skin temperature (12) c. Told it would have no effect on skin temperature (13)	i. Perceptions of skin temperature ($a>b$, $p<.001$; $a>c$, $p<.05$; b vs c, ns)	N/A
Put et al. (2004) a,b,c,e	W	Asthma patients (32, 40.0, 50.0)	Sham inhaler	a. Told it would have no effect on breathing b. Told it was a bronchoconstrictor c. Told it was a bronchodilator	i. Obstruction ($b>c$, $p<.01$; a vs b, a vs c, ns) ii. Dyspnoea ($b>c$, $p<.01$; a vs b, a vs c, ns) iii. Fatigue (ns) iv. Hyperventilation (ns) v. Anxiety (ns) vi. Irritation (ns)	Symptom suggestion x Negative affect i+ii. Higher after condition b than c for participants with high negative affect (i, $p<.01$; ii, $p<.05$) iii-vi. ns No significant interactions with

						social desirability
Read and Bohr (2014) a,b,c,e	Non RCT (B)	Volunteers without photosensitive epilepsy (177, 25.3, U/K)	Sham 3D TV	a. Told it was 3D and wore passive 3D glasses (22) b. Told it was 3D and wore active no shuttering 3D glasses (33) c. Told it was 2D and did not wear glasses (122)	i. Symptom checklist score (a+b>c, p=.03; a vs b, ns)	Not assessed
Schweiger and Parducci (1981) e	RCT B)	Students (34, U/K, 52.9)	Sham electric current	a. Told a low current would be delivered, too mild to be felt but had produced mild headaches in the past (17) b. Told current would be too weak to be felt, but some people develop mild headaches as a side effect (17)	i. Headache pain rating (ns)	N/A
Walach et al. (2002)	RCT (B)	Coffee drinkers (159, 25.5, 58.0)	Sham coffee	a. Received an information leaflet describing the pharmacological effects of caffeine (U/K) b. Received no further information (U/K)	i. General wellbeing score (ns)	No significant interaction with likelihood suggestion
Winters et al. (2003) e	Non RCT (B+W)	18-30 year olds (32, U/K,15.6)	Odour	a. Given leaflet describing widespread chemical pollution of the environment is a potential cause of multiple chemical sensitivity (16) b. No information given (16)	i. Total symptom score (ns) ii. Arousal symptom score (ns) iii. Respiratory symptom score (ns) iv. Cardiac symptom score (ns) v. Tingling symptom score (ns) vi. Unclassified symptom score (ns) vii. Dummy symptom score (ns)	Symptom suggestions x Conditioning i+iii+iv+vi. Higher following odour which was paired with CO2 when given

						symptom suggestions (i, $p<.01$; iii+iv+vi, $p<.05$) ii+v+vii. ns No other interactions assessed
Wise et al. (2009) c	RCT (B)	Patients with poor asthma control (241, 39.0, 29.5)	Sham asthma drug	a. Emphasized benefit of treatment and described potential side effects (121) b. Expressed uncertainty about improvement following treatment and did not describe potential side effects (120)	i. Headaches ($a>b$, $p=.03$) ii. Lethargy (ns) iii. Gastrointestinal distress (ns) iv. Fever (ns) v. Rhinitis (ns) vi. Cough (ns) vii. Flu (ns) viii. Skin rash (ns)	N/A
Witthöft and Rubin (2013)	RCT (B)	Adult English speakers (147, 29.8, 32.7)	Sham EMF	a. Watched a documentary concerning the potential adverse health effects of Wi-Fi (76) b. Watched a BBC News report concerning the security of the internet and mobile phone data (71)	i. Total symptom score (ns) ii. Anxiety (ns) iii. Head and concentration (ns) iv. Tingling sensations (ns)	Symptom suggestion x Anxiety i+iii. Increased in people with high anxiety who were in condition a (i, $p=.008$; iii, $p<.001$) ii+iv. ns No significant interactions with age, gender, level of education or

						personality
Zimmermann -Viehoff et al. (2013) b,e	RCT (B)	Health Caucasians (92, 24.5, 41.3)	Sham arousal oral spray	a. Told it contained a drug to increase BP (33) b. Told it contained a drug to decrease BP (29) c. Told it was a placebo (30)	i. Perceived drug effect (a>c, p=.04; b>c, p=.003; a vs b, ns)	N/A

Note: RCT = Randomised Controlled Trial, Non RCT = Non randomised controlled trial, B = Between subjects design, W = Within subjects design, U/K= Unknown, ns = non-significant, italicised = not directly given but has been extrapolated from the available data, **a** = high risk random sequence generation bias, **b** = high risk allocation concealment bias, **c** = high risk blinding of participants and personnel bias, **e** = did not mention an a priori sample size calculation, N/A = no other risk factors assessed

Table 2-9 Miscellaneous risk factors for symptom development in response to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Manipulation	Experimental conditions (n)	Main effect on symptoms measured	Interaction(s) with other risk factors
Faasse et al. (2013) b,c,e	RCT (B)	Healthy students (60, 19.4, 43.5)	Sham anti-anxiety tablet	Verbal suggestion (Brand)	a. Branded reformulation change (20) b. Generic reformulation change (20) c. No change (20)	i. Number of expected symptoms (b>c, p=.03; a vs b, ns; a vs c, ns) ii. Number of unexpected symptoms (ns)	N/A
Geers, Weiland, et al. (2005) e	RCT (B)	Healthy students (57, U/K, 35.1)	Sham caffeine pill	Cooperation prime	a. Given a scrambled sentence test with a cooperation prime (U/K) b. Given a scrambled sentence test with a neutral prime (U/K)	i. Caffeine symptom questionnaire score (ns)	Cooperation prime x Arousal suggestion i. Higher in condition a than b when told they were given coffee (p=.02) No significant interactions with caffeine consumption
Jensen and Karoly (1991) e	RCT (B+W)	Students (86, U/K, 45.3)	Sham sedative pill	Verbal suggestion (social desirability)	a. Type B personality is more positive than type A. Type B have been shown to respond more to pills (43) b. Relationship between type A and B personality and response to pills is very weak (43)	i. General placebo response rating (a>b, p<.05) ii. Adjective symptom checklist score (a>b, p<.05)	No significant interactions with dose or gender

Walach et al. (2001)	RCT (B)	Coffee drinkers (157, 28.1, 34.0)	Sham coffee	Experimenter expectancy	a. Experimenter told the physiological effects from a caffeine placebo are real (proplacebo) (U/K) b. Experimenter told the effects of caffeine placebos are just due to artefacts (antiplacebo) (U/K)	i. General wellbeing score (ns)	No significant interactions with likelihood suggestion
Van Diest et al. (2006) e	RCT (B+W)	Students (28, U/K, 21.4)	Odours	Type of breathing	a. Test odours given with normocapnic breathing trial (U/K) b. Test odours given with spontaneous breathing (U/K)	i. Paresthesia (ns) ii. Cerebral (ns) iii. Cardiac (ns) iv. Gastrointestinal (ns) v. Respiratory (a>b, no statistics given) vi. Anxiety (ns) vii. Neuropsychological (ns) viii. Unclassified (ns) ix. Dummy (ns) x. Feeling unreal (ns)	Not assessed
Devriese et al. (2000) a,e	Non RCT (B+W)	Healthy students (56, U/K, 41.1)	Odours	Timing	a. Test phase immediately after conditioning trials (28) b. Test phase one week after conditioning trials (28)	i. Total symptom score (ns) ii. Arousal (a>b, no statistics given) iii. Respiratory (ns) iv. Cardiac (ns) v. Tingling (ns) vi. Unclassified (ns) vii. Dummy (ns)	Not assessed

Note: RCT = Randomised Controlled Trial, B = Between subjects design, W = Within subjects design, U/K= Unknown, ns = non-significant, italicised = not directly given but has been extrapolated from the available data, **a** = high risk random sequence generation bias, **b** = high risk allocation concealment bias **c** = high risk blinding of participants and personnel bias, **e** = did not mention an a priori sample size calculation, Not assessed = did not assess interactions with another risk factor, N/A = no other risk factors assessed

2.4.4 Baseline risk factor categories

Nineteen prospective studies and also 33 experimental studies which assessed baseline risk factors were included which fell into six different categories as discussed below.

2.4.4.1 Demographics

Twenty studies looked at the risk of demographic characteristics, finding no demonstrable evidence for their role in placebo effects (see Table 2-10). Five of these investigated age and found it did not predict any symptom outcomes (de la Cruz, Hui, Parsons, & Bruera, 2010; Geers, Helfer, et al., 2005; Goetz et al., 2008; Lombardi, Gargioni, Canonica, & Passalacqua, 2008; Witthöft & Rubin, 2013). As four of these studies were of higher quality, this is good evidence that age is not linked with the development of placebo effects. Eighteen studies (Angelucci & Pena, 1997; Casper, Tollefson, & Nilsson, 2001; Geers, Helfer, et al., 2005; Geers et al., 2011; Goetz et al., 2008; Harrell & Juliano, 2012; Jensen & Karoly, 1991; Liccardi et al., 2004; Lombardi et al., 2008; Lorber et al., 2007; Mazzoni et al., 2010; Papoiu et al., 2011; Read & Bohr, 2014; Strohle, 2000; Szemerszky et al., 2010; Van den Bergh et al., 1997, 1998; Witthöft & Rubin, 2013) looked at gender and only four reported significant results suggesting women are more susceptible to placebo effects than men (Casper et al., 2001; Liccardi et al., 2004; Strohle, 2000; Szemerszky et al., 2010). Of the remaining 14 showing non-significant effects, 12 were of high quality suggesting there is very little evidence for the role of gender in placebo effects. The effects of level of education (de la Cruz et al., 2010; Witthöft & Rubin, 2013) were equivocal in two high quality studies, whereas employment (Drici et al., 1995), was not a significant predictor.

2.4.4.2 Clinical characteristics

Fourteen studies investigated clinical characteristics, finding mixed evidence for a link with placebo effects (see Table 2-11). Six studies of high quality looked at the

effect of baseline symptom scores, finding mixed evidence for a link with placebo effects. Two found no significant effects (Andre-Obadia et al., 2011; Casper et al., 2001). For the other four, results were mixed. Danker-Hopfe, Dorn, Bornkessel, and Sauter (2010) and de la Cruz et al. (2010) found that higher symptom scores at baseline predicted higher symptom scores after exposure to sham EMF and treatment respectively, whereas Flaten et al. (2003) and Goetz et al. (2008) found the opposite after drinking decaffeinated coffee and taking sham medication for Parkinson's respectively. Six studies of high quality looked at the effect of type of clinical condition, with five finding a significant effect. They showed that suffering from a condition that is exacerbated by the suggested sham exposure significantly increased symptom reporting compared to healthy volunteers, strongly supporting a link with placebo effects. Nevelsteen et al. (2007) found that depression did not predict symptoms in response to a sham magnetic field. However, Papoiu et al. (2011), Strohle (2000), De Peuter et al. (2005) and Bogaerts et al. (2010) showed that suffering from atopic dermatitis, panic disorder, asthma or medically unexplained dyspnoea resulted in significantly more symptoms in response to sham histamine, sham panic disorder trigger, sham inhaler and breathing trials with room air, respectively, compared to healthy volunteers. In addition Szemerszky et al. (2010) found that the level of perceived sensitivity to EMFs was positively correlated with symptom scores after sham EMF exposure. The remaining two studies looked at previous drug reactions finding weak evidence for a link with placebo effects. Lombardi et al. (2008) found no significant effects of type or severity of previous drug reaction on symptoms in response to a sham allergen pill. However, a higher quality study by Mrna and Skrivanek (1985) found the reaction to another sham drug was significantly correlated with perceived drug effect.

2.4.4.3 Expectations

Thirteen studies looked at the effect of participant expectations on symptom reporting, broadly supporting a link with placebo effects (see Table 2-12). Eleven of these studies looked at participants' symptom expectations, of which five higher quality studies revealed no significant effects (Angelucci & Pena, 1997; Molcan & et al., 1982; Walach et al., 2001) including Walach and Schneider (2009) exp 1 and 2. The remaining six studies demonstrated that expectations of symptoms significantly predicted (Fillmore & Vogel-Sprott, 1992; Köteles & Babulka, 2014; Vase et al., 2013) or correlated (De Peuter et al., 2005; Flaten et al., 2003; Szemerszky et al., 2010) with symptom reporting. Five of these studies were of higher quality therefore broadly supporting a link with placebo effects. Three studies also looked at expectations in terms of the substance taken finding weak evidence for its role in placebo effects. Link, Haggard, Kelly, and Forrer (2006) found that participants who believed they had taken an active pill reported more symptoms than those who thought they had taken a sham pill, however this was a low quality study. Higher quality studies by Bayer et al. (1998) and Walach et al. (2001) also investigated this but found no significant effects.

Table 2-10 Demographic predictors of symptom development to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Risk factor(s)	Symptoms measured	Interaction(s) with other risk factors
Angelucci and Pena (1997) e	RCT (B)	Student caffeine consumers (148, U/K, 23.0)	Sham Coffee	1. Gender	I. Stimulation/alertness (ns) ii. Anxiety/irritability (ns) iii. Subjective symptoms (ns)	Not assessed
Casper et al. (2001) e	P	Nonpsychotic major depressive patients (876, U/K, 42.8)	Sham fluoxetine treatment	1. Gender	i. Number of people reporting one or more symptoms (F>M, p<.01) ii. Specific symptoms (F reported a higher incidence of pain in general, chest pain, infections, accidental injuries, nausea, increased appetite, and nervousness, ps<.043. M were more likely to report somnolence, tremor, and asthma, ps<.048)	Not assessed
de la Cruz et al. (2010) e	P	Patients with cancer related fatigue (105, U/K, 40.0)	Sham treatment	1. Age 2. Education level	i. Nausea (1 ns; higher 2 increases i, p=.05)	Not assessed
Drici et al. (1995) b,e	P	Healthy volunteers (52, 23.5, 50.0)	Sham paracetamol eye drop	1. Employment	i. Subjective side effect rating scale (ns)	Not assessed
Geers et al. (2011) e	RCT (B)	Healthy students (102, 20.5, 21.6)	Sham caffeine capsule	1. Age 2. Gender	i. Placebo response index- anxious, sluggish, energized, calm, irritated, lazy, relaxed, and excited (1 ns; 2 ns)	No significant interactions with likelihood suggestion
Geers, Helfer, et al. (2005)	RCT (B)	Healthy students (54, 21.0, 29.6)	Sham over-the-counter pill	1. Age 2. Gender	i. Affect questionnaire - Anxiety, restlessness, relaxed, irritable, and perspiration (1 ns; 2 ns)	No significant interactions with self-awareness, likelihood

e						suggestion or optimism
Goetz et al. (2008) e	P	Parkinson's patients with dyskinesia (484, U/K, U/K)	Sham medication	1. Age 2. Gender	i. UPDRS score worsening (1 ns; 2 ns)	Not assessed
Harrell and Juliano (2012) e	RCT (B)	Adult smokers (43, 28.7, 67.4)	Sham cigarette	1. Gender	i. Cigarette evaluation scale - cravings (ns)	No significant interaction with performance suggestion
Jensen and Karoly (1991) e	RCT (B+W)	Students (86, U/K, 45.3)	Sham sedative pill	1. Gender	i. General placebo response rating (ns) ii. Adjective symptom checklist score (ns)	No significant interaction with dose or social desirability
Liccardi et al. (2004) b,e	P	Patients with ADRs (600, 42.0, 30.3)	Sham allergen pill	1. Gender	i. Number of people reporting reactions (F>M, p=.01)	Not assessed
Lombardi et al. (2008) a,d,e	P	Patients with ADRs (435, 39.7, 32.0)	Sham allergen pill	1. Age 2. Gender	i. Number of recorded symptoms (1 ns; 2 ns)	Not assessed
Lorber et al. (2007) e	RCT (B)	Students without upper respiratory conditions (86, U/K, 40.7)	Sham environmental toxin	1. Gender	i. Verbal symptom ratings: specified-headache, nausea, itchy skin, drowsiness and additional - watery eyes, scratchy throat, chest tightness, and breathing difficulty (ns)	Gender x Observation i. Higher in observation compared to no observation conditions when participants are female (p<.05)
Mazzoni et al. (2010) e	RCT (B)	Healthy students (120, 20.7, 50.0)	Sham environmental toxin	1. Gender	i. Verbal symptom ratings: specified-headache, nausea, itchy skin, drowsiness and additional - watery eyes, scratchy throat, chest tightness, and breathing difficulty (ns)	Not assessed

Papoiu et al. (2011) e	RCT (W)	Healthy volunteers and patients with atopic dermatitis (25, U/K, 44.0)	Sham histamine	1. Gender	i. Average itch intensity rating (ns) ii. Scratching behaviour (ns)	No significant interactions with social observation
Read and Bohr (2014) e	Non RCT (B)	Volunteers without photosensitive epilepsy (177, 25.3, U/K)	Sham 3D TV	1. Gender	i. Symptom checklist score (ns)	Not assessed
Strohle (2000) e	P	Healthy adults and patients with panic disorder (U/K, 33.5, 56.6)	Sham panic disorder trigger	1. Gender	i. Acute panic inventory rating scale (Healthy adults, ns; patients F>M, p<.05)	Gender x Condition i. Increases for females with panic disorder (p<.05)
Szemerszky et al. (2010) e	W	Healthy students (40, 22.8, 27.5)	Sham EMF	1. Gender	i. Overall symptom score (weak suggestion, F>M, p<.05; strong suggestion, ns)	Not assessed
Van den Bergh et al. (1997) a,e	Non RCT (B+W)	Psychosomatic patients (28, 36.0, 50.0)	Odours	1. Gender	i. Total symptom score (ns) ii. Arousal (ns) iii. Respiratory (ns) iv. Cardiac (ns) v. Tingling (ns) vi. Unclassified (ns) vii. Dummy (ns)	Not assessed
Van den Bergh et al. (1998) e	RCT (B+W)	Healthy adults (56, 42.5, 50.0)	Odours	1. Gender	i. Total symptom score (ns) ii. Arousal (ns) iii. Respiratory (ns) iv. Cardiac (ns) v. Tingling (ns) vi. Unclassified (ns) vii. Dummy (ns)	Not assessed

Witthöft and Rubin (2013)	RCT (B)	Adult English speakers (147, 29.8, 32.7)	Sham EMF	1. Age 2. Gender 3. Level of education	i. Total symptom score (1 ns; 2 ns; 3 ns) ii. Anxiety (1 ns; 2 ns; 3 ns) iii. Head and concentration (1 ns; 2 ns; 3 ns) iv. Tingling sensations (1 ns; 2 ns; 3 ns)	No significant interactions with personality, anxiety or symptom suggestion

Note: RCT = Randomised Controlled Trial, Non RCT = Non randomised controlled trial, P = Prospective design, B = Between subjects design, W = Within subjects design, U/K= Unknown, italicised = not directly given but has been extrapolated from the available data, F = Female, M = Male, ns = non-significant, Not assessed = did not assess interactions with another risk factor, **a** = high risk for selection bias, **b** = high risk for confounding factors, **d** = high risk for low generalizability, **e** = did not mention an a priori sample size calculation

Table 2-11 Clinical characteristics as predictors of symptom development to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Risk factor(s)	Symptoms measured	Interaction(s) with other risk factors
Andre-Obadia et al. (2011) e	RCT (W)	Chronic neuropathic pain patients (45, 55.0, 37.8)	Sham rTMS	1. Pain ratings	i. Pain rating (ns)	No significant interaction with prior experience
Bogaerts et al. (2010) e	P	Patients with medically unexplained dyspnoea and healthy controls (58, U/K, 0.0)	Breathing trial with room air	1. Clinical condition	i. Dyspnoea score (patients reported higher scores than controls, $p<.05$)	Not assessed
Casper et al. (2001) e	P	Nonpsychotic major depressive patients (876, U/K, 42.8)	Sham fluoxetine treatment	1. Depression severity	i. Number of people reporting one or more symptoms (ns)	Not assessed
Danker-Hopfe et al. (2010)	P	German villages with weak RF-EMF sources (397, U/K, 49.1)	Sham EMF	1. Sleep quality	i. Subjective sleep quality (lower 1 decreased i, $p<.001$)	Not assessed
de la Cruz et al. (2010) e	P	Patients with cancer related fatigue (105, U/K, 40.0)	Sham treatment	1. Cancer performance status 2. Well being 3. Cognitive status 4. Nausea 5. Sleep quality 6. Anxiety symptoms	i. Dizziness (worse 1 increased i, $p=.03$) ii. Insomnia (lower 2 increased ii, $p=.01$; higher 3 increased ii, $p=.01$; higher 4 increased ii, $p=.04$; lower 5 increased ii, $p=.04$) iii. Nausea (higher 4 increased iii, $p=.004$) iv. Restlessness (higher 6 increased iv, $p=.002$)	Not assessed

De Peuter et al. (2005) e	RCT (W)	Asthma patients and healthy controls (40, 23.9, 52.5)	Sham inhaler	1. Clinical condition	i. Total symptom score (ns) ii. Obstruction (ns) iii. Dyspnoea (ns) iv. Fatigue (ns) v. Hyperventilation (Asthma patients scored higher than healthy controls, $p < .05$) vi. Anxiety (ns) vii. Irritation (ns)	No significant interaction with association. No other interactions assessed.
Flaten et al. (2003) e	W	Coffee drinkers (20, U/K, 50.0)	Sham coffee	1. Symptoms	i. Alertness (ns) ii. Contentedness (ns) iii. Calmness (for 1 cup $r = -.69$, $p < .01$; for 2 cups $r = -.71$, $p < .01$) iv. Arousal (for 1 cup $r = -.76$, $p < .01$; for 2 cups $r = -.6$, $p < .01$) v. Stress (for 1 cup $r = -.67$, $p < .005$; for 2 cups, ns)	Not assessed
Goetz et al. (2008) e	P	Parkinson's patients with dyskinesia (484, U/K, U/K)	Sham medication	1. Dyskinesia severity 2. UPDRS motor score 3. Daily L-dopa dose 4. Dyskinesia duration 5. Adverse events 6. Adverse event severity	i. UPDRS score worsening (lower 1 increased i, $p < .0001$; 2 ns; 3 ns; 4 ns; 5 ns and 6 ns)	Not assessed
Lombardi et al. (2008) a,d,e	P	Patients with ADRs (435, 39.7, 32.0)	Sham allergen pill	1. Atopic status 2. Previous reaction severity 3. Type of previous reaction	i. Recorded symptoms (1 ns; 2 ns; 3 ns)	Not assessed

Mrna and Skrivane (1985) e	W	Healthy volunteers (21, 17.0, 47.6)	Sham arousal drug	1. Response to other placebo	i. Drug effect questionnaire score (K =.67)	Not assessed
Nevelsteen et al. (2007) e	RCT (B)	Healthy males (59, 48.4, 100.0)	Sham magnetic field	1. Depression	i. Subjective vigilance feelings (ns) ii. Profile of mood states (ns) iii. 24 Physical symptoms scale (ns)	Not assessed
Papoiu et al. (2011) e	RCT (W)	Healthy volunteers and patients with atopic dermatitis (25, U/K, 44.0)	Sham histamine	1. Clinical condition	i. Average itch intensity rating (higher in itch video compared to neutral video for patients, p=.027; healthy volunteers, ns) ii. Itching behaviour (patients scratched more frequently in areas beyond the itch site, p=.001, compared to healthy volunteers when watching the itch video)	Not assessed
Strohle (2000) e	P	Healthy adults and patients with panic disorder (U/K, 33.5, 56.6)	Sham panic disorder trigger	1. Clinical condition	i. Acute panic inventory rating scale (patients scored higher than healthy volunteers, p<.05)	Condition x Gender i. Increased in Females with panic disorder (p<.05)
Szemerszky et al. (2010) e	W	Healthy students (40, 22.8, 27.5)	Sham EMF	1. IEI EMF score	i. Overall symptom score (for weak suggestion r=.46, p<.01; for strong suggestion; r=.48, p<.01; regression, ns)	Not assessed

Note: RCT = Randomised Controlled Trial, P = Prospective design, B = Between subjects design, W = Within subjects design, U/K= Unknown, italicised = not directly given but has been extrapolated from the available data, UPDRS = Unified Parkinson's disease rating scale, IEI-EMF = idiopathic environmental intolerance attributed to electromagnetic fields, ns = non-significant, Not assessed = did not assess interactions with another risk factor, **a** = high risk for selection bias, **d** = high risk for low generalizability, **e** = did not mention an a priori sample size calculation

Table 2-12 Expectations as predictors of symptom development to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Risk factor(s)	Symptoms measured	Interaction(s) with other risk factors
Angelucci and Pena (1997) e	RCT (B)	Student caffeine consumers (148, U/K, 23.0)	Sham coffee	1. Expectations of the effect of coffee	I. Stimulation/alertness (ns) ii. Anxiety/irritability (ns) iii. Subjective symptoms (ns)	Not assessed
Bayer et al. (1998) a,e	RCT (B)	Job seekers (62, U/K, 82.0)	Sham electrical shock	1. Believed what they were told	i. Subjects reporting pain (ns)	Not assessed
De Peuter et al. (2005) e	RCT (W)	Asthma patients and healthy controls (40, 23.9, 52.5)	Sham inhaler	1. Symptom expectations	i. Total symptom score (overall, $r=0.52$, $p<.001$; control, ns; asthma patients, $r=0.69$, $p<.001$)	Not assessed
Fillmore and Vogel-Sprott (1992) e	P	Male students (56, U/K, 100.0)	Sham coffee	1. Symptom expectations	i. Alertness score (higher 1 increased i, $p<.001$) ii. Tension score (higher 1 increased ii, $p<.001$)	N/A
Flaten et al. (2003) e	W	Coffee drinkers (20, U/K, 50.0)	Sham coffee	1. Symptom expectations	i. Alertness (for 1 cup $r=.63$, $p<.005$; for 2 cups $r=.76$, $p<.001$) ii. Discontentedness (for 1 cup $r=.57$, $p<.01$; for 2 cups, ns) iii. Calmness (ns) iv. Arousal (ns) v. Stress (ns)	Not assessed

Köteles and Babulka (2014) a,d,e	P	Adult volunteers (33, 37.7, 15.2)	3 types of Essential oils (Randomised to 1)	1. Symptom expectations	i. Perceived change in alertness: rosemary oil (ns), lavender oil (higher 1 increased i, $p<.001$), eucalyptus oil (ns) ii. Perceived change in heart rate: rosemary oil (ns), lavender oil (ns), eucalyptus oil (ns) iii. Perceived change in BP: rosemary oil (ns), lavender oil (ns), eucalyptus oil (ns)	Not assessed
Link et al. (2006) a,b,c,d,e	P	Students (36, 22.7, 44.0)	Sham herbal supplement	1. Belief they had taken active supplement	i. Number of symptoms reported (those who thought they had taken the active supplement reported more symptoms than those who thought they had taken the placebo, $p=.003$)	Not assessed
Molcan and et al. (1982) b,e	P	Medical students (48, U/K, 52.1)	Sham arousal pill	1. Symptom expectations	i. Symptom scale score (ns)	Not assessed
Szemerszky et al. (2010) e	W	Healthy students (40, 22.8, 27.5)	Sham EMF	1. Symptom expectations	i. Overall symptom score (for weak EMF $r=.49$, $p<.01$; for strong EMF $r=.42$, $p<.01$; regression ns)	Not assessed
Vase et al. (2013) e	P	Patient with pain due to tooth removal (U/K, 25.5, 47.5)	Sham acupuncture	1. Symptom expectations	i. Pain intensity (higher 1 increased i, $p=.001$) ii. Pain unpleasantness (higher 1 increased ii, $p<.001$)	Not assessed
Walach et al. (2001)	RCT (B)	Coffee drinkers (157, 28.1, 34.0)	Sham coffee	1. General expectations about coffee on wellbeing 2. Subjective probability of receiving coffee	i. General wellbeing score (1 ns; 2 ns)	Not assessed

Walach and Schneider (2009) Exp 1	RCT (B)	Healthy adults coffee drinkers (60, 32.3, 23.3)	Sham caffeine beverage	1. Symptom expectations	i. Mean change in mood (ns) ii. Mean change in calmness (ns) iii. Mean change in alertness (ns)	Not assessed
Walach and Schneider (2009) Exp 2	RCT (B)	Healthy adults coffee drinkers (30, 29.9, 33.3)	Sham caffeine beverage	1. Symptom expectations	i. Mean change in mood (ns) ii. Mean change in calmness (ns) iii. Mean change in alertness (ns)	Not assessed

Note: RCT = Randomised Controlled Trial, P = Prospective design, B = Between subjects design, W = Within subjects design, U/K= Unknown, italicised = not directly given but has been extrapolated from the available data, ns = non-significant, Not assessed = did not assess interactions with another risk factor, N/A = no other risk factors assessed, **a** = high risk for selection bias, **b** = high risk for confounding factors, **c** = high risk for insufficient follow-up, **d** = high risk for low generalizability, **e** = did not mention an a priori sample size calculation

2.4.4.4 Anxiety

Nine studies looked at the influence of anxiety on symptom reporting, finding weak evidence for a link with placebo effects (see Table 2-13). Six studies of mixed quality looked at state anxiety (Bogaerts et al., 2010; Link et al., 2006; Molcan & et al., 1982; Nevelsteen et al., 2007; Szemerszky et al., 2010; Witthöft & Rubin, 2013) but only Nevelsteen et al. (2007) found a significant effect, with state anxiety predicting physical symptom scores. Molcan and et al. (1982) and Nevelsteen et al. (2007) found no significant effects of trait anxiety. Angelucci and Pena (1997) found combined state and trait anxiety scores significantly predicted anxiety, but did not report results for state and trait anxiety separately. However no such effect of combined state and trait anxiety was found on symptom reporting to an odour (Van den Bergh et al., 1997), although this was a lower quality study. Finally, a high quality study by Danker-Hopfe et al. (2010) found that anxiety towards a local base station predicted subjective sleep quality after sham EMF exposure.

2.4.4.5 Personality

Twenty-two studies looked at different aspects of personality as predictors of symptoms (see Table 2-14). Twelve studies showed significant effects of personality of which only three were of low quality, finding evidence broadly supporting a link with placebo effects. There were no significant effects of suggestibility (Angelucci & Pena, 1997), sensitivity to anxiety (Nevelsteen et al., 2007), restraint (Heatherton et al., 1989), or social desirability (Link et al., 2006; Put et al., 2004; Stegen, Van Diest, Van de Woestijne, & Van den Bergh, 2000). However, studies did show significant effects of the following on at least one symptom outcome: Type A personalities reported more side effects than type B (Drici et al., 1995); pain catastrophizing positively correlated with side effect reports (Sullivan, Lynch, Clark, Mankovsky, & Sawynok, 2008); blunting behaviour predicted symptom reporting (Van den Bergh et al., 1997); positive

affect and vigilance predicted symptom scores (Nevelsteen et al., 2007); “frail and submissive” personality correlated with the exposure’s perceived effect (Slanska et al., 1974); somatisation and motivation predicted symptom score (Szemerszky et al., 2010); and modern health worries and somatosensory amplification predicted symptom scores (Withhöft & Rubin, 2013). There was mixed evidence for the role of negative affect (Bogaerts et al., 2010; De Peuter et al., 2007; De Peuter et al., 2005; Devriese et al., 2000; Devriese et al., 2004; Nevelsteen et al., 2007; Put et al., 2004; Stegen et al., 1998; Stegen et al., 2000; Van den Bergh et al., 1995), neuroticism (Davis et al., 1995; Mazzoni et al., 2010), and pessimism (Geers, Helfer, et al., 2005; Szemerszky et al., 2010).

2.4.4.6 Miscellaneous

Thirteen studies looked at baseline factors which did not fit into the above categories (see Table 2-15). These included caffeine consumption (Geers, Weiland, et al., 2005; Geers et al., 2011), olfactory sensitivity (Dalton, 1999), perceived cue odour (Devriese et al., 2004), visibility of a mobile phone base station and pre-occupation with EMF (Danker-Hopfe et al., 2010), geographical site of enrolment (Goetz et al., 2008), hospital centre (Liccardi et al., 2004), stress experienced whilst wearing a helmet delivering sham EMF (Nevelsteen et al., 2007), ability to predict which odour produced the most symptoms (Meulders et al., 2010) and risk perception (Nevelsteen et al., 2007), which had no significant effects. Köteles and Babulka (2014) however found that odour pleasantness predicted perceived change in alertness for eucalyptus oil. In addition, odour reactivity predicted symptom responding to odours (Dalton, 1999) and high regard for medications positively correlated with perceived drug effect (Goldman et al., 1965). Mazzoni et al. (2010) found that if the gender of the model matched the participant this predicted symptom development in social observation studies. Nevelsteen et al. (2007) found that less comfort under the helmet delivering the sham

EMF predicted symptoms. Finally Wendt et al. (2014) reported that significantly more symptoms were reported in val/val homozygous carriers compared to val 158/Met 18 and Met/Met 158 homozygous carriers after sham treatment.

Table 2-13 Anxiety as a predictor of symptom development to an inert exposure

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Risk factor(s)	Symptoms measured	Interaction(s) with other risk factors
Angelucci and Pena (1997) e	RCT (B)	Student caffeine consumers (148, U/K, 23.0)	Sham coffee	1. State and trait anxiety	I. Stimulation/alertness (ns) ii. Anxiety/irritability (higher 1 increased ii, $p<.0001$) iii. Subjective symptoms (ns)	Not assessed
Bogaerts et al. (2010) e	P	Patients with medically unexplained dyspnoea and healthy controls (58, U/K, 0.0)	Breathing trial with room air	1. State anxiety	i. Dyspnoea score (ns)	Not assessed
Danker-Hopfe et al. (2010)	P	Villages in Germany with weak RF-EMF sources (397, U/K, 49.1)	Sham EMF	1. General fear/anxiety towards risks of RF-EMF 2. Fear/anxiety towards base station	i. Subjective sleep quality (1 ns; higher 2 decreased i, $p<.05$)	Not assessed
Link et al. (2006) a,b,c,d,e	P	Students (36, 22.7, 44.0)	Sham herbal supplement	1. State anxiety	i. Number of symptoms reported (ns)	Not assessed
Molcan and et al. (1982) b,e	P	Medical students (48, U/K, 52.1)	Sham arousal pill	1. State anxiety 2. Trait anxiety	i. Symptom scale score (1 ns; 2 ns)	Not assessed
Nevelsteen et al. (2007) e	RCT (B)	Healthy males (59, 48.4, 100.0)	Sham magnetic field	1. State anxiety 2. Trait anxiety	i. Subjective vigilance feelings (1 ns; 2 ns) ii. Profile of mood states (1 ns; 2 ns)	Not assessed

					iii. 24 Physical symptoms scale (higher 1 increased iii, p<.001; 2 ns)	
Szemerszky et al. (2010) e	W	Healthy students (40, 22.8, 27.5)	Sham EMF	1. State anxiety	i. Overall symptom score (ns)	Not assessed
Van den Bergh et al. (1997) a,e	Non RCT (B+W)	Psychosomatic patients (28, 36.0, 50.0)	Odours	1. State and trait anxiety	i. Total symptom score (ns) ii. Arousal (ns) iii. Respiratory (ns) iv. Cardiac (ns) v. Tingling (ns) vi. Unclassified (ns) vii. Dummy (ns)	Not assessed
Witthöft and Rubin (2013)	RCT (B)	Adult English speakers (147, 29.8, 32.7)	Sham EMF	1. State anxiety	i. Total symptom score (ns) ii. Anxiety (ns) iii. Head and concentration (ns) iv. Tingling sensations (ns)	Anxiety x Symptom suggestion i+iii. Increased in people with high levels of anxiety who were in Wi-Fi group (i, p=.008; iii, p<.001). ii+iv. ns No significant interactions with age, gender, level of education or personality

Note: RCT = Randomised Controlled Trial, P = Prospective design, B = Between subjects design, W = Within subjects design, U/K= Unknown, ns = non-significant, Not assessed = did not assess interactions with another risk factor, **a** = high risk for selection bias, **b** = high risk for confounding factors, **c** = high risk for insufficient follow-up, **d** = high risk for low generalizability, **e** = did not mention an a priori sample size calculation

Table 2-14 Personality as a predictor of symptom development to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Risk factor(s)	Symptoms measured	Interaction(s) with other risk factors
Angelucci and Pena (1997) e	RCT (B)	Student caffeine consumers (148, U/K, 23.0)	Sham coffee	1. Suggestibility	I. Stimulation/alertness (ns) ii. Anxiety/irritability (ns) iii. Subjective symptoms (ns)	Not assessed
Bogaerts et al. (2010) e	P	Patients with medically unexplained dyspnoea and healthy controls (58, U/K, 0.0)	Breathing trial with room air	1. Negative affect	i. Dyspnoea score (ns)	Not assessed
Davis et al. (1995) a,d,e	P	Healthy Adults (27, U/K, 55.6)	Sham anti-depressant pill	1. Neuroticism 2. Somatosensory amplification	i. Side effect checklist (1, “significant positive correlation”; 2, ns)	Not assessed
De Peuter et al. (2005) e	RCT (W)	Asthma patients and healthy controls (40, 23.9, 52.5)	Sham inhaler	1. Negative affect	i. Total symptom score (ns) ii. Obstruction (ns) iii. Dyspnoea (ns) iv. Fatigue (ns) v. Hyperventilation (ns) vi. Anxiety (ns) vii. Irritability (higher 1 increased vii, p<.05)	Not assessed
De Peuter et al. (2007) e	P	Asthma patients (30, 38.0, 26.7)	Sham histamine inhalation	1. Negative affect	i. Obstruction (higher 1 increased i, p<.05) ii. Dyspnoea (ns) iii. Fatigue (higher 1 increased iii, p<.001)	N/A

					iv. Hyperventilation (ns) v. Anxiety (ns) vi. Irritability (higher 1 increased vi, $p<.001$)	
Devriese et al. (2000) a,e	Non RCT (B+W)	Healthy students (56, U/K, 41.1)	Odours	1. Negative affect	i. Total symptom score (ns) ii. Arousal (ns) iii. Respiratory (ns) iv. Cardiac (ns) v. Tingling (ns) vi. Unclassified (ns) vii. Dummy (ns)	Conditioning x Odour x Negative affect i+iii. Higher in response to odour paired with CO2 but only when the odour was ammonia and participants had high negative affect ($p<.05$) ii, iv-vii. ns Odour x Negative affect x Generalisation i+iii. Higher in response to butyric and acetic acid than citric aroma when ammonia was paired with CO2 and participants had high negative affect ($p<.05$) iv. Higher in response to butyric acid than acetic acid or citric aroma when ammonia was paired with CO2 and participants had high negative affect ($p<.05$) ii+ v-vii. Ns No other interactions assessed
Devriese et al. (2004) a,e	Non RCT (B+W)	Healthy students (53, U/K, U/K)	Odours	1. Negative affect	i. Total symptom score (ns) ii. Arousal (ns) iii. Respiratory (ns) iv. Cardiac (ns)	Not assessed

					v. Tingling (ns) vi. Unclassified (ns) vii. Dummy (ns)	
Drici et al. (1995) b,e	P	Healthy volunteers (52, 23.5, 50.0)	Sham paracetamol eye drop	1. Type A Personality 2. Type B Personality	i. Subjective side effect reports (1>2, p=.03)	Not assessed
Geers, Helfer, et al. (2005) e	RCT (B)	Healthy students (54, 21.0, 29.6)	Sham over-the-counter pill	1. Optimism-pessimism	i. Affect questionnaire - Anxiety, restlessness, relaxed, irritable, and perspiration (ns)	Optimism x Likelihood suggestion i. Increased score for pessimists than optimists in deceptive group than the control (p<.05), no significant difference between conditional group and control. No significant interaction with age, gender or self-awareness
Heatherton et al. (1989) e	RCT (B)	Female students (59, U/K, 0.0)	Sham vitamin pill	1. Restraint	i. Hunger ratings (ns)	No significant interaction with symptom suggestion
Link et al. (2006) a,b,c,d,e	P	Students (36, 22.7, 44.0)	Sham herbal supplement	1. Social desirability	i. Number of symptoms reported (ns)	Not assessed
Mazzoni et al. (2010) e	RCT (B)	Healthy students (120, 20.7, 50.0)	Sham environmental toxin	1. Openness 2. Conscientiousness 3. Extraversion 4. Agreeableness 5. Neuroticism	i. Verbal symptom reports (1 ns; 2 ns; 3 ns; 4 ns; 5 ns)	Not assessed
Nevelsteen et al. (2007) e	RCT (B)	Healthy males (59, 48.4, 100.0)	Sham magnetic field	1. Positive affect 2. Negative affect 3. Sensitivity to	i. Subjective vigilance feelings (1 ns; 2 ns; 3 ns; 4 ns)	Not assessed

				anxiety 4. Vigilance	ii. Profile of mood states (1 ns; 2 ns; 3 ns; 4 ns) iii. 24 Physical symptoms score (higher 1 decreased ii, p<.001; 2+3 ns; higher 4 increased iii, p<.001)	
Put et al. (2004) a,b,c,e	W	Asthma patients (32, 40.0, 50.0)	Sham inhaler	1. Negative affect 2. Social desirability	i. Obstruction (higher 1 increased i, p<.01; 2 ns) ii. Dyspnoea (higher 1 increased ii, p<.01; 2 ns) iii. Fatigue (higher 1 increased iii, p<.05; 2 ns) iv. Hyperventilation (higher 1 increased iv, p<.05; 2 ns) v. Anxiety (higher 1 increased v, p<.05; 2 ns) vi. Irritation (higher 1 increased vi, p<.05; 2 ns)	Symptom suggestion x negative affect i+ii. Higher after bronchoconstriction than bronchodilator suggestions for those with high negative affect (i, p<.01; ii, p<.05) iii-vi. ns No significant interactions with social desirability
Slanska et al. (1974) a,e	Non RCT (B)	Medical students (33, U/K, U/K)	Indifferent salt solution	1. Stability – instability 2. Activity – passivity 3. Submissive – dominance 4. Rationality – sensuousness 5. Introversion - extraversion	i. Perceived effect ("correlated with 1+3 personality characteristics. Whereby significant changes in the direction of suggestion mainly affecting individuals unstable and submissive")	Not assessed
Stegen et al. (1998)	RCT (W)	Healthy psychology	Breathing trial with	1. Negative affect	i. Total symptom score (ns) ii. General arousal (ns)	Prior experience x Negative affect i+ii. Higher in participants scoring

e		students (72, U/K, 48.6)	room air		iii. Respiration (ns) iv. Cardiac (ns) v. Tingling (ns) vi. Unclassified (ns) vii. Gastrointestinal (ns) viii. Dizziness (ns)	high on negative affect compared to low when room air trial was before CO2 trial (i, $p<.001$; ii, $p<.005$) iii-viii. ns
Stegen et al. (2000) a,b,d,e	P	Healthy psychology students (44, U/K, 27.3)	Breathing trial with room air	1. Negative affect 2. Social desirability	i. Somatic experience intensity (higher 1 increased i, $p<.01$; 2 ns) ii. Unpleasantness (1 ns; 2, ns) iii. General arousal (1 ns; 2 ns) iv. Respiration (higher 1 increased iv, $p<.05$; 2 ns) v. Cardiac (1 ns; 2 ns) vi. Tingling (higher 1 increased vi, $p<.05$; 2 ns) vii. Gastrointestinal (1 ns; 2 ns) viii. Unclassified sensations (higher 1 increased viii, $p<.05$; 2 ns) ix. Dummy sensations (1 ns; 2 ns)	Not assessed
Sullivan et al. (2008) e	P	Patients with neuropathic pain (24, 54.7, 62.5)	Sham cream treatment	1. Pain catastrophizing	i. Side effects reported ($r=0.29$, $p<.05$)	N/A

Szemerszky et al. (2010) e	W	Healthy students (40, 22.8, 27.5)	Sham EMF	1. Dispositional optimism 2. Somatisation 3. Somatosensory amplification 4. Motivation	i. Overall symptom score (1+4 significant negative correlation; 2+3 significant positive correlation for weak and strong; regression of 2,3,4 was significant for weak suggestion, only 2+4 were significant for strong suggestion)	Not assessed
Van den Bergh et al. (1995) a,e	Non RCT (B+W)	Healthy students (28, U/K, 50.0)	Odours	1. Negative affect	i. Total symptom score (ns) ii. Arousal symptom score (ns) iii. Respiratory symptom score (ns) iv. Cardiac symptom score (ns) v. Tingling symptom score (ns) vi. Unclassified symptom score (ns)	Not assessed
Van den Bergh et al. (1997) a,e	Non RCT (B+W)	Psychosomatic patients (28, 36.0, 50.0)	Odours	1. Blunting behaviour	i. Total symptom score (Higher 1 increased i, $p<.002$) ii. Arousal symptom score (ns) iii. Respiratory symptom score (ns) iv. Cardiac symptom score (ns) v. Tingling symptom score (ns)	Not assessed

					vi. Unclassified symptom score (Higher 1 increased vi, p<.005)	
					vii. Dummy symptom score (ns)	
Witthöft and Rubin (2013)	RCT (B)	Adult English speakers (147, 29.8, 32.7)	Sham EMF	1. Perceived sensitivity to EMF 2. Modern health worries 3. Somatisation 4. Somatosensory amplification	i. Total symptom score (1 ns; higher 2 increased i, p<.001; 3 ns; higher 4 increased i, p=.046) ii. Anxiety (ns) iii. Head and concentration (1ns; higher 2 increased iii, p<.001; 3 ns; 4 ns) iv. Tingling sensations (ns)	No significant interactions with age, gender, level of education, anxiety or symptom suggestion

Note: RCT = Randomised Controlled Trial, Non RCT = Non randomised controlled trial, P = Prospective design, B = Between subjects design, W = Within subjects design, U/K= Unknown, ns = non-significant, Not assessed = did not assess interactions with another risk factor, N/A = no other risk factors assessed, **a** = high risk for selection bias, **b** = high risk for confounding factors, **c** = high risk for insufficient follow-up, **d** = high risk for low generalisability, **e** = did not mention an a priori sample size calculation

Table 2-15 Miscellaneous baseline predictors of symptom development to an inert exposure.

Reference and quality	Study design	Population (N, Mean age, %Male)	Inert exposure	Risk factor(s)	Symptoms measured	Interaction(s) with other risk factors
Dalton (1999) e	RCT (B)	Healthy volunteers (180, 31.7, 49.4)	Odours	1. Olfactory sensitivity 2. Odour reactivity	i. Symptom reports (1 ns; higher 2 increases i, $R^2=0.74$)	Not assessed
Danker-Hopfe et al. (2010)	P	Villages in Germany with weak RF-EMF sources (397, U/K, 49.1)	Sham EMF	1. Visibility of the base station 2. Preoccupation with EMF	i. Subjective sleep quality (1 ns; 2 ns)	Not assessed
Devriese et al. (2004) a,e	Non RCT (B+W)	Healthy students (53, U/K, U/K)	Odours	1. Perceived cue odour	i. Total symptom score (ns) ii. Arousal symptom score (ns) iii. Respiratory symptom score (ns) iv. Cardiac symptom score (ns) v. Tingling symptom score (ns) vi. Unclassified symptom score (ns) vii. Dummy symptom score (ns)	Perceived cue odour x Odour i. Higher to butyric acid than ammonia when butyric acid was thought to have been paired with CO ₂ ($p<.05$) ii-vii. ns No other interactions assessed
Geers et al. (2011) e	RCT (B)	Healthy students (102, 20.5, 21.6)	Sham caffeine capsule	1. Average caffeinated beverage consumption	i. Placebo response index-anxious, sluggish, energized, calm, irritated, lazy, relaxed, and excited (1 ns; 2 ns)	No significant interactions with likelihood suggestion

				2. Caffeinated beverages consumed so far that day		
Geers, Weiland, et al. (2005) e	RCT (B)	Healthy students (57, U/K, 35.1)	Sham caffeine pill	1. Caffeine consumption	i. Caffeine symptom questionnaire score (ns)	No significant interaction with arousal suggestion
Goetz et al. (2008) e	P	Parkinson's patients with dyskinesia (484, U/K, U/K)	Sham medication	1. Geographical site of enrolment 2. Study (1 or 2)	i. UPDRS score worsening (1 ns; 2 ns)	Not assessed
Goldman et al. (1965) e	Non RCT (B)	Male veterans with Schizophrenia (64, 44.0, 100.0)	Sham arousal treatment	1. High regard for hospital medications	i. Reported symptoms identified through interviews (U/K) ii. Increase in reported drug effects identified through interviews (C=.30, p<.01) iii. Ward activity (U/K)	Not assessed
Köteles and Babulka (2014) a,d,e	P	Adult volunteers (33, 37.7, 15.2)	3 types of Essential oils (Randomised to 1)	1. Pleasantness of odour	i. Perceived change in alertness: rosemary oil (ns), lavender oil (ns), eucalyptus oil (increased, p<.05) ii. Perceived change in heart rate: rosemary oil (ns), lavender oil (ns), eucalyptus oil (ns) iii. Perceived change in BP: rosemary oil (ns), lavender oil (ns), eucalyptus oil (increased, p<.05)	Not assessed

Liccardi et al. (2004) b,e	P	Patients with ADRs (600, 42.0, 30.3)	Sham allergen pill	1. Hospital centre	i. Number of people reporting reactions (ns)	Not assessed
Mazzoni et al. (2010) e	RCT (B)	Healthy students (120, 20.7, 50.0)	Sham environmental toxin	1. Gender of model	i. Verbal symptom ratings (more symptoms were reported when participant and confederate were the same gender, $d=0.24$)	Not assessed
Meulders et al. (2010) a,e	Non RCT (B+W)	Healthy adults (58, 22.0, 48.3)	Odours	1. Ability to predict which odour produced the most symptoms	i. Total symptom score (ns) ii. Arousal (ns) iii. Respiratory (ns) iv. Cardiac (ns) v. Tingling (ns) vi. Unclassified (ns) vii. Dummy (ns)	Conditioning x Ability to predict i. Higher in response to odours which had been paired with CO2 compared to room air when participants were able to predict which odour had caused the most symptoms ($p<.05$) ii-vii. ns Conditioning x Ability to predict x Odour i-iv+vii. Higher in response to butyric acid which had been paired with CO2 compared to room air when participants were able to predict which odour had caused the most symptoms (i-iv, $p<.01$; vii, $p<.05$) v+vi. ns No other interactions assessed
Nevelsteen et al. (2007) e	RCT (B)	Healthy males (59, 48.4, 100.0)	Sham magnetic field	1. Discomfort under the helmet 2. Stress under	i. Subjective vigilance feelings (1 ns; 2 ns; 3 ns) ii. Profile of mood states (1	Not assessed

			the helmet 3. Risk perception	ns; 2 ns; 3 ns) iii. 24 Physical symptoms scale (higher 1 increased iii, p<.001; 2, ns; 3, ns)	
Wendt et al. (2014) e	P	Healthy males (24, 25.0, 100.0)	Sham immuno- suppressive capsule	1. Genes i. Number of symptoms reported (More side effects in the Val/Val homozygous carriers compared to the Val158/Met158 groups, p<0.001 and the Met158 homozygous groups, p<.01)	N/A

Note: RCT = Randomised Controlled Trial, P = Prospective design, B = Between subjects design, U/K= Unknown, ns = non-significant, Not assessed = did not assess interactions with another risk factor, N/A = no other risk factors assessed, **a** = high risk for selection bias, **b** = high risk for confounding factors, **d** = high risk for low generalizability, **e** = did not mention an a priori sample size calculation

2.4.5 Interactions between risk factor categories

As well as investigating the main effects of each risk factor in its category, some studies also looked at the interactions between different risk factor categories, as displayed in the last column of each results Table. The following section discusses the interactions found within each risk factor.

2.4.5.1 Learning

For prior experience, Bayer et al. (1998) reported a significant interaction with the risk factor ‘dose’ for the outcome pain intensity over time. Pain intensity significantly increased with increasing settings shown on a stimulator, but only for participants who had been exposed to physical pain induction prior to the sham stimulation. In addition Dinnerstein and Halm (1970) reported a significant interaction with the type of arousal to expect from a liquid on three out of six symptom measures. For the outcome ‘friendly,’ they found that when participants received suggestions that the liquid was an energiser, those who received aspirin before reported feeling less friendly than those who received lactose, and when they received the suggestion that the liquid was a tranquiliser the opposite effects were found. For the other two symptoms, ‘unhappy’ and ‘clear thinking,’ when participants received energiser suggestions those who received aspirin reported a high score on these measures compared to those who received lactose, with the opposite results found when participants received tranquiliser suggestions. An interaction was also found with ‘negative affect,’ with high negative affect participants reporting more arousal and symptoms on the whole to a room-air breathing trial when this preceded rather than followed a CO₂ breathing trial (Stegen et al., 1998).

For social observation Lorber et al. (2007) found a significant interaction with gender, showing there were significantly higher scores on symptom ratings when

females observed a confederate compared to no observation. However, Papoiu et al. (2011) found no significant interactions with gender.

In addition, 'classical conditioning' showed interactions with 'odour'; pairing an odour with CO₂ elicited symptoms to the odour alone, only if the odour was foul smelling (Devriese et al., 2000; Van den Bergh et al., 1995; Van den Bergh et al., 1997; Winters et al., 2003). This interaction between 'classical conditioning' and 'odour' was also found to more likely occur among people with high 'negative affect' (Devriese et al., 2000) and those manipulated to have higher 'self-awareness' (Van den Bergh et al., 1998).

2.4.5.2 Perceived dose

As mentioned for the previous risk factor, Bayer et al. (1998) found significant interaction between 'dose' and 'prior experience' for pain intensity rating over time. In addition, Kirsch and Weixel (1988) found a significant interaction between 'quadratic dose effect' and 'likelihood suggestion' for mean change in tension. They found that tension increased with increasing teaspoons of coffee but then dropped off at eight teaspoons for those who were deceptively told they would receive coffee, whereas tension decreased with increasing teaspoons of coffee but then increased for eight teaspoons for those who were given double-blind suggestions.

2.4.5.3 Self-awareness

Geers et al. (2006) found a significant interaction with 'likelihood suggestion.' This interaction demonstrated that symptom responding was significantly higher in participants who were given deceptive suggestions compared to those who were given double-blind suggestions or told they would ingest an inactive pill, but only when they were asked to monitor their bodily sensations. In addition they found that symptom responding was higher in participants who were told to monitor their sensations compared to those who were not given any monitoring instructions, but only when they

were given deceptive suggestions. However, this interaction is somewhat contrary to the results from Gibbons et al. (1979) who found that increasing self-awareness through having a mirror facing participants' actually reduced perceived arousal compared to not having a mirror. This was also shown in the interactions with 'symptom suggestions' reported by Gibbons et al. (1979) which showed that salient symptom reporting was lower in participants who were facing a mirror compared to those who were not facing a mirror when participants were misinformed about the drug and told they were taking an active drug.

2.4.5.4 Verbal suggestions on performance

Interactions with other risk factors were assessed, but none were found.

2.4.5.5 Verbal suggestions of likelihood

Despite finding no main effects, Geers, Helfer, et al. (2005) did find a significant interaction with 'pessimism.' Participants who were told they would receive a pill with unpleasant side effects scored significantly higher on the symptom measures compared to those who were told they would ingest an inactive pill, but only if those participants were pessimists (Geers, Helfer, et al., 2005). In addition Geers et al. (2006) found a significant interaction with 'self-awareness' and Kirsch and Weixel (1988) found a significant interaction with 'quadratic dose effect' as already discussed above.

2.4.5.6 Verbal suggestions of arousal

Geers, Weiland, et al. (2005) found a significant interaction with 'cooperation prime,' demonstrating that when participants were primed for cooperation, they reported significantly more symptoms when they were told they were given coffee as compared to those who received no mention of caffeine. Dinnerstein and Halm (1970) also reported a significant interaction with 'prior experience,' as previously addressed.

2.4.5.7 Verbal suggestions of symptoms

Witthöft and Rubin (2013) reported a significant interaction with ‘state anxiety,’ in which total symptom score and head/concentration symptoms significantly increased in people with high levels of anxiety but only if they were warned about the side effects of WiFi. Put et al. (2004) reported a significant interaction with ‘negative affect’ higher obstruction and dyspnoea symptom scores after suggestions of bronchoconstriction compared to bronchodilation for a sham inhaler if participants had high negative affect. Dalton (1999) reported a significant interaction with ‘odour type’ in which there were more symptom reports following suggestion of symptoms if the odour was unpleasant. Winters et al. (2003) also reported a significant interaction with ‘classical conditioning’ with higher total, respiratory, cardiac and unclassified symptom scores following exposure to an odour previously paired with CO₂ if participants received symptom suggestions. In addition, Gibbons et al. (1979) report a significant interaction with ‘self-awareness’ as previously discussed above.

2.4.5.8 Miscellaneous

The only significant interaction was found by Geers, Weiland, et al. (2005) for ‘cooperation prime’ and ‘arousal suggestion,’ which has been previously discussed.

2.4.5.9 Baseline risk factors

Out of the 52 studies examining baseline risk factors for symptom development, only one study showed a significant interaction that has not been previously discussed. This was Strohle (2000) who found a significant interaction between ‘gender’ and ‘clinical characteristics’ with females reporting increased panic in response to a sham panic disorder trigger only if they suffered from panic disorder.

2.5 Discussion

2.5.1 Summary of main results

From the 89 studies that met the inclusion criteria, 14 categories of risk factor for a placebo effect were identified, including nine experimentally induced risk factor categories and six baseline risk factor categories. Of these categories, ‘learning/social observation,’ ‘perceived dose,’ ‘verbal suggestions of arousal and symptoms,’ and ‘baseline symptom expectations’ appeared to be the strongest predictors of placebo effects. There was some evidence for the role of ‘personality’ in placebo effects; however which facets of personality are more strongly linked with placebo effects needs further research. In addition, although not strong predictors on their own, learning/classical conditioning, likelihood suggestion, self-awareness and negative affect consistently interacted with other risk factors.

Given the proposed psychological mechanisms behind placebo effects it is perhaps unsurprising that these factors have been consistently identified in the literature. Specifically looking at the expectation mechanism, it is intuitive that verbal suggestions of symptoms can generate expectations of these effects leading to symptom reporting. In support of this, participants’ own baseline expectations can trigger symptoms, while perceived dose presumably affects symptom reports through a mediating effect of expectations, with a higher dose associated in a participant’s mind with a stronger effect. This could also explain the significance of medication brand, with branded medication being generally expected by the public to be better quality than generic unbranded medication and therefore less likely to cause side effects (Faasse et al., 2013). Expectations could also explain why four studies which measured symptom reports both for pre-warned and non-warned symptoms found stronger effects for symptoms that had previously been suggested (Faasse et al., 2013; Gibbons et al., 1979; Lorber et al., 2007; Mazzoni et al., 2010). It also explains why no effect was found for

performance suggestions, as this should not directly influence expectations of symptoms from the exposure.

It is important not to over-emphasise the nature of the results with respect to expectation, however. In particular, it was striking that other categories of risk factor that might be hypothesised to affect expectation did not appear to be relevant in the generation of placebo effects. In particular, type of administration, and verbal suggestions of the likelihood of the substance taken. Despite both of these having been identified as predictors of a placebo effect (Lidstone et al., 2010; Zhang, Robertson, Jones, Dieppe, & Doherty, 2008), I was unable to find strong evidence of an effect in this review. Possibly, the influence of these factors on expectations is weaker than might be thought. Alternatively, methodological factors may account for the lack of effect. For example, both studies assessing type of administration used patient samples (Goldman et al., 1965; Kaptchuk et al., 2006). Given their greater experience with medical procedures, merely changing an intervention from a pill to an injection may not have triggered a substantial change in expectations. For three of the likelihood suggestion studies (Walach et al., 2001; Walach et al., 2002) including Walach and Schneider (2009) exp 1, it was suggested that the absence of an effect could have been because of cultural differences, with the caffeine effect stereotype not as strong in Germany as it is in the USA.

The overall support for the role of expectations identified in my review still allows for at least two ‘sub-mechanisms’ to exist. The first is a role for attentional bias and symptom detection (Hahn, 1997). The second is a more direct effect, where-by expectations affect emotional state (Kirsch, 1997b; Stewart-Williams, 2004). For example Kirsch (1997b) pointed out that the expectation of anxiety is likely to be anxiety provoking, thereby directly causing the outcome. This could explain the strong results seen for manipulating verbal suggestions of arousal on symptom reporting, as the

expectation of arousal or relaxation is itself likely to be arousing or relaxing. However, these results on arousal could also be interpreted as part of the placebo response, as noted earlier in the difficulty of defining when an outcome is aversive or beneficial.

With regards to misattribution as a mechanism, I expected that clinical characteristics and self-awareness would have been significant predictors, as these factors promote current symptoms/sensations to be misattributed as symptoms caused by the inert exposure (Petrie et al., 2004). However, the evidence from the studies that investigated self-awareness as a risk factor did not support this, with the two most directly relevant studies that instructed participants to monitor for any sensations failing to find an effect. Equally, for the six studies investigating the effect of baseline symptoms on symptom reporting the results were mixed providing inconclusive support for misattribution. However five studies (Bogaerts et al., 2010; De Peuter et al., 2005; Papoiu et al., 2011; Strohle, 2000; Szemerszky et al., 2010), showed that suffering from a condition with symptoms similar to those being induced was a predictor of symptom reporting. While this mechanism remains plausible, further evidence is required to clarify its importance.

For the learning mechanism support was found from studies investigating the risk factor ‘association,’ with the taste of decaffeinated coffee being enough to elicit caffeine related symptoms (Flaten & Blumenthal, 1999; Mikalsen et al., 2001). For prior experience, the results were weak but this could have been due to a lack of experience as this manipulation was typically a one off event. However, there was evidence for the role of social observation, with two out of three studies showing a significant effect. In addition, support for learning was seen in the studies using classical conditioning, which involved a number of trials. Almost half of the studies showed that conditioning CO₂ inhalation with any odour is enough to elicit symptoms

to the odour itself, and a reliable finding amongst the studies was that this was especially the case if the odour was unpleasant.

For baseline risk factors, anxiety did not come out as a strong predictor despite the role it could play through misattribution (generating physical symptoms that are available to be misattributed) and expectations (apprehension of symptoms). One possible explanation for this advanced by Szemerszky et al. (2010) is that scores of anxiety could reach a ceiling effect due to advance information about the risks of taking part in the study. For other baseline risk factors, many different types of personality were implicated such as: type A personality (Drici et al., 1995), lower positive affect, vigilance (Nevelsteen et al., 2007), pessimism, motivation to cooperate, somatisation, somatosensory amplification, modern health worries (Szemerszky et al., 2010; Withhöft & Rubin, 2013), and neuroticism (Davis et al., 1995). A lack of consistency in the personality traits studied makes it difficult to interpret these findings, but many would seem to fit with expectation and/or misattribution mechanisms as they tend to increase negative expectations and therefore symptom monitoring which prompts symptoms or sensations to be attributed to the exposure.

With regards to demographic risk factors, as discussed in Chapter 1 it is often reported that there is a significant effect of gender, but this was not the case in the literature reviewed here. According to this review, women are at no more risk of placebo effects than men. Only four out of 16 studies found a significant effect for gender, with women reporting more symptoms than men (Casper et al., 2001; Liccardi et al., 2004; Strohle, 2000; Szemerszky et al., 2010). However, since conducting the literature search, one additional study that would have met the inclusion criteria has become apparent and which is relevant here. This study by Faasse, Grey, Jordan, et al. (2015) investigated the risk factor of observing a female confederate display symptoms, demonstrating a significant effect on symptom reporting in females. It is interesting to

note that Lorber et al. (2007), who also studied social observation, also only found a significant effect in females. One possibility is that it may be something inherent to social observation that makes females more vulnerable to nocebo effects. Other demographic factors such as age, employment status or level of education were also not risk factors. Interestingly no study looked at culture and this is perhaps something that can be investigated in the future.

As well as Faasse, Grey, Jordan, et al. (2015), since conducting the literature search another 10 studies have been identified that would have met the inclusion criteria for this review. These studies support the findings stated here showing inconsistent results for the influence of type of administration on symptom reporting (Beissner et al., 2015; Szemerszky, Dömötör, Berkes, & Koteles, 2016) as well as personality (Beissner et al., 2015; Dömötör, Doering, & Köteles, 2016; Niederstrasser et al., 2015; Szemerszky et al., 2016). They also support the effect of medication branding (Faasse, Martin, Grey, Gamble, & Petrie, 2016) and classical conditioning (Quinn, MacDougall, & Colagiuri, 2015; Rheker, Winkler, Doering, & Rief, 2017) in generating nocebo effects, the effect social influence on nocebo effects in females (Crum, Phillips, Goyer, Akinola, & Higgins, 2016), and the lack of influence of gender (Bavbek, Aydin, Sözen, & Yüksel, 2015). Investigating a new predictor that has not been studied before however, Bartley, Faasse, Horne, and Petrie (2016) show the importance of treatment choice, with a lack of choice over treatment received increasing nocebo responding to a placebo beta-blocker medication for pre-examination anxiety.

Comparing these results to the active exposure nocebo literature, it appears that many of the risk factors overlap. For example, verbal suggestions about the symptom experience to expect are strong predictors of symptom reporting in the active exposure literature (Bartels et al., 2014; Benedetti et al., 2006; Bialosky, Bishop, Robinson, Barabas, & George, 2008; Mondaini et al., 2007; Van Laarhoven et al., 2011;

Varelmann et al., 2010; Vijayan, Scott, Brownlie, Male, & Chin, 2014). Similarly baseline expectations about the exposure also appear to be risk factors (Colagiuri et al., 2013; Olver, Taylor, & Whitford, 2005; Van den Broeke, Geene, van Rijn, Wilder-Smith, & Oosterman, 2014). As well as this the active exposure literature has also implicated learning mechanisms such as observation of a model (Swider & Babel, 2013) and conditioning (Bartels et al., 2014; Jensen et al., 2012), as well as the misattribution mechanism (Petrie et al., 2005; Petrie et al., 2004). Similarly the risk factor of anxiety does not appear to be as strong as expected (Papakostas et al., 2004; Staats, Staats, & Hekmat, 2001) and personal characteristics such as negative affect, catastrophizing, pessimism and somatisation have also been implicated as risk factors (Fillingim et al., 2005; Hanssen, Vancleef, Vlaeyen, & Peters, 2014; Tomba, Baldassarri, Coletta, Cesana, & Basilisco, 2012).

As well as this, risk factors studied that have not come up in the inert exposure literature include beliefs about expectation biases (Handley, Fowler, Rasinski, Helfer, & Geers, 2013) cue to exposure delay (Hauck et al., 2007), chronotype (if you are a ‘morning’ or an ‘evening’ person) (Jankowski, 2013) subjective helplessness (Müller & Netter, 2000) and altering the framing used to convey side effect risk (O'Connor et al., 1996). It would be beneficial for future research to carry out a replication of this review focusing on these active exposures for a more systematic comparison to be able to take place.

As well as the active exposure literature, it is also interesting to look at the placebo literature to see if nocebo effects really are the ‘flip side’ to placebo effects or if different mechanisms and risk factors are at play. At a first look the mechanisms appear to be similar, if acting in the opposite direction. For example the expectancy mechanism has been implicated through factors such as verbal suggestions and participants’ own baseline expectations which lead to positive expectations for pain or symptom relief

(Benedetti et al., 2003; Kam-Hansen et al., 2014; Montgomery & Kirsch, 1997; Price et al., 1999; Vits et al., 2013). In addition, learning mechanisms are also at play with conditioning and prior experience being implicated in the opposite direction to nocebo responses, whereby prior experience of pain relief or conditioning people to experience pain relief results in subsequent placebo responses (Benedetti et al., 1998; Colloca & Benedetti, 2006; Leech, Mazzone, & Farrell, 2012; Suchman & Ader, 1992). As well as this, social observation of someone experiencing pain relief also predicts the placebo response (Colloca & Benedetti, 2009). It also seems that opposite personality characteristics to those implicated in the nocebo literature also predict placebo responding e.g. optimism (Geers, Kosbab, Helfer, Weiland, & Wellman, 2007) as opposed to pessimism. One notable exception, however, would be the misattribution of pre-existing symptoms, as logically this can only be relevant for nocebo: one cannot misattribute the absence of pre-existing symptoms to an exposure. However it is possible one could misattribute and fixate on a coincidental decline in symptoms after taking a sham tablet, and misattribute their improved wellbeing to the tablet.

2.5.2 Quality of original research

It is possible that some of my conclusions may be due to differences in quality between those studies that found an effect and those that did not. I did not observe any clear trend for lower quality studies to report more or fewer significant results than higher quality studies. However, on the whole the quality of the studies included in this review was limited due to poor reporting of key issues in experimental research such as randomisation, allocation concealment, blinding, and not registering a study protocol prior to initiating recruitment. Prospective studies had fewer quality concerns, however given that experimental studies allow the control of more variables the results of these carry more weight overall. It is also worth noting that almost half of studies did not mention receiving ethical approval. In an area of research requiring deception, or at

least withholding information in order to deliberately cause symptoms, this is surprising. Another common occurrence was that studies claimed participants gave informed consent. When researching placebo effects the results are dependent on participants' expectations for developing side effects. Informing participants of the true study purpose or that they are receiving a non-active exposure would substantially affect the integrity of the study. In these situations it is very difficult for participants to actually give fully informed consent, and authors should be aware of this (Miller & Kaptchuk, 2008). Another surprising limitation of many of the studies included in this review was the lack of a priori sample size calculations. Only 10 out of 89 studies included in this review mentioned carrying out a sample size calculation in order to make sure the sample was adequately powered to test their research question(s). As a result I could not assess the quality of studies based on their sample size in the large majority cases. Although it would have been useful to score each study for their strength of evidence, due to this lack of clear reporting and the heterogeneity across studies it was too hard to quantify the strength of each study using the same scale.

2.5.3 Quality of this review

A strength of this review is that I did not include studies in which participants were exposed to an active exposure capable of eliciting symptoms through physiological mechanisms (e.g. experiments altering the information given to participants about a genuine medication). Such studies do not assess the pure placebo effect, described as the undesirable effects experienced from an inert exposure (Kennedy, 1961) and can prove more difficult to interpret (Neukirch & Colagiuri, 2014). The process of defining an exposure as inert or active in the screening process was complex in some cases. According to the definition by Stedman (2005) an inert substance is "devoid of active chemical properties" and has "no pharmacological or therapeutic action." For the most part this definition was easily used to classify

exposures as inert or active. However for some exposures such as essential oils where a pharmacological and therapeutic action is questionable, I decided to include it in the review as an inert exposure. It is important to note here that although studies with patient populations were included in this review, the patient's condition itself was not considered an 'active exposure.' In these cases if patients' illness symptoms were measured after exposure to an inert substance, these were classed as measures of symptom exacerbation.

The search resulted in a large number of results. As the term 'nocebo' is still not widely used and may be preferentially used by those studies identifying a significant increase in symptoms in their participants, I deliberately adopted a broader search strategy than that used in previous reviews, e.g. Petersen et al. (2014). Despite this, it is not certain every study that met the inclusion criteria has been included, especially as nearly a quarter of included studies were identified through personal contacts. This inconsistent use of terminology makes the nocebo literature difficult to search and will continue to limit reviews in this area. I could have included terms such as 'adverse effects or negative outcome' in the search strategy in order to broaden it still further, but exploration of this strategy suggested that the number of results would have been unmanageable as it would include many clinical trials that would not meet the inclusion criteria. On medline alone, such search terms return over 97,000 results. This is also one of the reasons why I did not simply use 'placebo' as one of the search terms: every study which described itself as "placebo-controlled" would be returned. Not only this, the search strategy of two search terms was relatively short compared to the lengthy search strategies that are employed by most systematic reviews. Upon reflection this could have been more sophisticated by including terms such as 'expect*' and 'learn*' etc. Whether this would have revealed a substantially larger number of papers to

include, or would have dramatically altered the conclusions from this review, is uncertain.

In addition to limitations resulting from the search strategy, it is possible that some studies could have been falsely rejected after title and abstract screening. I suspect that this is unlikely to have occurred often. In order to have been included, such studies would have had to a) manipulated factor(s) in order to affect placebo responding or b) looked at baseline measures as predictors of placebo responding, which many do not do. For example, many studies passed through abstract screening as they mentioned participants experiencing negative symptoms or patients feeling worse after placebo exposure. However, going through the full manuscript the majority of these studies would not explore the possible reasons why, e.g. baseline predictors. Therefore I feel this is not something to be too concerned about.

In addition, studies published in non-European languages may have been less likely to have been identified as well as studies that were not reported in the conventional peer-reviewed literature. Such studies may be less likely to report significant effects than those published in English language journals.

Other limitations of the review reflect the way I grouped the results. I aggregated studies based on the independent variable. Because of this and due to the fact that there are no direct replications each risk factor grouping contains several different outcomes. It is possible that an interaction exists between independent and dependent variables: for example, some outcomes may be more susceptible to the effects of changes in expectations than others. Unfortunately, I did not have enough data to explore this in depth.

As this review focused on identifying all the possible risk factors of placebo effects that have been investigated in the literature, I included studies with different research populations, e.g. students, healthy volunteers and patients. There could be

differences between the groups in terms of which mechanisms are more likely to be at play. For example, it is likely the misattribution mechanism is more important for the development of placebo effects in patient samples than healthy volunteers.

Finally, the interaction between the mechanisms, outcomes and mode of delivery may also be important, but could not be explored in detail given the data available to us. For example, different forms of sham intervention e.g. sham tablets vs sham caffeine vs sham EMF, may be more or less likely to trigger certain psychological mechanisms, and be more or less likely to affect certain outcomes, e.g. Szemerszky et al. (2016).

2.5.4 Implications for clinical practice

The results suggest clinicians keen to reduce side effects induced by any placebo effect associated with their interventions could: 1) identify patient expectations of the adverse effects of an intervention and provide reassurance if these seem excessive; 2) avoid giving suggestions of side effects associated with the intervention; 3) down-play the dose that is being provided; 4) reduce patient exposure to other patients experiencing side effects. Wells and Kaptchuk (2012) suggest the use of contextualised informed consent, whereby clinicians should identify high risk patients and tailor the medication side effect information so that these patients only receive drug specific side effect information, which is less susceptible to the placebo response. My review supports this and suggests that such tailoring may be especially required for those who have at-risk personality types. Clearly, these suggestions also have a downside, however, as they reduce informed consent and patient autonomy by restricting the information that is being provided. Alternative ways to reduce placebo effects while maintaining the ability of a patient to give full informed consent are required. There is scope for researchers to develop innovative ways to reduce placebo effects that does not require withholding of information. This has been shown by (Crichton & Petrie, 2015)

who found that informing participants about placebo effects effectively reduced symptoms to infrasound noise. In addition Bingel (2014) provides some suggestions on how to avoid placebo effects which are supported by this review such as improving the communication in PILs to make them more patient-orientated and reduce negative expectations of potential adverse effects.

2.5.5 Future research

Additional research should aim to replicate risk factors which have so far received limited research, such as the more rarely investigated personality characteristics. It would also be advisable to look again at the risk factor ‘type of administration’ in a healthy volunteer sample and to assess this manipulation on expectations to explore possible mechanisms. It is also time for authors to use consistent terminology allowing easier identification of papers, and to enhance the quality of their research in this area. Simple acts such as being more explicit about randomisation and blinding procedures and publishing protocols will also help enhance the transparency of the research in this area whilst also helping to alleviate some of the controversy surrounding placebo research. Given the nature of the research involving inducing symptoms in participants, placebo studies should be carried out with the same degree of rigour as seen in other areas of clinical research.

2.6 Conclusions

This review found that there is a mix of factors which predict whether someone will experience a placebo effect. Given the implications placebo effects have on patients’ quality of life and the health costs they create, it is important for research to start developing interventions to prevent placebo effects from occurring whilst still trying to uphold informed consent. This systematic review provides a useful starting point for researchers to develop evidenced based interventions designed to negate placebo effects, whilst also highlighting areas that need further investigation and improvement.

It is interesting that the results of the systematic review found no studies which have looked at the potential effects of risk communication on placebo effects. This is something that has been studied before in the active exposure literature by O'Connor et al. (1996) and is potentially able to reduce the likelihood of a placebo effect across the sizeable number of patients who read medication PILs. The studies which form the rest of this PhD build on current placebo research using risk communication, specifically the way side effects are portrayed in PILs as a novel way of preventing symptoms in response to an inert exposure.

Chapter 3 Introduction, aims and hypotheses for the experimental study

3.1 Introduction

Given the problems that placebo effects can cause in relation to patient well-being, non-adherence and costs to health services, it is clearly important to find ways to prevent placebo effects from occurring.

Looking at the different mechanisms of placebo effects, the most cost-effective way to intervene would seem to be using explicit suggestions. More specifically, altering the information provided in PILs is something that could be relatively easily introduced throughout the health care system. So far, research in the field of risk communication has looked at different ways of communicating the potential side effects of medications in PILs on people's expectations of developing such side effects. This shows that using numbers to convey the probability of developing side effects compared to verbal descriptors results in lower expectancies (Büchter et al., 2014), and that natural frequencies, e.g. 1 in 100 people, lead to lower risk perceptions than percentages, e.g. 1%, (Knapp, Gardner, et al., 2009). In addition, positively framing numerical risk in terms of those who will not be affected (e.g. 9 in 10 people will not be affected) results in lower perceptions of side effect risk than negatively framed numerical risk (e.g. 1 in 10 people will be affected) (Peters et al., 2011).

However these studies have not assessed whether these changes in side effect risk perception and expectations translate into subsequent changes in symptom reporting. Only one study in the placebo literature has specifically investigated this; O'Connor et al. (1996). This team reframed the information given to participants about the likelihood of side effects following an influenza vaccination from negative (e.g. 1% experience nausea) to positive wording (e.g. 99% do not experience nausea) and found a significant decrease in the side effects reported as a result. This intervention has the

added benefit of not acting as a barrier to informed consent. Patients received accurate information about the risk of side effects in both arms of the study. Despite this, some authorities remain cautious about interventions based around changes to risk communication. For example, the Medicines & Healthcare Products Regulatory Agency (MHRA; which is responsible for ensuring that medicines and medical devices work and are acceptably safe in the United Kingdom) recommends that positive framing should not be used in information leaflets when explaining possible side effects, as they believe patients may see it as a “marketing ploy,” although no evidence was provided to support this assertion (MHRA, 2005). It is also notable that the work by O’Conner et al. (1996) has never been replicated.

As well as investigating ways to prevent nocebo responses to medicines, it is also important that research it carried out to further our understanding of the mechanisms underlying nocebo effects. Previous research has suggested that expectations (Bingel et al., 2011; Hahn, 1997), learning (Van den Bergh et al., 1995; Vogtle et al., 2013) and misattribution of coincidental symptoms (Petrie et al., 2005; Petrie et al., 2004) are important in explaining the occurrence of nocebo effects. Whether some people are particularly predisposed to experiencing a nocebo effect remains unclear. Several potential predisposing factors have been suggested including gender (Liccardi et al., 2004), anxiety (Nevelsteen et al., 2007), somatisation (Szemerszky et al., 2010), somatosensory amplification (Witthöft & Rubin, 2013), low optimism (Geers, Helfer, et al., 2005) and baseline symptoms (de la Cruz et al., 2010). However my systematic review in Chapter 2 highlighted inconsistent findings with regards to the importance of these factors. Other potential predictors such as general beliefs about medicines, perceived sensitivity to medicines, and worries about the health effects of modernity have previously been implicated in side effect reporting to medicines and environmental exposures, but have been less-well researched (Heller et

al., 2015; Nestoriuc, Orav, Liang, Horne, & Barsky, 2010; Petrie et al., 2004; Rief et al., 2012).

3.2 Aims

Given these uncertainties, the aims of the main study reported in Chapters 7 to 8 of this thesis were to: 1) test the effects of using positive framing in PILs on symptom reporting relating to an inert tablet and on participants' perceptions of the PIL and 2) identify those participants most at risk of developing nocebo effects.

To do this I conducted an RCT in which participants were randomised to receive one of two forms of a PIL relating to an inert tablet. One information leaflet was akin to the information leaflets used in current practice, as guided by the EC (2009) and MHRA (2005) recommendations. The other PIL was identical, with the only difference being that the side effects listed were framed positively. After reading the leaflet participants took a tablet, which they were informed was a well-known tablet whose identity could not be revealed to them until after the study. After an hour they were asked to report any symptoms they experienced. As part of the RCT, I also included measures to assess: demographics, somatisation tendency, somatosensory amplification, anxiety, optimism, medicine-related beliefs, previous symptoms, and symptom expectations to test their association with the attribution of symptoms to the sham medicine. Participants' thoughts on the credibility of, and their satisfaction with, the information in the PIL were also sought.

3.3 Hypotheses

I hypothesised that

1. There will be a significant difference in the number of people who attribute symptoms to the tablet between the two conditions
2. There will be a significant difference in the number of symptoms attributed to the tablet between the two conditions

3. There will be a significant difference in the severity of symptoms attributed to the tablet between the two conditions
4. There will be a significant difference in participant-rated satisfaction with the PIL between the two conditions
5. There will be a significant difference in participant-rated credibility of the information between the two conditions
6. There will be significant associations between baseline measures and the attribution of symptoms to the sham medicine.

Chapter 4 Ethical issues surrounding the study of placebo effects

4.1 Introduction

Before describing in more detail the methods and results of the main RCT conducted as part of my work, it is important to consider the ethical issues that arise when planning and conducting a study in this field. Placebo research commonly involves some element of deception, with experimenters often deliberately lying to participants about the nature of the experimental stimulus. Such procedures are often essential for studies to produce valid findings – informing participants about the true nature of a placebo study may dramatically change their expectations relating to any side effects they will experience, and hence their experience of symptoms. This reliance on deception raises a number of ethical concerns, not least in terms of informed consent. How can participants give valid consent for a study, when they are being deliberately misled as to its nature? Given these concerns, it is notable, and alarming, that almost half of all studies identified in the systematic review in Chapter 2 did not mention having received ethical approval.

Since Milgram's controversial use of deception in obedience research (Milgram, 1963), ethical review boards at universities have become more rigorous in their scrutiny of deception. Milgram's obedience experiments were often assumed to have caused psychological harm to the research participants, although the extent of this harm is contested (Bortolotti & Mameli, 2006). Thus, the use of deception in research has become discouraged, making placebo effects notoriously difficult to study. Only a few institutional review boards allow scientists to use deception to induce pain in their participants (Scudellari, 2013). For example Paul Enck has explained that his ethics committee at the University of Tübingen in Germany will only allow him to carry out his placebo research if he tells participants that they are being deceived, defeating the purpose of the research (Scudellari, 2013).

While the adverse ethical implications of deceptive studies are a concern, the costs of not conducting deceptive research should also be considered. If nocebo effects are one of the underlying mechanisms for the development of non-specific side effects to medication, then a poor understanding of it could have serious implications. As discussed in Chapter 1, nocebo effects could impede emergency responses to public health crises, affect patients' quality life, and change their decision to adhere to their medication, all of which represent a preventable cost to the NHS. Research to understand these nocebo-induced side effects and how to reduce them could improve adherence, reduce costs, and save lives.

4.2 Aim

The aim of this Chapter is to provide an overview of what counts as deception in research, the current guidelines for using deception, the effects of deception on participants and what researchers can do to limit the potential harmful effects of deception. A suggestion on ways to lessen the ethical impact of deception and hence facilitate nocebo research is given. This then has direct practical implications for the subsequent research described in this thesis, and will be a useful overview for any nocebo researchers designing similar studies.

4.3 What counts as deception?

Before exploring how to resolve such ethical issues in nocebo research we must first look at what we mean by deception. According to the economist John Hey (1998) there is a difference between withholding information from participants, and telling them the wrong thing; and it is telling them the wrong thing which counts as deception. This assertion that withholding information does not necessarily constitute deception seems to be common among some researchers, e.g. Adair, Dushenko, and Lindsay (1985), Baumrind (1979), and Hertwig and Ortmann (2008). However, others include violations of participants' default assumptions in their definition of deception. For

example, according to Pierce (2008) withholding information can result in participants forming false beliefs about a study. Any description that conceals the true nature of a study by withholding information can cause participants to form an incorrect view of a study, hence guidelines for informed consent often require full disclosure of the study purpose. In light of this, Pierce (2008) suggests a more appropriate definition of deception in human participant research is communication that intentionally allows a participant to have, or maintain, a belief that the investigator knows is not true.

4.4 Current guidelines for using deception

Work in the 1960s suggested that deception was unnecessarily widespread (Kelman, 1967) and used even where alternatives were possible (Lindsey, 1984). Partly as a result of such work, guidelines were developed by the British Psychological Society (BPS) and others to regulate the use of deception in research.

Although discouraged, deception is not ‘banned’ in social science research. The BPS guidelines state that potential participants must be given ample opportunity to understand the nature, purpose, and anticipated consequences of any research participation, so that they may give informed consent (BPS, 2009). However, they do allow researchers to withhold information from participants in exceptional circumstances when necessary to preserve the integrity of research (BPS, 2009). This is a prime example of the situation involved when researching nocebo effects as the results are often dependent on a participant’s expectation of developing side effects from what they think is a noxious stimulus. Informing participants of the true study purpose and that they are receiving a non-active treatment or exposure will eliminate the expectation. In these situations some type of deception is therefore required.

The BPS provision for deceptive research is not a carte blanche for researchers however. It does stipulate that some additional requirements be met. These requirements include that deception should only be used: 1) if there are no other effective procedures

to obtain the desired experimental results; 2) where the research objective has a strong scientific merit; 3) where there is an appropriate risk management and harm alleviation strategy; and 4) if when deception is revealed later it is unlikely to lead to discomfort, anger or objections from the participants (BPS, 2014). The code also requires that research participants be allowed to withdraw from the experiment at any time and that experimenters debrief the participants as soon and as sensitively as possible after the experiment. In addition, if a proposed research study involves deception, it should be designed in such a way that it protects the dignity and autonomy of the participants. Moreover withholding of information should be specified in the project protocol that is subjected to ethical review and explicit procedures should be put in place to avoid any potential harm arising from the withholding of such information (BPS, 2014). Similar requirements are also stipulated by the American Psychological Association (APA, 2010) and other professional bodies.

4.5 The effects of deception

Though allowed by the ethical guidelines, the use of deception in psychology is still hotly debated. There is a contested trade-off between the need to use deception because the type of study necessitates it and the potential consequences this could have on participants' psychological and physical health, autonomy and future involvement in other studies, as well as on the reputation of the individual research team and the discipline of psychology as a whole. According to Bortolotti and Mameli (2006), if the psychological harm inflicted on the research participant as a result of deception goes beyond a certain threshold, then the experiment is not permissible, regardless of how great its potential benefits to society are. Although an intuitively sensible suggestion, where this threshold lies has not been made explicit. As such to avoid any potential untoward problems resulting from deception some ethics boards completely prohibit the

use of deception (as noted by Enck), as well as professional bodies representing entire disciplines, such as economics (Jamison, Karlan, & Schechter, 2008).

Evidence on the impact of deception on a participant's psychological well-being and future behaviour is mixed. In a review of studies that assessed research participants' reactions to being involved in deception experiments, Christensen (1988) concluded that participants do not perceive that they have been harmed as a result of deception and do not mind having been misled. Instead, he claimed that participants who were involved in deceptive experiments enjoyed the experience more and felt they received more educational benefit than those who participated in non-deceptive experiments (Christensen, 1988). A commentary by Kimmel (1998) also concluded that deception in research has minimal effects on participants and that participants do not become resentful about being deceived. More recently, Boynton, Portnoy, and Johnson (2013) found limited negative psychological effects of three different types of deception (deceptive task instructions; false feedback; and the interpersonal deception of experimenter professionalism) on university students, and that any negative effects on mood and attitudes toward psychological researchers were alleviated by debriefing. However an updated review by Hertwig and Ortmann (2008) on participants' feelings about the use of deception noted that this is not always the case. For example participants who have been deceived during an experiment have been annoyed (Allen, 1983) and a confederate partaking in a study involving deception has noted the angry reactions and discomfort it can cause to participants once they find out they have been deceived (Oliansky, 1991).

Beyond the effect of deception on individual participants, there are also some broader effects to consider. For example, there is research to suggest that the use of deception can affect the reputation of individual laboratories and the profession as a whole (Lawson, 2001). However, studies have shown that although participants who

have taken part in studies that have involved deception before are more suspicious of the truthfulness of experimenters, this does not seem to affect their beliefs about psychologists' trustworthiness in general (Cook et al., 1970). In addition the use of deception has been found to have no negative effects on deceived participants' attitudes towards psychological research (Kimmel, 1996; Sharpe, Adair, & Roese, 1992).

One of the reasons why evidence regarding people's feelings after deception could be so mixed is because the type of deception is different in each study (Hertwig & Ortmann, 2008). Unless constituting a direct replication (something that is famously rare in psychology), no two studies deceive their participants in the same way. It seems logical that different types and degrees of deception will have different effects. In acknowledgement of this, the BPS note that deception is more likely to be a problem if the information given to participants implies a more benign topic of study than is actually being carried out. Deception in which information given to participants implies a more harmful topic of study than is actually being carried out should be received more favourably. However in reality it is hard to predict what kind of an effect deception will have on participants as many studies that use it fail to report how the deception was received by participants, something that once again is notably lacking in the nocebo research reviewed in Chapter 2.

4.6 Limiting the potential deleterious effects of deception

Despite evidence suggesting that the type of deception habitually used in the field of psychology does not produce severe negative effects, deceptive research is not risk free. Researchers should always be wary of any potential deleterious effects of deception. As studying nocebo effects requires some form of deception whether by deliberate misinformation or withholding information there are various approaches researchers can take as precautions, some of which are required by codes of ethics and some that can be considered as supplementary.

4.6.1 Patient and public involvement

Researchers could help limit the negative effects of deception on participants at the planning and designing phase of their study by the use of patient and public involvement (PPI). PPI is an initiative promoted by the UK's National Institute of Health Research, through INVOLVE, which is a national advisory group to support active public involvement in NHS, public health and social care research. PPI is important as it allows researchers to see things through the eyes of the public when designing studies by carrying out research *with* the public rather than *about* them (Involve, 2015). Carrying out PPI can help make sure that the right research is done, improve research quality and make sure the research is conducted properly. The use of PPI is a good way for researchers studying placebo effects to talk to the public about their opinions on the use of deception in an upcoming study. Doing this could help researchers come up with ways to reduce the amount of deception required and to discuss strategies that members of the public would like to see to limit the effects of deception both during the conduct of the study and after. In this way researchers can carry out their study with the backing of a separate group of the public that have been involved in advising about its planning and design.

4.6.2 Authorised deception

In the process of recruiting participants, authorized deception can be used before people consent to participate by alerting them to the use of deception in the research but without disclosing what the specific nature of the deception will be (Wendler & Miller, 2004). In using authorized deception, participants are typically informed that some statements about the research are inaccurate or misleading, that deception is necessary for the integrity of the research, that the study has been approved by an ethics committee and that they will receive the full accurate details of the study after participation (Miller & Kaptchuk, 2008). Although this procedure still falls short of full

informed consent, it does promote autonomy by allowing potential participants to decide whether or not they are willing to participate in a study that involves deception (Miller & Kaptchuk, 2008). This allows participants to maintain control over their participation as their initial consent is conditional on the renewing of their consent at the moment of debriefing, where they have the option to withdraw their data (Bortolotti & Mameli, 2006). Bortolotti and Mameli (2006) also note that authorised deception is similar to the procedure used in clinical trials. Before clinical trials, participants receive detailed information about the purposes of the research and the risks involved, but they are not told whether they will receive the potential treatment or the placebo. As long as the participants give consent with the understanding that information is being withheld, this does not constitute a violation of their autonomy.

Miller and Kaptchuk (2008) however note that whilst authorised deception is not a novel approach, it is not commonly used. Researchers may be reluctant to use it as letting participants know the study involves deception may compromise the scientific validity of the study almost as much as revealing the true nature of the study. It may also make it more difficult to recruit participants. Martin and Katz (2010) have investigated the use of authorized deception to see if it creates any differences in the magnitude of the placebo effect between participants randomised to receive authorised deception or non-authorised deception. They found that authorized deception did not have any impact on the magnitude of a placebo effect, recruitment or retention of participants, nor did it result in any significant psychological harm. The majority of participants who received this form of consent preferred it to the traditional approach in which the participants are not alerted to the presence of deception. These findings suggest that the use of authorized deception is a viable and ethically preferable alternative consent process for studies on placebo analgesia. However no studies have

looked at the effect of authorized deception in placebo studies. It is unknown if authorised deception would be as suitable in this situation.

4.6.3 Nominated informed consent

A variant on authorised deception is for the potential participant to nominate a person they trust to receive all the information about the experiment (Clarke, 1999). This person can then judge whether it is acceptable for the participant to take part and gives consent on the participant's behalf. This does come with some problems however. The nominee may have different values and needs from the participant in question and thus may give consent when the participant themselves would not have done (Patry, 2001). To address this Patry (2001) suggests that in addition to nominated informed consent, participants should also be told: 1) their participation is voluntary and they can withdraw at any time without consequence; 2) they can get more information about the study (providing it is not necessary to withhold); 3) they could get false or incomplete information; 4) they will be completely informed at the end of the study; 5) the duration of the study; 6) the description of the procedures and what they will have to do in the study; 7) information about the expected risks as a result of participation. In this way by providing some information to the participant, the use of nominated informed consent also helps to provide additional protection to the participant.

4.6.4 Debriefing participants

When using deception most ethics boards require researchers to debrief their participants. According to BPS guidelines the debrief should explain that the need for deception was an essential feature of the study design and explain the conduct of the experiment. It should be made clear to participants that deception is only used when no risk of significant harm is present to participants and when important results are at stake. The debrief must be given to participants as early as is feasible, but no later than at the conclusion of the data collection. Once the debrief has been given, participants

should also be allowed to withdraw their data. Giving participants the opportunity to withdraw their data after they have learned about the true nature of the study restores a degree of autonomy to participants who were deceived during the consent process (Miller & Kaptchuk, 2008). Therefore participants do not have to contribute to research which they would have declined to participate had they known the true nature of the study (Miller & Kaptchuk, 2008).

4.7 Assessing and reporting the impact

Many papers reporting on placebo effect research are not transparent about their use of deception. It is not enough just to follow the guidelines when carrying out research involving deception, it is also important for researchers to assess their use of deception and the strategies they used to limit any negative effects as well as to report the impact their deception had on participants. Miller and Kaptchuk (2008) suggest that the scientific journals can play a role in this by requiring researchers to be more explicit about their use of deception, and what methods they used to negate any potential deleterious effects (Miller & Kaptchuk, 2008). More than this, however, it could be argued that researchers using deception have a moral obligation to check that they have not done harm, if for no other reason than to reassure themselves and their ethics board. The debrief that is a requirement for all studies using deception offers an opportunity to obtain feedback from participants. This should be used and the impact of deception on participants should be reported in papers. Making sure researchers assess and report the impact of their use of deception will help to improve the transparency of placebo research and the ethical design of future studies.

4.8 My approach to studying placebo effects in this thesis

As Martin and Katz (2010) have shown that authorised deception does not affect the magnitude of the placebo effect, I thought this would be a good approach to use for also researching placebo effects. However instead of using deception that deliberately

misinforms participants, my approach has been to be as truthful as possible but to withhold any information that would jeopardise the study.

Past research has suggested that one can elicit placebo effects without withholding information at all. For example Kaptchuk et al. (2010) have shown that patients with irritable bowel syndrome randomised to receive open-label placebo pills presented as "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes" showed significantly higher improvement scores and reduced symptom severity scores compared to those in a control group who received no treatment. However this study has not been replicated and although they labelled the pills as 'placebos,' most of the wording focused on the fact that the pills will have an effect. No study has looked at whether one can elicit nocebo effects in a similar open-label technique. Given this and the lack of replication it is not known if it is a viable option to induce nocebo effects. In light of this, I decided not to use this approach and instead be as truthful as possible to participants but, where needed, withhold information and let them know I was doing so.

To do this, participants took an inert tablet which I told them is a well-known tablet available without prescription. They were told (correctly) that I could not tell them what the tablet is in case it biases their views about it. They were also told that there are two different PILs that have been developed for the tablet and they would get one of them to read. I informed them the difference between the two leaflets were some slight changes to the wording, to see if this influences what they think about the tablet, but that I could not tell them where the changes in the leaflet were. Therefore I openly informed them that I would be withholding information from them, similar to the authorised deception procedure. In terms of the information on the leaflet, it was specifically designed to be truthful for an inert tablet. For example sections on the

leaflet which cover information about what happens if you take too many tablets explained that this can result in more severe side effects (as has been shown by the inert tablet overdose example in Chapter 1 (Reeves et al., 2007) and by studies reviewed in Chapter 2 showing the importance of dose on the magnitude of placebo effects). Similarly, all the potential side effects listed on the leaflet were the nonspecific side effects that are commonly reported during a placebo response.

In addition to this use of authorised deception, all participants were debriefed at the end of data collection by informing them of the purpose of the study and what the tablet was. Participants had the opportunity to withdraw at this point if they wished to, upholding their participant autonomy. I also collated any feedback received from participants following the debrief. Planning of the study was discussed with members of the public drawn from a population that was similar to the intended participant pool for the study, allowing me to get their input on whether this proposed approach was appropriate and how to minimise any ethical issues still further.

4.9 Conclusions

Although there is no single agreed definition of deception, primarily due to disagreement as to whether withholding information constitutes as deception, current guidelines from the BPS and APA include withholding information as deception and allow deception in research as long as it adheres to several guidelines. The use of deception is often criticised due to the potential psychological harm this can cause participants as well as the impact on the reputation of individual researchers and the discipline as a whole. However, evidence from the literature suggests that these criticisms are often unfounded. Nonetheless, maintaining high ethical standards in an area this controversial is important. The proposed strategy for use in my study included deception by omission, rather than commission, authorised deception and debriefing, together with a preliminary discussion of ethical issues with a PPI panel.

Chapter 5 Patient and public involvement

5.1 Introduction

Before carrying out the experimental study I obtained feedback from a sample of the general public about the proposed study. Researchers often have a different sense of normality compared to that of the general public. Obtaining a lay perspective can often help improve the study design. This can be done through a process of patient and public involvement (PPI), whereby research is carried out ‘with’ or ‘by’ members of the public rather than ‘to,’ ‘about’ or ‘for’ them (Involve, 2015).

The intended benefits of carrying out PPI are two-fold. First, it can help make sure that the right research is done by challenging research that may be unnecessary or driven solely by the interests of researchers (Involve, 2015). Second, it can help to make sure that research is done to a higher standard. The success of research is determined by people agreeing to take part, therefore PPI can help with this by making sure that researchers clearly explain their study, communicate effectively, ask the right questions in a way that the public understand, approach people in the right way and design studies that are easy to take part in and efficient (Involve, 2015).

5.2 Aim

As part of my PhD I carried out PPI as a means to help ensure that the right research was carried out and that the research was done appropriately. The aim was to go through my proposed research with a group of lay public and get their feedback and suggestions on my research design and materials, specifically asking for what they thought would work well and what they would change. The feedback was then used to inform how I proceeded with my research.

5.3 Initial design of the patient information leaflet

I based the control PIL on an existing leaflet which follows current best practice guidelines. This was changed so as to remove information about what the tablet is and

what it is used for, its interactions with other medication, the recommended dose, and what the tablet contains. This information was removed to prevent participants being able to guess the identity of the tablet. Text for these sections of the leaflet were replaced with a single large 'X.' The possible side effects section of the control PIL followed current guidelines for describing their probability, using phrasing such as "Common side effects (1 in 10 people will be affected)."

The intervention PIL was exactly the same as the control, apart from what appeared in the section relating to possible side effects. In the intervention PIL the probability of possible side effects were positively framed following O'Connor et al. (1996). This was achieved by rewording the verbal descriptor, presenting the number of people who would not be affected and using percentages which have previously been shown to elevate perceptions of likelihood compared to natural frequencies (Knapp, Gardner, et al., 2009). Side effect information therefore took the form of: "Very uncommon side effects (90% of people will not be affected)." The side effects listed in the leaflets were selected as those commonly reported in everyday life and during a nocebo response (14 items), e.g. nausea, headache, tiredness (Wells & Kaptchuk, 2012). Figure 5-1 shows the difference between the leaflets. For a full copy of the initial leaflet design see Appendix A.

<u>Standard worded leaflet (Control)</u>	<u>Positively framed leaflet (Intervention)</u>
Very common side effects (<i>More than 1 in 10 people will be affected</i>)	Uncommon side effects (<i>80% of people will not be affected</i>)
• Headache • Nausea	• Headache • Nausea
Common side effects (<i>1 in 10 people will be affected</i>)	Very uncommon side effects (<i>90% of people will not be affected</i>)
• Cough • Dizziness • Pain in limb • Runny nose • Sore throat • Stomach ache • Tiredness • Bloating	• Cough • Dizziness • Pain in limb • Runny nose • Sore throat • Stomach ache • Tiredness • Bloating
Uncommon side effects (<i>1 in 100 people will be affected</i>)	Rare side effects (<i>99% of people will not be affected</i>)
• Itchy skin	• Itchy skin
Rare side effects (<i>1 in 1,000 people will be affected</i>)	Very rare side effects (<i>99.9% of people will not be affected</i>)
• Confusion • Agitation • Anxiety	• Confusion • Agitation • Anxiety

Figure 5-1 The difference between the two PILs.

5.4 Method

5.4.1 Design

The PPI session was run as a discussion group on 4th March 2015.

5.4.2 Participants

Participants were recruited through posts on social media and offered £40 in exchange for their time. A total of eight people (one male and seven females) were recruited and the majority were students from King's College London. This reflected the intended population for the main study.

5.4.3 Procedure

The session was voice recorded and participants were made aware of this at the beginning of the session. Each participant was provided with a booklet with all the research materials we would cover for them to read through and annotate during the discussion.

I first gave an introduction to the session to explain who I was, why I asked them to come and what the session would involve. At this point I made clear that I would be recording the session and set down a few 'rules' to emphasise that everyone's opinion was welcome, there are no such things as a 'stupid' question or comment and they should try not to speak over anyone. At this point I also asked if there were any questions before we got started.

Before going into the details of the research I showed them a study flowchart. This outlined the research design and participant flow through the study so they could see how each part of the study fit together and also the order in which we would go through the study together.

The first research material we discussed was the information sheet, which I read out to the group. After reading through it I asked for the groups' thoughts and where necessary prompted them for anything they found worrying after reading the sheet, if they understood it, and if there was anything else that should be on it. I also asked one member of the group to provide a summary of the information sheet to see if they understood it. The true purpose of the study was not revealed to the group at this stage, to help them visualise the experiment as a participant would experience it.

I next read through the baseline questionnaires. For each questionnaire I asked for feedback on the basic layout and formatting, on the instructions for the questionnaire to see if it was easy to understand how to fill it in, and also on the readability and coherence of the questionnaire items themselves.

Following this we went through the control and intervention PILs. I read through the control leaflet and then read the altered section in the intervention leaflet. I asked the group if the leaflets were what they would expect a PIL to look like, if they were clear, understandable, and if there was anything else they would expect to see. I also asked if they thought the difference between the leaflets would have an effect on symptom reporting and asked for their suggestions on how to make sure participants would actually read the PIL during the study itself.

We then went through the remaining questionnaires that would be used in the study. As before, for each questionnaire I asked for feedback on the basic layout and formatting, on the instructions for the questionnaire to see if it was easy to understand and also on the readability and coherence of the questionnaire items themselves.

The group were asked specific questions about aspects of the research design that I had not established yet. This included asking the group's opinion on what participants should do in the hour between taking the tablet and completing the final questionnaires, and how I should ask participants to guess what they thought the tablet was.

Finally I read through the proposed debrief email that I had developed for participants. After going through it I asked the group for their thoughts on the content, as well as the timing of when to debrief participants. After reading the debrief, which revealed the study's aims, I asked what the group thought about the use of deception in the study and how they thought the participants might receive it. I also asked the group if the 'cover story' given in the information sheet was believable, if they were ever suspicious of it, or if they had a better cover story that we could consider.

After finishing the group discussion I explained we had come to the end of the session and let the group know the true purpose of the study. I also updated the group on the progress of my study so far. At this point I thanked them for taking part, and

asked if they had any other questions/comments. I also handed them a feedback form to fill in.

5.4.4 Outcomes

During the exercise, when issues were raised by the group, I asked the group for suggestions on how they would change or address it and these were discussed until a conclusion was reached together. A summary of the discussion was then reflected on with my supervisory team.

5.5 Results

5.5.1 Information sheet

The group thought that participants might have some worries or concerns after reading my proposed study information sheet. To address this, following the group discussion, I:

- Moved a section about the ‘risks of taking part’ to earlier in the information sheet to reassure participants from the beginning that the risks of taking part were low.
- Made explicit that any side effects experienced as a result of the study would be short-term, lasting no more than two hours.
- Made clear to participants in the information sheet that they would find out what the tablet was at the end of data collection.
- Mentioned the procedures that were in place if a participant did experience side effects and that if the situation necessitated it, then I would tell them what the tablet was.

5.5.2 Questionnaire items

There was confusion about some of the symptoms listed in the questionnaire so to make them more clear following the group suggestions I removed the symptom ‘nervousness’ from an item based on the Patient Health Questionnaire – 15 (Kroenke,

Spitzer, & Williams, 2002) which initially mentioned ‘irritability, nervousness,’ as it was suggested that nervousness could be interpreted as equivalent to anxiousness, a symptom which was already listed earlier. In addition, I renamed the symptom ‘hot flashes’ to ‘hot flushes’ as the majority thought this was a typographical error.

For a health concern relating to ‘amalgam dental fillings’ (an item in the Modern Health Worries scale (Petrie et al., 2001)) the majority did not know what this was. After explaining it was a type of filling that used mercury, they suggested that I should change this concern to ‘mercury dental fillings,’ which I did.

For the Beliefs about Medicines questionnaire (Horne, Weinman, & Hankins, 1999) the group thought the statement ‘Doctors use too many medicines’ was not clear and could be changed to ‘Doctors prescribe too many medicines’. Although this would have perhaps reduced confusion for participants about what ‘use’ means, as it is a standardised questionnaire my supervisor and I agreed the benefits of the change were not sufficient to justify it.

In the middle of the 15 item patient health questionnaire (Kroenke et al., 2002) there was a women-only item. The group thought men could misinterpret the accompanying instructions to mean that all of the subsequent items were for women only. To prevent this I moved this item to the bottom of the questionnaire.

The group noted that there were anxiety questionnaires after reading the PIL and after taking the tablet, but there was no anxiety questionnaire at baseline. They thought it would be useful to have this as a baseline measurement, and I concurred.

5.5.3 Filler tasks

It was suggested that simply waiting for an hour was not realistic of what people would normally do after taking a tablet in a clinical trial. A proposed idea of having a vigilance test such as a flicker fusion test was met with suggestions that this could bring on symptoms if participants had to do this for the full hour. As a result other tasks such

as getting participants to read pre-selected material, complete cognitive tasks or watch a video of neutral content were suggested. Following the discussion with the group I decided that in order to keep participants occupied and give a better suggestion of a formal clinical trial, I would include a vigilance test as well as other cognitive tasks that were not too taxing such as pen and paper memory, digital symbol and category fluency tests.

5.5.4 Guess at tablet identity

When initially asked to guess the identity of the tablet being used in the study, the group had no idea what it could be. They therefore suggested that a multiple choice question would be easier for participants asked to guess the identity of the tablet during the real study. However, as no-one from this PPI group thought that the tablet might be a placebo, my supervisor and I thought that having a multiple choice question including placebo as an option might encourage people to pick this, falsely elevating the apparent number who had correctly guessed its identity. Therefore I decided to keep this as an open question during the real study but to add a confidence rating scale to allow participants to express that they were guessing, if applicable.

5.5.5 Debrief email

Once I revealed to the group that the tablet participants take would be a placebo, they were surprised. They did not feel that the reveal would be taken badly by participants as the study implied they were taking a more ‘harmful’ tablet than they actually were. In addition, the group noted that the information materials clearly told participants that I would be withholding information. However, a lively discussion ensued about when to debrief participants, the content of the email, the opportunity to withdraw and the clarity of the email in order to keep any negative effects of the deception to a minimum. In addressing these points, I made the following changes in accordance with the groups’ suggestions.

- Due to the risk of participants telling others about the study and the fact the tablet was inert, it was agreed that it would be better to keep the debrief to the end of data collection for the study as whole. This was felt to be appropriate providing that participants were told at the start of the study and in the information sheet that they would have to wait till the end of data collection to find out what the tablet was.
- To reduce participant concern, as suggested I elected to remind participants again in the debrief email that all their data would be anonymous and could not be linked back to them.
- To promote participant autonomy, I included an opportunity for participants to withdraw their data for a short period after they received the debrief email, and I let participants know about this opportunity in the information sheet and consent form.
- I made the wording in the debrief email clearer about the use of percentages in the intervention patient leaflet as there was some confusion over this when reading it through with the group.

These changes were approved through a modification request to the King's College London Research Ethics Committee.

5.6 Discussion

Overall the changes made to my research following the PPI involved making certain parts of the research material clearer for participants to understand and making the information sheet and debrief email more reassuring to reduce any potential worry or concern. This exercise was useful in picking up on aspects of my research that I had not considered and getting feedback on aspects that I was unsure on how to proceed with. It was reassuring to learn that the design of the study was perceived as appropriate and that the intervention was seen as plausible.

Although I felt the session was successful there may have been ways to enhance it still further. First, the session could have been longer. For practical reasons, the length was restricted to 1 hour and in practice overran by 10 minutes. Although I managed to cover everything in this time and there was plenty of discussion, I did feel time pressured. Second, when discussion started to go off topic I could have been quicker getting it back on track. Being accompanied by a moderator with more experience in PPI may have allowed me to obtain additional input from the group.

Chapter 6 Pilot study: The effect of using positively framed side effect risk communication on symptom expectations

6.1 Introduction

A pilot study was conducted prior to beginning the main RCT, to check that the intervention PIL I had developed would have the intended effect of reducing symptom expectations in comparison to the control PIL. Although this did not directly test the effects of the leaflet on symptom development, my systematic review in Chapter 2 showed how important expectations are in contributing to nocebo effects. If the results from a pilot study showed that the intervention PIL did not reduce symptom expectations then there would be no grounds for running the main RCT study. The pilot study was also used as an opportunity to test how participants rated their satisfaction with the information in the PILs and the perceived credibility of the PILs.

6.2 Aim

To carry out a pilot study to test the effect of the standard worded PIL and positively framed PIL on symptom expectations and on rated satisfaction with, and credibility of, the PIL.

6.3 Hypotheses

1. There will be a significant difference in the number of expected symptoms between the two conditions.
2. There will be a significant difference in the perceived likelihood of expected symptoms between the two conditions.
3. There will be a significant difference in participant rated satisfaction of the PIL between the two conditions.
4. There will be a significant difference in participant rated credibility of the PIL between the two conditions.

6.4 Method

6.4.1 Design

I used a randomised crossover design, in which participants each received the control and intervention PIL, but the order they received them in was randomised. Randomisation was carried out using the online randomisation service Sealed Envelope Ltd (2016). Sealed Envelope created a randomised list of 30 entries telling me which leaflet to give first to each of my participants, but making sure 15 received the intervention leaflet first, and 15 received the control leaflet first. Participants were told they were evaluating two different leaflets that had been designed for a well-known tablet and therefore did not know the true aim of the study or the difference between the two leaflets until the end of the study. I was not blind to which leaflet participants were receiving. Ethical approval for the pilot study was granted by the Psychiatry, Nursing and Midwifery ethics subcommittee at King's College London in conjunction with approval for the full RCT (PNM:14/15-62) (see Appendix B) and was subsequently modified following PPI (see Appendix C).

6.4.2 Participants

Participants were recruited through university circular emails and posts on KCL student groups, social media and twitter. The only inclusion criteria was that participants had to be 18 years of age or older, and fluent in English. I intended to recruit 30 participants as it is suggested that pilot studies should be at least 10% of the sample projected for the main study (Connelly, 2008; Hertzog, 2008). In this case I opted for 15%.

6.4.3 Materials

As detailed in Chapter 5 the PILs were based on an existing leaflet which follows current best practice guidelines. The only difference between the two leaflets was what appeared in the possible side effects section. The control PIL followed current

guidelines for describing their probability, using phrasing such as “Common side effects (1 in 10 people will be affected).” Whereas in the intervention PIL the probability of possible side effects were positively framed, using phrasing such as “Very uncommon side effects (90% of people will not be affected).” For a copy of the standard wording (control) and positively framed (intervention) PILs used in the pilot see Appendix A.

6.4.4 Measures

Before receiving any PILs participants completed questions about their age, gender, ethnicity, highest level of education and employment status.

After reading each leaflet participants completed a questionnaire about their side effect expectations. This was measured using a modified version of the generic assessment of side effects scale (GASE) (Rief, Glombiewski, & Barsky, 2009). Twenty-three symptoms were selected according to those commonly reported during a nocebo response and those listed on the GASE that could be detected within an hour of taking the tablet, and were not too serious (e.g. headache, dizziness, itchy skin). Fourteen of these symptoms were mentioned on the PILs and nine were not. Each symptom was rated on a 4 point scale ranging from 0 “not at all likely” to 3 “very likely.” Scores range from 0-23 for the expected number symptoms, and 0-69 for the expected likelihood. This has since been similarly used by Nestoriuc et al. (2016).

To measure participants’ satisfaction with the PILs I developed seven statements covering the coherence of the information, the type of information provided, the sufficiency of the information, and the overall satisfaction with the leaflet, which each participant rated on a 5 point scale ranging from 1 “strongly disagree” to “5 strongly agree.”

The credibility of the information in the PIL was measured using Myers et al. (1987)’s Credibility Index, in which participants rated the PILs on trust, accuracy, fairness, bias and disclosure using a five point scale from 1-5.

At the end of the study participants were asked to give their best guess as to what they thought the tablet described in the leaflet was, and rated how confident they were answer on a scale from 1 “not at all confident” to 5 “completely confident.” I also provided a space at the end of the questionnaire for participants to write any further comments on the PILs or the study in general.

For a copy of the full questionnaire and wording used see Appendix D.

6.4.5 Procedure

In the study adverts and information sheet participants were informed that they would be taking part in a pilot study to assess the quality of two different PILs that had been developed for a well-known tablet that is available without prescription. I told participants that the identity of the tablet could not be revealed as it could influence how they answered the questions about the leaflets. The study took place within university meeting rooms. After signing the consent form, participants completed questions about their demographics and then received one of the leaflets to read depending on the randomisation order. Participants were given enough time to read the leaflet once before passing it back to the researcher and completing questions about their side effect expectations, how satisfied they were with the information in the leaflet and how credible they thought the leaflet was. After completing these questions for the first leaflet, they then received the second leaflet, and completed the same procedure again. After answering the questions about the second leaflet participants were then given the opportunity to guess at what the tablet might be and provide some qualitative feedback about the study. After giving their feedback participants were then thanked for their participation and received a monetary reward of £30. A full debrief was emailed to participants at the end of data collection explaining the true aims of the study. See Figure 6-1 for an outline of the procedure. For a copy of the information sheet and consent form see Appendix E and F.

6.4.6 Outcomes

The primary outcomes included the expected number of symptoms and the likelihood of those expected symptoms. A symptom was classed as expected if given a rating of 1 or more in the side effect questionnaire. The likelihood of symptoms was calculated as the sum of the ratings given for all symptoms in the same questionnaire.

Secondary outcomes included participants' satisfaction and credibility ratings of the leaflets.

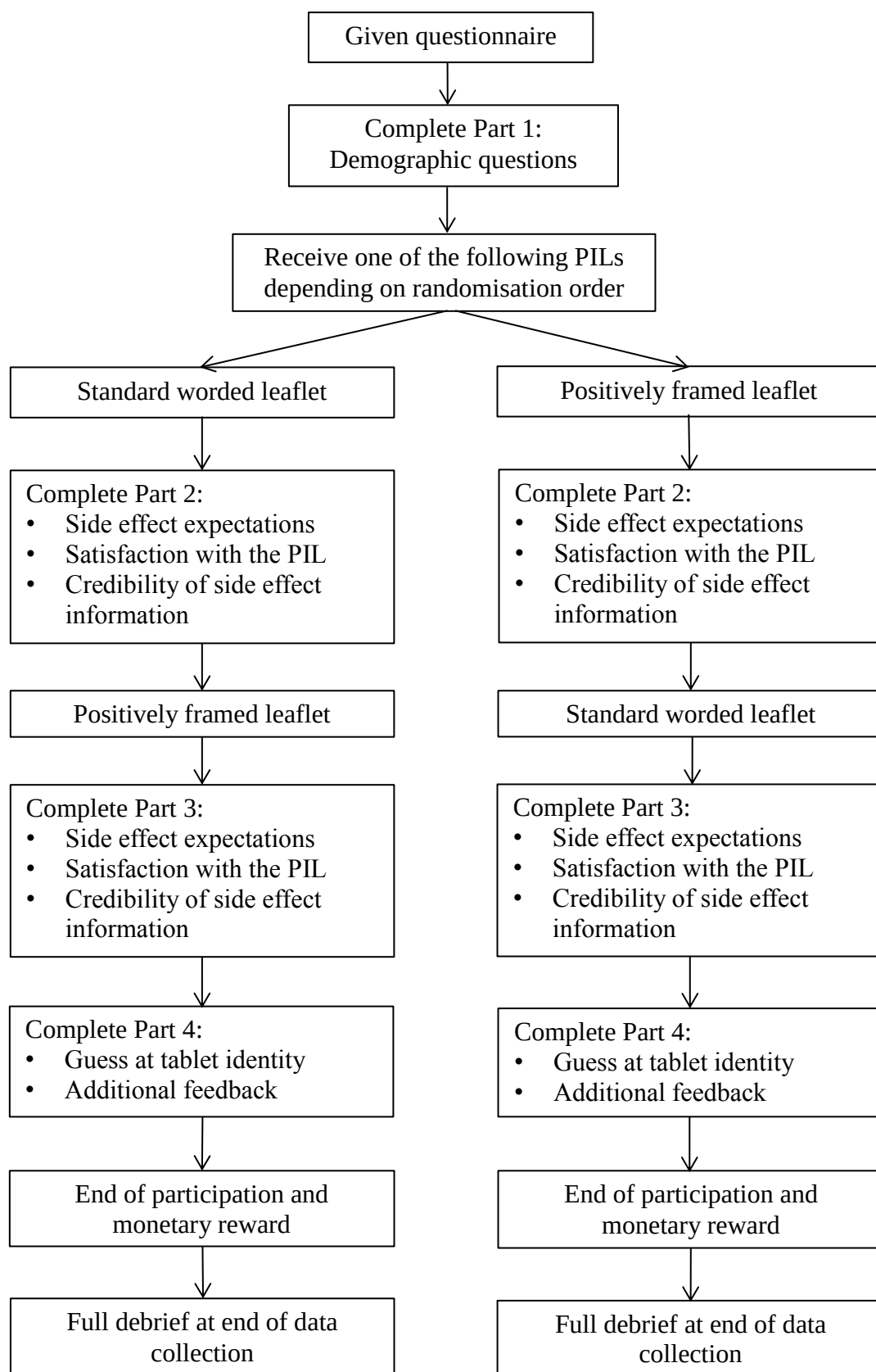


Figure 6-1 Pilot study participation procedure.

6.4.7 Analysis

A randomisation check was carried out to make sure participants who received the control or intervention leaflet first did not differ on any baseline characteristics.

In the side effect questionnaire there were 12 cases of missing data. In this instance for each case of missing data for a specific symptom the equivalent symptom in the other condition was removed from the analysis. Similarly there were two cases of missing data for the leaflet satisfaction questions. These were treated in the same way as the symptom expectation missing cases.

The majority of the variables failed to meet the assumption of normality for parametric tests. I therefore used a Wilcoxon Signed Ranks test to compare the expected number and likelihood of symptoms (both for mentioned, non-mentioned and all symptoms), satisfaction of information in the leaflets, and credibility of the information between the positively framed and standard worded leaflets. To account for the possibility of order effects a series of regressions were carried out to test whether the order of leaflets received predicted the results on either of the primary or secondary outcomes.

Participants' answers to the open ended question at the end of the study were analysed using thematic analysis to see what different aspects of the study participants were commenting on in general.

6.5 Results

6.5.1 Participant characteristics

Thirty three participants were recruited. Three did not attend their appointment, leaving 30 in the final sample. The mean age of the sample was 26.5 years with the majority of the sample being women (83.3%) and of White ethnicity (73.3%). For full baseline characteristics and a further breakdown of the demographic characteristics, see Table 6-1.

Table 6-1 Baseline Characteristics of the sample.

Participant Characteristic	Sample (N=30)
Age	26.5 (1.3)
Gender	
Male	5 (16.7%)
Female	25 (83.3%)
Ethnicity	
White	22 (73.3%)
Other	8 (26.7%)
Highest level of education	
Secondary education	3(10.0%)
Higher education	27 (90.0%)
Employment status	
Full time	7 (23.3%)
Part time	4 (13.3%)
Student	19 (63.3%)

Note: Data are mean (SD) or n (%)

6.5.2 Randomisation check for condition received first

No significant differences were observed in terms of gender, ethnicity, highest level of education and employment status for participants who received the positively framed PIL first and those who received the standard worded PIL first (Fisher's exact test, $p > .169$). In addition age was compared using a nonparametric Mann Whitney U test (due to the non-normal distribution) and again no significant difference was found ($p = .268$).

6.5.3 Primary outcome: Expected number of symptoms

For the symptoms that were mentioned in the two PILs, significantly more were expected after reading the standard worded leaflet (median = 10.0, Interquartile range (IQR) = 4.0) than after reading the positively framed leaflet (median = 8.5, IQR = 7.0), $p = .022$.

Out of the symptoms that were not mentioned in the PILs, there was no significant difference in the expected number of symptoms after reading the standard worded leaflet (median = 1.00, IQR = 3.0) or positively framed leaflet (median = 1.0, IQR = 4.0), $p = .986$.

Combining both the mentioned and non-mentioned symptoms together, the two variables met the assumption of normality. A parametric paired samples t test revealed that participants expected marginally more symptoms as a whole after reading the standard worded leaflet (median = 11.0, IQR = 8.0) compared to the positively framed leaflet (median = 10.0, IQR = 11.0) leaflet, $p = .054$.

6.5.4 Primary outcome: Expected likelihood of symptoms

Out of the symptoms that were mentioned in the two PILs, a significantly greater likelihood of symptoms was reported after reading the standard worded leaflet (median = 15.0, IQR = 12.0) than after reading the positively framed leaflet (median = 9.5, IQR = 13.0), $p < .001$.

For the symptoms that were not mentioned in the PILs, there was no significant difference in the expected likelihood of symptoms after reading the standard worded leaflet (median = 1.0, IQR = 4.0) or positively framed leaflet (median = 1.0, IQR = 4.0) leaflet, $p = .660$.

Combining both the mentioned and non-mentioned symptoms together, revealed that participants expected a significantly greater likelihood of symptoms as a whole after reading the standard worded leaflet (median = 17.5, IQR = 14.0) compared to the positively framed leaflet (median = 11.5, IQR = 17.0) leaflet, $p = .002$.

6.5.5 Secondary outcome: Satisfaction with the leaflet information

The control leaflet performed slightly better than the intervention leaflet on all but one satisfaction statement, see Table 6-2. However these differences were only statistically significant for the clarity of the leaflet, with the standard worded leaflet scoring higher than the positively framed leaflet ($p = .032$). Despite this the intervention leaflet still scored well on all statements as shown by its high median scores (see Table 6-2).

Table 6-2 The difference in satisfaction scores between the leaflets.

Items	Standard worded PIL (Median, IQR)	Positively framed PIL (Median, IQR)	p
Leaflet was clear	4.0, 1.0	4.0, 1.0	.032
Leaflet was easy to understand	4.0, 1.0	4.0, 1.0	.334
Leaflet contained words I did not understand	1.0, 1.0	1.0, 1.0	.739
Leaflet was similar to other leaflets	4.0, 1.0	4.0, 1.0	.662
There was enough information to make an informed choice	4.0, 1.0	4.0, 1.0	>.999
There was sufficient information about the risks and benefits	4.0, 1.0	4.0, 2.0	.755
Overall I am satisfied with the leaflet	4.0, 1.0	4.0, 0.0	.193

Note: IQR = Interquartile range

6.5.6 Secondary outcome: Credibility of the leaflets

The Wilcoxon signed ranks test revealed no significant differences between the two leaflets for their scores on the credibility scales (p s > .291). Similar to the satisfaction measure above, both leaflets scored well on each of the credibility scales, see Table 6-3.

Table 6-3 The difference in credibility scores between the leaflets.

Items	Standard worded PIL (Median, IQR)	Positively framed PIL (Median, IQR)	p
Trustworthy	4.0, 1.0	4.0, 1.0	.557
Accurate	4.0, 1.0	4.0, 1.0	.378
Fair	4.0, 1.0	4.0, 1.0	.392
Tells the whole story	3.0, 2.0	4.0, 1.0	.417
Unbiased	4.0, 2.0	4.0, 1.0	.926

Note: IQR = Interquartile range

6.5.7 Guess at tablet identity

Figure 6-2 presents the frequency of the different types of tablet that were suggested. The confidence the participants had in their answers was very low. The majority of participants thought the tablet was a prescription medication despite being told it was available over the counter (OTC). The more common of the prescription medications suggested included antibiotics, the contraceptive pill and antidepressants.

The second most common suggestion was a type of pain killer such as paracetamol, ibuprofen or aspirin. Other suggestions fell into the category of other OTC medications such as antihistamine, diet aids and cold/flu medication. Four participants could not guess what the tablet was and therefore did not have a confidence score.

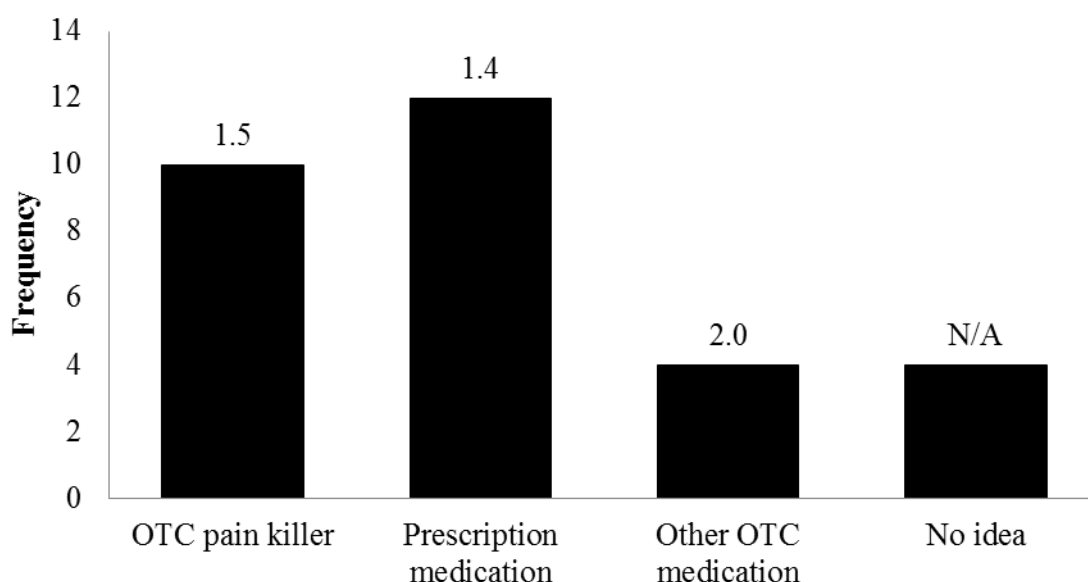


Figure 6-2 Frequency of the type of tablet suggested.

Note: The numbers on top of each bar represent the mean confidence of that category, rated from 1 (not at all confident) to 5 (completely confident), OTC = over-the-counter.

6.5.8 Order effects

All regressions were non-significant, $p > .062$ apart from one, which revealed that participants who received the intervention leaflet first scored it with a 0.40 higher agreement score for containing words that they did not understand, $B = .40$, $p = .012$.

6.5.9 Qualitative feedback

Out of the 30 participants, 25 participants gave extra feedback about the leaflets and/or the study. After analysing the comments five main themes emerged. Each theme is addressed in more detail below accompanied with exemplar quotes.

6.5.9.1 Presentation of side effect likelihood

Out of the 25 people who gave extra feedback, 20 commented on the presentation of side effect likelihood. This theme consisted of three sub themes. One of

these was perceived likelihood with participants explaining that presenting the side effect information as, for example, ‘90% won’t experience’ suggested that side effects were less likely to occur than presenting it as 1 in 10 will experience.

“Percentage of won’t experience compared to 1 in 10 will experience gave me more confidence that I wouldn’t experience side effects if taken” (P4)

The second sub theme addressed participant understanding of the leaflets. This varied across participants. Participants either understood the ‘90% will not be affected’ or ‘1 in 10 will be affected’ better, however there seemed to be a trend for more participants to understand the ‘1 in 10 will be affected’ better. This seems to be down to a personal preference and how participants interpret the numbers.

“The second version (control) I felt was much more accurate and truthful as the ratios were easier to understand and visualise” (P12)

“The second leaflet used ‘1 in 10’ instead of ‘90%’ which made it less user-friendly” (P6)

The last theme was familiarity. A few participants commented on the fact that percentages are not commonly used in PILs to display side effect likelihood. Therefore for some participants it came across as strange before realising the potential benefit it could have of displaying side effects this way.

“I found ‘99% of people will not get this’ quite strange, but I can see that people may find it reassuring” (P26)

6.5.9.2 Level of detail

Eleven participants commented on the level of detail in the leaflets. These broadly fell into subthemes that covered the level of detail needed by patients and the level of detail needed to answer the questions about the leaflet. For the level of detail needed by patients, participants felt there was sufficient information about how to take the tablet and dispose of it.

“I liked how the leaflet was more specific in terms of instructions for consumption 'best taken without food' and that is also indicates the best method for disposal and instructions for taking tablet when you missed a dose” (P7)

However, many participants felt there was not sufficient information about the effects of the drug on driving and what to do in the case of an overdose. More advice on these issues was suggested.

“The information it gave about driving and overdose was incomplete which made me feel unsure as to whether or not I would choose to take the tablet” (P26)

“I felt more advice on the drug and its effects and driving would be useful – am I still able to drive and use machinery? Is it at my discretion or advice from a Doctor? Do I need to inform the DVLA? (P15)

In terms of the level of detail needed to answer the questionnaires, a few participants raised the point that due to the information I had to withhold to prevent participants from being able to guess what the tablet was, they could not answer some of the questions I asked about the leaflet.

“I found it hard to assess whether I felt I understood the risks and benefits without seeing how the drug works and what it does” (P15)

6.5.9.3 Layout of the leaflets

On the whole the layout of the leaflets was deemed to be clear and easy to follow.

“Both of the leaflets order of information made sense and was clear to follow” (P20)

Some participants gave a few suggestions to increase the clarity of the layout such as highlighting the word ‘not’ in ‘will not be affected.’

6.5.9.4 Trustworthiness

A small theme that emerged from the data was the issue of trustworthiness. Some participants explained they found it hard to rate the trustworthiness of the side effect information due to not knowing the pharmaceutical company that produced the tablet and their general unease about pharmaceutical companies as a whole.

“I also believe the information on side effects can never be entirely trusted as other factors come into action where pharmacy companies conduct studies about medication” (P24)

6.5.9.5 Study design

Lastly participants also noted that the second leaflet might be remembered better than the first. For example one participant noted

“By the time I go to the questions after reading the leaflet I forgot the details that were relevant to the questions” (P6)

This was also made clear by some participants incorrectly stating there was more detail in the second leaflet

“Overall I would prefer leaflet two because it is more detailed” (P7)

6.6 Discussion

6.6.1 Summary of main results

This pilot study investigated if portraying side effect information in terms of the percentage of people who will not be affected reduces participant expectation of symptoms compared to side effect information portrayed in terms of the number of people who will be affected. I found that for those symptoms that were mentioned on the PIL, the intervention leaflet significantly reduced the expected number of symptoms as compared to the control leaflet, and the expected likelihood of these symptoms. No such effects were found for symptoms that were not mentioned in the leaflet. These results support previous studies looking at the effects of positive and negative framing

of side effects on expectations (Peters et al., 2011): in short, positive framing appears to be effective in reducing expectations.

In terms of satisfaction with the leaflets, participants thought both leaflets were equally easy to understand, similar to the leaflets currently used, had enough information to allow them to make an informed choice, and they were overall satisfied with them. However participants did think that the control leaflet was clearer than the intervention leaflet. My qualitative results suggest that this may have been due to lack of familiarity with the form of wording in the intervention leaflet, as it is not currently used in standard practice. Despite this, the intervention leaflet performed well on the majority of the outcomes and was still helpful to participants. Importantly, participants thought there was no difference in credibility between the control and intervention leaflet. Contrary to assertions by the MHRA (2005) guidelines, participants did not think that the positive framing for side effects was biased or reflected a marketing ploy by pharmaceutical companies.

No participant guessed that the tablet the PILs had been designed for was in fact a placebo. All participants who expressed an opinion thought the tablet was some sort of active drug that was currently available. Nearly half of the participants thought the tablet was an OTC medication such as a pain killer or hay fever tablet. Somewhat surprisingly, despite being told that the tablet was available without prescription, nearly half of the participants thought that the tablet was a prescription medication such as an anti-depressant or the contraceptive pill. This could have been because information from earlier in the study slipped their minds when it came to answer the question about its identity. This together with the fact that participants were reading the PIL in great detail and seeing all the potential symptoms (something which they might not do with OTC but may be more likely to do with prescription medicines) may have made the tablet seem 'stronger' than it is, and therefore presumed to be a prescription medicine.

6.6.2 Limitations

One limitation of this pilot study was the small sample size. A crossover design was used to ameliorate the effects of this. However, no power calculation was carried out, and I cannot be confident that the effect of the leaflets on symptom expectation was adequately powered. Some non-significant effects may have been type 2 errors.

Using a crossover design also came with limitations, in terms of order effects. However after statistical testing I found little evidence of the existence of this effect in the data.

Another limitation concerns the use of two primary outcomes, ideally there should only be one primary outcome cited, a specific measure at a specific time point, to specify what the real defined end point is. Although these two primary outcomes were pre-specified when designing the protocol for the pilot study, results can be cherry-picked. Therefore in retrospect it would have been better to have only chosen one primary outcome.

6.6.3 Implications for the main study

Despite the pilot study only looking at symptom expectations, the fact that the positively framed PIL resulted in significantly lower symptom expectations than the control PIL was promising and put me in a good position to start the main study.

In addition, no participant guessed correctly that the tablet being described was a placebo. This was a reassuring finding and confirmed the strength of the research design and ‘cover story.’ Finally the pilot study revealed that there were no differences in participant satisfaction or perceptions of bias between the control and intervention leaflet. This is important, as previous reports from the MHRA (2005) suggested that patient groups might not find positive framing helpful or might see it as a “marketing ploy.” My findings contradicted this.

6.6.4 Modifications to the main study

Following the pilot study some changes were made to the design of the main study. These included changes to both the intervention and the control PIL, one of the questionnaires and adding some additional questions.

Regarding the PILs, during the pilot study it appeared that some participants were using the milligram information provided in the PIL to guess what the tablet was, so I decided to remove this information for the main study. In addition some participants mentioned that they would like further information regarding the warnings for driving and using machinery, so I added this information to the leaflet.

One of the questions used in evaluating the PIL involved asking the participants to think about the risk and benefits of the tablet as informed by the leaflet. During the pilot, participants raised an important point that it was difficult to answer this question since no benefit information was actually present in the PILs. Therefore I changed this question so it focused solely on risk.

During the pilot study, the issue of trust in terms of the development of the tablet and the PIL by pharmaceutical companies was brought up by participants, therefore I decided to include some additional questions regarding participants' trust in the current medicine development, testing and approval process.

All these changes were made and approved through a modification request to my ethics committee. For a copy of the modification approval see Appendix G.

6.7 Conclusions

Positively framing the likelihood of side effects in PILs, in terms of those who will remain side effect free, significantly reduced the number and likelihood of expected side effects. In addition using positive frame did not reduce participant satisfaction with the leaflet or perception of the leaflet's credibility. This pilot study confirmed the usefulness of the intervention leaflet design and supported its use for the main study.

Chapter 7 The effect of positively framed risk information in patient information leaflets on side effect reporting: A double-blind randomised controlled trial.

7.1 Introduction

The pilot study showed the impact of framing side effect information on side effect expectations. In addition, contrary to the MHRA's concerns about how positive framing would be seen by patients (MHRA, 2005), I found no difference in participant ratings of satisfaction with the information or the credibility of the information between the two leaflets.

In this Chapter, I describe the results of a full RCT which tested whether positively framing side effect risk in a PIL reduces placebo induced side effects to a sham medicine and whether it affects satisfaction with or perceived credibility of the PIL.

The next two Chapters report on data from the same study. This Chapter reports the findings from the RCT, whilst Chapter 8 examines the effects of the baseline predictors on symptom reporting in the whole sample.

7.2 Aims

To test the effect of the positively framed PIL versus the standard worded PIL on symptoms attributed to a sham medicine, and the rated satisfaction and credibility of the information.

7.3 Hypotheses

1. There will be a significant difference in the number of people who attribute symptoms to the tablet between the two conditions
2. There will be a significant difference in the number of symptoms attributed to the tablet between the two conditions

3. There will be a significant difference in the severity of symptoms attributed to the tablet between the two conditions
4. There will be no significant difference in participant-rated satisfaction with the information between the two conditions
5. There will be no significant difference in participant-rated credibility of the information between the two conditions

7.4 Method

7.4.1 Design

I conducted a single centre double blind RCT, with a between participants design. This took place at the Wellcome Trust King's Clinical Research Facility in the UK. Ethical approval for the study was granted by the Psychiatry, Nursing and Midwifery ethics subcommittee at King's College London (see Appendix B) and was subsequently modified following PPI (see Appendix C) and piloting (see Appendix G). Reference number: PNM 14/15-62.

The trial was prospectively registered at the ISRCTN registry, trial registration number: ISRCTN47470030.

7.4.2 Participants

I invited participants who were healthy, aged 18 or over, and fluent in English to take part. Participants with chronic or acute illnesses which were currently symptomatic or those who were pregnant or breast feeding were excluded to prevent any interference with symptom reporting. Participants were asked to list any allergies to medicines and/or the inactive ingredients often found in them. Examples of the potential inactive ingredients were given and these examples covered all the ingredients in the tablet. Participants who listed allergies to any of the substances in the tablet were excluded. Participants who had taken any pain killers within 4 hours before taking part, or who had been drinking alcohol on the day of participation were rescheduled.

7.4.3 Sample size

The sample size calculation was based on the assumption that 25% of participants in the control condition would develop symptoms (Barsky et al., 2002), and that I am interested in reducing this to 10% or lower, and detecting this in a study with 80% power. Based on these assumptions, 100 participants were required in each group to detect this difference as significant at $p < 0.05$, using a z-test for independent proportions.

7.4.4 Measures

For a copy of the full questionnaire and wording used see Appendix H.

7.4.4.1 Pre-patient information leaflet

7.4.4.1.1 Demographics

Participants were asked their age, gender, ethnicity, highest level of education and employment status.

7.4.4.1.2 Other baseline measures

A number of other baseline measures were obtained and these are described in Chapter 8.

7.4.4.1.3 Symptoms in the past 24 hours

A modified version of the generic assessment of side effects scale (Rief et al., 2009) was used to assess participants' symptom experience in the past 24 hours. The GASE is an instrument to assess side effects in clinical trials (e.g. drug trials) and supports the early detection of drug-induced adverse events. The side effects listed in the GASE were selected according to those commonly reported during a placebo response (14 items), with the remainder drawn from what is already listed on the GASE that could be detected within an hour of taking the tablet, and were not too serious (9 items). Participants rated each symptom on a four point scale ranging from 0 "not

present” to 3 “severe.” Scores range from 0-23 for the number of previous symptoms, and 0-69 for the severity of previous symptoms.

7.4.4.1.4 Anxiety

This was assessed using the state anxiety inventory – short version (Marteau & Bekker, 1992). This includes six items which participants rated on a four point scale ranging from 1 “not at all” to 4 “very much.” The scores range from 6-24 with higher scores indicating greater anxiety.

7.4.4.2 Post-patient information leaflet / Pre-tablet ingestion

7.4.4.2.1 Anxiety

This was assessed as before with the state anxiety inventory-short version (Marteau & Bekker, 1992).

7.4.4.2.2 Questions about the patient information leaflet

Participants were presented with seven statements about the clarity of the information, the type of information provided and their satisfaction. Participants rated each statement on a five point scale ranging from 1 “strongly disagree” to 5 “strongly agree.” Participants were also presented with the Meyer (1988) Credibility Index, asking them to rate the information about side effects on a continuum of 1-5 regarding how trustworthy, accurate, fair, unbiased, and disclosed the information was.

7.4.4.3 Post tablet ingestion

7.4.4.3.1 Filler task

After taking the tablet all participants engaged in a series of filler tasks for one hour in order to standardise the time after participants took the tablet. These included the Rey auditory verbal learning test (Rey, 1941), a critical flicker fusion task, digital symbol test, category fluency test and a Stroop test.

7.4.4.3.2 Symptom reports

This was assessed similarly to the symptoms experienced in the past 24 hours, with a modified version of the generic assessment of side effects scale (Rief et al., 2009). The side effects listed were the same, and participants rated each symptom on a four point scale ranging from 0 “not present” to 3 “severe,” but they were also asked if any symptom they experienced was related to taking the tablet: “yes” or “no.” Scores range from 0-23 for the number of symptoms, and 0-69 for the severity of symptoms.

7.4.4.3.3 Guess at tablet identity

Participants were asked to give their best guess at what the tablet was and rate how confident they were about their answer, ranging from 1 “not at all confident” to 5 “completely confident.”

7.4.4.3.4 PIL reading behaviour

Participants were asked how often they read the accompanying PIL when taking new medication on a five point scale ranging from 1 “never” to 5 “always.”

7.4.4.3.5 Qualitative questions

Finally I used a series of qualitative questions to understand what participants were thinking during the study. These included questions asking whether they were ‘looking out’ for any symptoms after they took the tablet; why they attributed any symptoms to the tablet; what they thought the difference between the two leaflets could be; and what changes they would make to improve the risk information in the leaflet they read. Lastly I also asked whether their experience would affect their decision to take the tablet again, hypothetically.

7.4.5 Intervention

The intervention was based on positively framing side effect risk as a way to reduce participant’s expectations of side effects, making them less likely to occur. The intervention was delivered by means of a PIL printed on an A4 sheet of paper.

Participants could receive a standard worded PIL akin to those used in current practice, or the intervention PIL. As described in section 5.3 of Chapter 5 the leaflets were designed to be accurate for an inert tablet, providing information on what might be expected solely as a result of placebo or nocebo effects. As participants were not told what the tablet was, certain sections of the PIL were redacted, with text replaced by a single, large “X”; these included the sections: ‘What XXXXXXXX is and what it is used for,’ ‘other medicines and XXXXXXXX,’ ‘recommended doses,’ and ‘what XXXXXXXX contains.’ The only difference between the two leaflets was the ‘possible side effects’ section. The standard worded PIL followed current guidelines for describing side effect risk, e.g. ‘Common side effects (1 in 10 people will be affected).’ The intervention PIL applied positive framing to the risks, by rewording the verbal descriptor, presenting the number of people who would not be affected and using percentages which have previously been shown to elevate perceptions of likelihood compared to natural frequencies (Knapp, Gardner, et al., 2009). Refer to Chapter 5, Figure 5-1 to see the difference between the leaflets. For full copies of the leaflets used in the RCT see Appendix I.

7.4.6 Randomisation and masking

Randomisation was carried out by the King’s Clinical Trial Unit (KCTU) using randomly varying block sizes, stratified by gender. Participants’ details were entered onto an online randomisation system provided by KCTU after they gave consent and an email was immediately sent back to the researcher providing a unique envelope number to give to the participant. The envelope contained either the standard worded or positively framed PIL. The envelopes were opaque and were pre-packed and sealed in advance by a separate member of the team. I was blind to the contents of the envelope. Participants were not told the difference between the two leaflets.

7.4.7 Procedure

Participants were recruited between Dec 1, 2015 to Dec 5, 2016 through adverts on university circular emails and posts on GumTree. These adverts presented an outline of the study, inclusion criteria and an email address to contact us for further information. Interested participants were emailed an information sheet and screening questionnaire. The information sheet explained that the study aim was to “assess the severity of short-term side effects to a well-known tablet.” It explained that I could not tell participants what the tablet is or what it is used for as I “do not want to bias your views about it” and that the tablet would be referred to in written materials as “XXXXXXX.” The information sheet explained that the tablet has been shown to have beneficial effects for people and that no prescription is needed to take it. It stated that the tablet can cause short term side effects and that I wanted to assess how severe these side effects are. The information sheet also explained that as part of the study I would randomise participants to receive one of two PILs that have been developed for this tablet to see if they influence what people think about it. Participants were told that the only difference between the two PILs was small changes to the wording, but that I could not tell them what would be changed. This procedure minimised the amount of deception required in this study and was used in accordance with the principles of “authorised deception” (Miller, Wendler, & Swartzman, 2005).

Eligible participants arranged a time with the researcher to participate. After booking in at the reception of the clinical research facility, they were led to a fully equipped testing room (see Figure 7-1) where I double-checked the participants’ screening questionnaire. Participants were asked to give written consent. Given the nature of the research, consent was not fully informed, although participants were aware that information was being withheld from them. After providing consent, participants answered questions about demographics, recent symptoms and anxiety. Participants

were randomised to receive one of two leaflets about the tablet, which they read immediately. Participants then answered questions about the credibility of the information in the leaflets and their anxiety. Once these questions were completed participants took the tablet with water. The tablet was manufactured by Guy's and St Thomas Pharmacy and contained the inactive ingredients lactose, microcrystalline cellulose and magnesium stearate. It was round, white and had a breakline through the centre.

Over the next hour, participants completed a variety of vigilance and cognitive tasks, chosen to enhance the appearance that this was a formal clinical trial for a drug. In reality, data from these 'filler' tasks were discarded. Participants then completed questions about their symptom experience, their anxiety, and what they thought the tablet was. All participants received £40 for taking part via shopping vouchers or bank transfer.

After all participants had been tested, I contacted participants to explain the real nature of the study and to provide an opportunity to withdraw their data if they wished: none did. A summary of the procedure can be seen in Figure 7-2.

For a copy of the information sheet and consent form see Appendix J and K.

7.4.8 Outcomes

The primary outcomes included the number of participants who reported one or more symptoms which they attributed to the tablet; the number of symptoms attributed to the tablet; and the severity of symptoms attributed to the tablet.

In a change to the registered protocol, I also included satisfaction and credibility scores for the two leaflets as secondary outcomes.



Figure 7-1 Testing room.

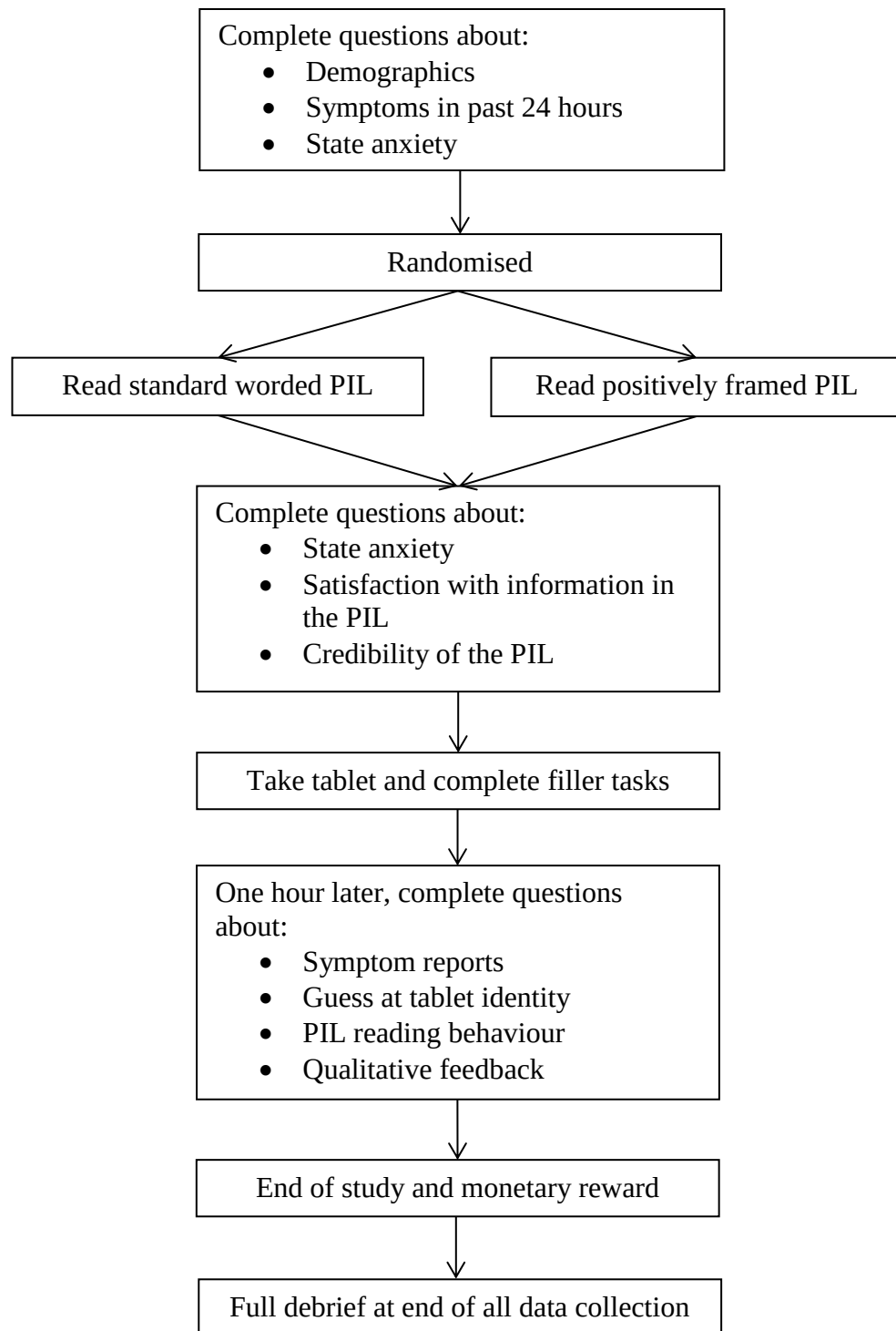


Figure 7-2 Participation procedure.

7.4.9 Analysis

7.4.9.1 Randomisation check

Participants in the experimental and control conditions were compared on all the dependent variables that should be unaffected by the manipulation to ensure that randomisation was successful. Thus, age, severity of symptoms in the past 24 hours,

baseline anxiety, and PIL reading behaviour were compared between the experimental and control conditions using Mann-Whitney U tests due to non-normal distributions. Number of symptoms in the past 24 hours was compared using negative binomial regression, due to being count data. Gender, ethnicity, education, employment, and PIL reading behaviour were compared using chi-squared tests. Ethnicity groups were collapsed into 'White' and 'other,' and employment into 'working' and 'not-working' to meet the requirements for minimum expected cell counts for carrying out a chi-square.

7.4.9.2 Primary outcomes

Following consultation with a biostatistician, in a change to the registered protocol I used a hurdle model to assess the effect of the intervention on number of participants attributing symptoms to the tablet and the number of symptoms attributed to the tablet. This consisted of a joint logistic and truncated negative binomial regression. This is a more powerful analysis to use for count data when there is an excess number of zeros than would be expected by a negative binomial regression. The logistic regression identified the effect of leaflet condition on the odds of participants experiencing symptoms as opposed to not experiencing symptoms, whilst the truncated negative binomial regression identified the effect of leaflet condition on the rate of symptoms attributed to the tablet. A truncated negative binomial regression was favoured to a truncated Poisson regression due to over-dispersion in the data. Due to the effect that baseline symptoms could have on symptom reporting at follow-up due to misattribution (Petrie et al., 2005; Petrie et al., 2004), we controlled for baseline symptoms in these analyses to give a more accurate result for the effect of leaflet condition on reported symptoms. As symptom severity was based on scale data, and had a non-normal distribution the effect of the intervention on the severity of symptoms that were attributed to the tablet were analysed using Mann-Whitney U tests. These analyses

were carried out three times, once for attributed symptoms mentioned on the PILs, once for attributed symptoms not mentioned in the PIL but appeared on the symptom questionnaire, and once for all attributed symptoms.

The three dependent variables were correlated with each other ($r = 0.69-0.98$, $p < .001$), and measured overlapping constructs. However, as the registered protocol stated the primary outcomes in advance, and in order of importance, I did not use a Bonferroni-type correction to adjust for the number of outcomes. There are concerns that Bonferroni corrections are too conservative and should not be used when primary outcomes are identified in advance (Perneger, 1998; Pocock, 1997).

7.4.9.3 Secondary outcomes

Due to non-normal distributions the difference in satisfaction and credibility scores between the PILs was examined using Mann-Whitney U tests.

7.4.9.4 Qualitative feedback

Participants' answers to the qualitative questions at the end of the study were analysed using thematic analysis to identify patterns in the data (Braun & Clarke, 2006).

7.4.9.5 Post-hoc analysis

Due to the influence that baseline anxiety has had on previous experimental studies in placebo research e.g. Withöft and Rubin (2013), I carried out a post-hoc analysis using logistic regression, controlling for the number of baseline symptoms to assess the interaction between the leaflets participants were randomised to receive and baseline anxiety to see if this influenced the odds of participants attributing any symptom to the tablet.

7.4.9.6 Excluded data

Because of a computer failure, which resulted in data for one participant being irretrievably lost, and because I excluded data from the first two participants who I used as pilot runs for the study, the clinical trials unit advised us to recruit an additional six

participants to ensure the eventual sample size would exceed 100 in each arm. Data for 203 participants were therefore included in the analyses. All analyses were carried out using SPSS version 24.0, apart from the hurdle model which was carried out using Stata version 15.

7.5 Results

7.5.1 Participant characteristics

The final sample contained 203 participants (see Figure 7-3 for a diagram of participant flow through the study). There were 101 participants who received the standard worded leaflet and 102 who received the positively framed leaflet. The mean age of the sample was 27.15 years and contained 65 males and 138 females with the majority of the sample being of White ethnicity (59.6%). For full baseline characteristics of the sample see Table 7-1.

Table 7-1 Baseline characteristics of the sample.

Variable	Standard worded leaflet (n = 101)	Positively framed leaflet (n = 102)	Total sample (N = 203)
Age	27.28 (8.69)	27.03 (8.61)	27.15 (8.63)
Number of baseline symptoms	2.38 (2.51)	2.81 (2.87)	2.60 (2.70)
Severity of baseline symptoms	2.65 (2.94)	3.24 (3.59)	2.95 (3.29)
Baseline anxiety	9.51 (2.58)	9.69 (2.84)	9.60 (2.71)
PIL reading behaviour	3.75 (1.24)	3.56 (1.13)	3.66 (1.19)
Gender			
Male	32 (31.7%)	33 (32.4%)	65 (32.0%)
Female	69 (68.3%)	69 (67.6%)	138 (68.0%)
Ethnicity			
White	65 (64.4%)	56 (54.9%)	121 (59.6%)
Other	36 (35.6%)	46 (45.1%)	82 (40.4%)
Education			
Secondary school	37 (36.6%)	34 (33.3%)	71 (35.0%)
Higher education	64 (63.4%)	68 (66.7%)	132 (65.0%)
Employment			
Working	45 (44.6%)	33 (32.4%)	78 (38.4%)
Not working	56 (55.4%)	69 (67.6%)	125 (61.6%)

Note: Data are mean (SD) or n (%).

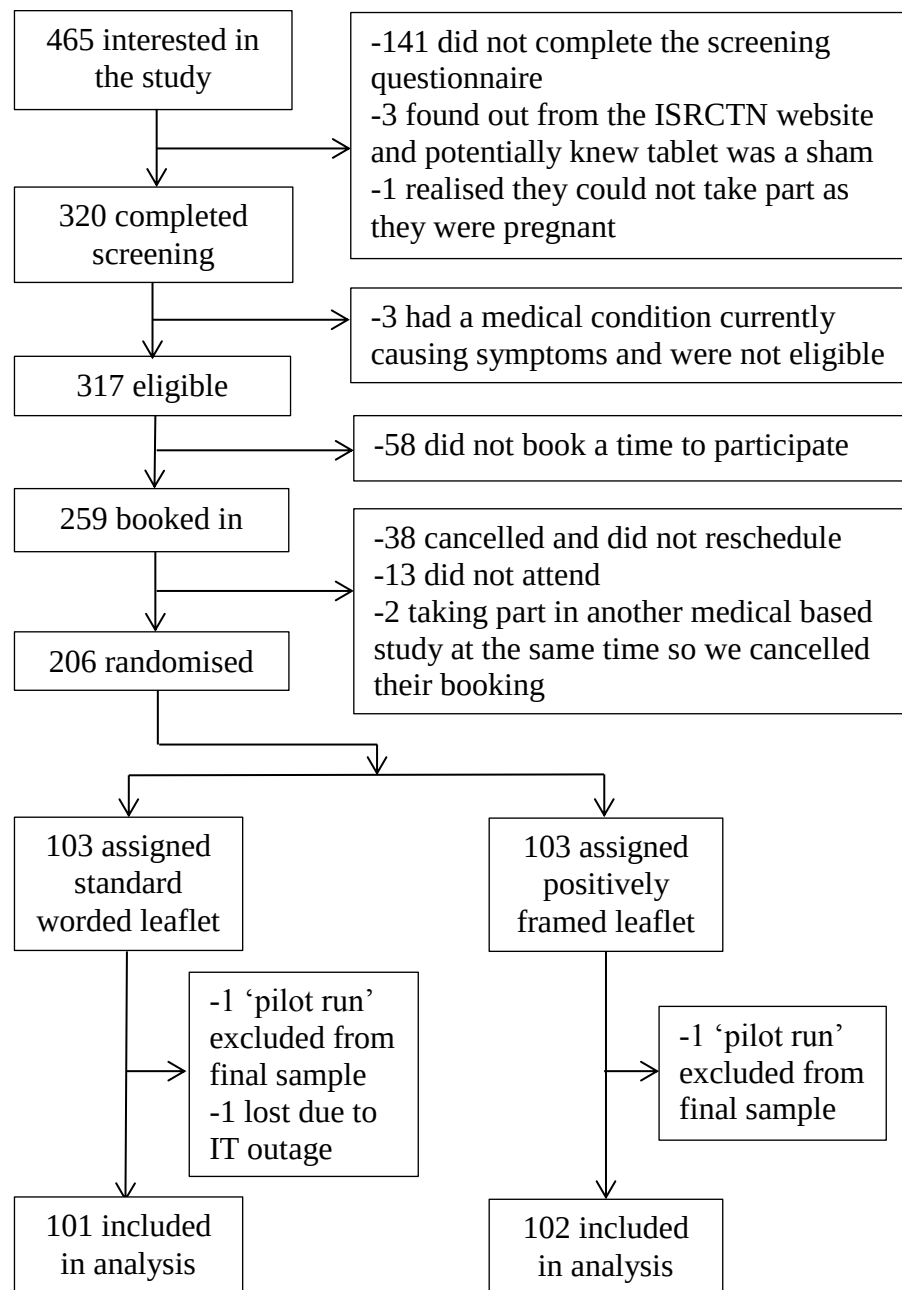


Figure 7-3 Participant flow through the study.

7.5.2 Randomisation check

All tests were non-significant. For age, severity of symptoms at baseline, and baseline anxiety, $U = 4583.5$ to 5080.0 , $p_s > .161$; for number of symptoms at baseline, Wald $\chi^2(1, N = 203) = 1.04$, $p = .307$; and for gender, ethnicity, education, employment, and PIL reading behaviour $\chi^2(1, N = 203) = 0.01$ to 3.19 , $p_s > .07$.

7.5.3 Primary outcomes: Side effect experience

Table 7-2 shows the results from the primary outcomes. Fifty-five (54.5%) participants who received the standard worded PIL experienced symptoms which they attributed to the tablet, compared with 40 (39.2%) participants who received the positively framed PIL, representing a significant difference and an odds ratio of 0.66, adjusting for number of baseline symptoms. Similarly, participants who received the positively framed PIL were significantly less likely to attribute symptoms mentioned in the PIL to the tablet than participants who received the standard worded PIL, with an odds ratio of 0.66 also. There was no difference in the odds of attributing symptoms not mentioned in the PIL to the tablet. There was no significant difference between the leaflets for the number (all p values > .067) and severity (all p values > .149) of symptoms reported that were attributed to the tablet, see Table 7-2.

7.5.4 Secondary outcomes: Satisfaction and credibility of the leaflet

There was no significant difference between the leaflets in terms of satisfaction with or credibility of the PILs (see Table 7-3). Both leaflets scored well for both outcomes. In addition there was no difference in anxiety scores after reading either leaflet.

7.5.5 Post-hoc analysis

For the post-hoc analysis there was no significant interaction between the leaflet type and participants' baseline anxiety scores, controlling for number of baseline symptoms, OR = 1.056, p = .054, 95% CI [0.999 to 1.116].

Table 7-2 The difference in symptom reporting between the two leaflets.

Outcome	Standard worded PIL (n = 101)	Positively framed PIL (n = 102)	Test*	Effect size (95% CI)
Symptoms mentioned in PIL				
Experienced	47 (46.5%)	33 (32.4%)	z = -2.25	OR = 0.66
Did not experience	54 (53.5%)	69 (67.6%)	p = .024	(0.46-0.95)
Number of symptoms	0.72 (0.92)	0.69 (1.06)	z = 1.83	RR = 1.22
			p = .067	(0.99-1.50)
Severity of symptoms	0.78 (1.05)	0.78 (1.43)	U = 4645.0	r = - 0.10
			p = .168	
Symptoms not mentioned in PIL				
Experienced	24 (23.8%)	22 (21.6%)	z = -0.52	OR = 0.90
Did not experience	77 (76.2%)	80 (78.4%)	p = .606	(0.61-1.33)
Number of symptoms	0.32 (0.65)	0.33 (0.71)	z = 0.73	RR = 1.09
			p = .467	(0.86-1.34)
Severity of symptoms	0.38 (0.83)	0.40 (0.95)	U = 5063.0	r = - 0.02
			p = .774	
Any symptoms				
Experienced	55 (54.5%)	40 (39.2%)	z = -2.35	OR = 0.66
Did not experience	46 (45.5%)	62 (60.8%)	p = .019	(0.46-0.93)
Number of symptoms	1.04 (1.22)	1.01 (1.73)	z = 1.45	RR = 1.19
			p = .148	(0.94-1.50)
Severity of symptoms	1.16 (1.46)	1.21 (2.14)	U = 4596.5	r = - 0.10
			p = .149	

Note: Data are n (%) or mean (SD), OR = Odds ratio, RR = rate ratio, PIL = patient information leaflet, * = all adjusted for number of baseline symptoms apart from symptom severity tests, r = Pearson's correlation which can be calculated from Mann-Whitney U output. 95% CI for r is not able to be calculated from Mann-Whitney U output.

Table 7-3 The difference in satisfaction and credibility scores between the two leaflets.

Outcomes	Standard worded PIL (n = 101)	Positively framed PIL (n = 102)	Test	Effect size
Satisfaction				
Leaflet was clear	4.0 (1.0)	4.0 (1.0)	$U = 5024.5$ $p = .730$	$r = -0.02$
Leaflet was easy to understand	4.0 (1.0)	4.0 (1.0)	$U = 4971.0$ $p = .617$	$r = -0.04$
Leaflet contained words I did not understand	1.0 (1.0)	1.0 (1.0)	$U = 5021.0$ $p = .718$	$r = -0.03$
Leaflet was similar to other leaflets	4.0 (1.0)	4.0 (1.0)	$U = 4934.5$ $p = .557$	$r = -0.04$
There was enough information to make an informed choice	3.0 (2.0)	4.0 (0.0)	$U = 5118.5$ $p = .932$	$r = -0.01$
There was sufficient information about the risks	4.0 (1.0)	4.0 (1.0)	$U = 4980.5$ $p = .642$	$r = -0.03$
Overall I am satisfied with the leaflet	4.0 (1.0)	4.0 (1.0)	$U = 4870.0$ $p = .451$	$r = -0.05$
Anxiety after reading the leaflet	9.0 (3.0)	9.00 (3.5)	$U = 5037.0$ $p = .783$	$r = -0.02$
Credibility				
Trustworthy	4.0 (1.0)	4.0 (0.0)	$U = 4691.0$ $p = .202$	$r = -0.09$
Accurate	4.0 (0.0)	4.0 (0.0)	$U = 5003.0$ $p = .690$	$r = -0.02$
Fair	4.0 (0.0)	4.0 (0.0)	$U = 5126.0$ $p = .946$	$r = -0.01$
Tells the whole story	3.0 (1.0)	3.0 (1.0)	$U = 5096.5$ $p = .892$	$r = -0.01$
Unbiased	4.0 (1.0)	4.0 (1.0)	$U = 4639.5$ $p = .191$	$r = -0.09$

Note: Data are median (IQR), pearson's correlation r has been calculated as an effect size from Mann-Whitney U output. 95% CI for r is unable to be calculated from Mann-Whitney U output.

7.5.6 Guess at tablet identity

Figure 7-4 shows the frequency of the different types of tablet that participants thought they had received. The confidence the participants had in their answers was very low, with the mean confidence score being 1.88 out of 5 for those participants who did not give an answer of 'Don't know.' About half (49.8%) of participants thought the tablet was an OTC pain killer such as paracetamol, ibuprofen, or aspirin. Only 9 out of

the 203 participants guessed that the tablet was a placebo, and the mean confidence of participants who guessed this was 2.22 out of 5.

7.5.7 Sensitivity analyses

Excluding the nine participants who guessed it was a placebo from the analyses did not change the outcome of any of the results, apart from the post-hoc analysis. In this instance for each one point increase in baseline anxiety score participants were 1.06 times more likely to experience symptoms if they received the standard worded PIL compared to the positively framed PIL. See Appendix L for full results of sensitivity analyses.

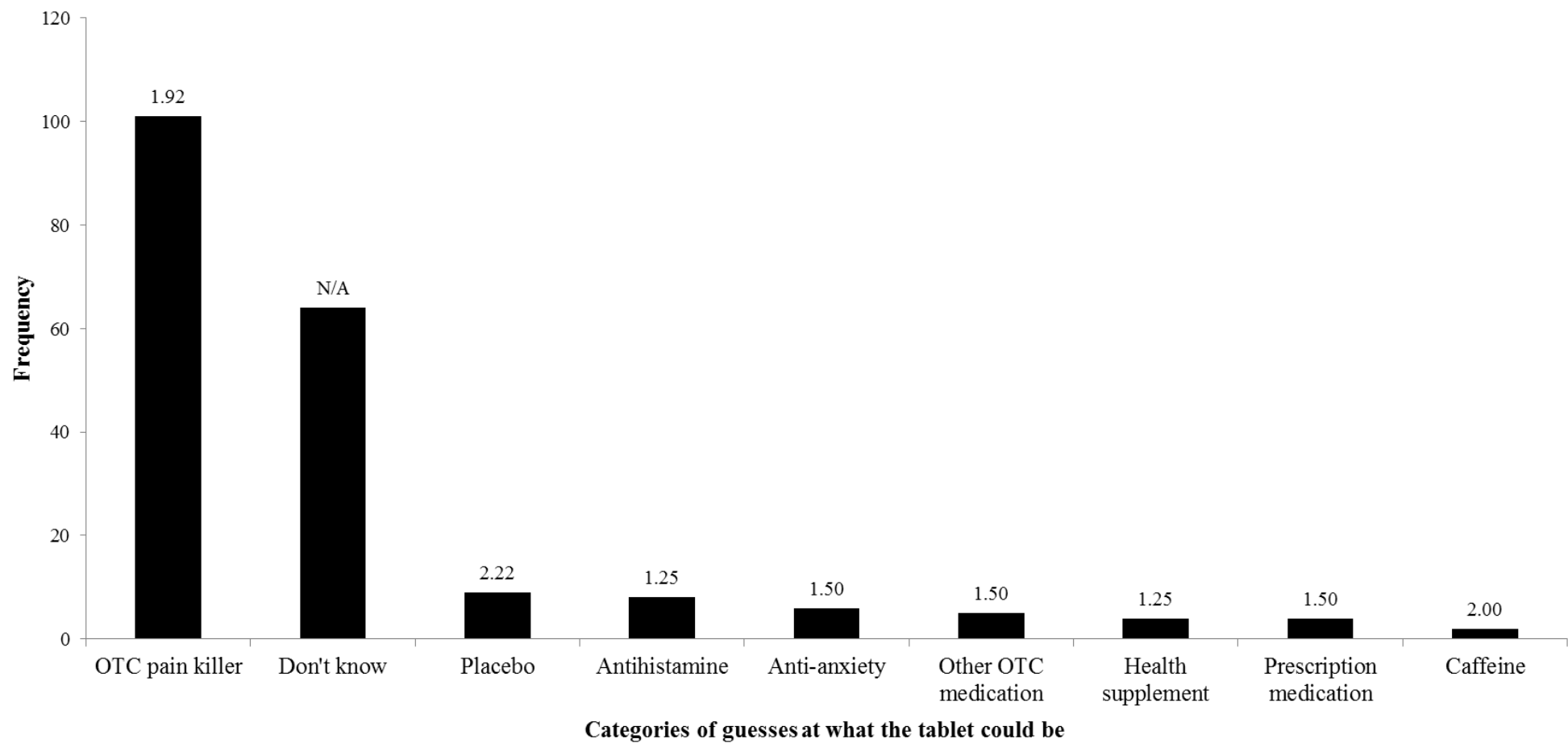


Figure 7-4 Frequency of participants' guesses as to what the tablet could be.

Note: The numbers on top of each bar represent the mean confidence of that category, rated from 1 (not at all confident) to 5 (completely confident), OTC = over-the-counter.

7.5.8 Qualitative feedback

Responses to the open-ended questions at the end of the study provided more insight into what participants were thinking during the study.

7.5.8.1 Symptom monitoring

The first of these questions asked if participants were ‘looking out’ for any symptoms after they took the tablet. Responses to this question fell into three different themes. Those that were continuously monitoring and checking how they were feeling.

“I was staying aware of how I was feeling throughout, and looking out for anything that was changing” (P215)

Those that were checking periodically.

“Not while doing the tasks, but in-between I was checking. In particular I was looking out for the side effects listed on the leaflet” (P324)

And those that were not looking out at all.

“No I wasn't looking out for any potential symptoms. Also I wasn't really thinking about how I was feeling. Thought I would notice if anything felt different” (P321)

The majority of participants were checking and monitoring how they were feeling periodically, either checking in-between tasks, when they remembered and/or when they were filling in the symptom reports at the end. For those that were not thinking about how they were feeling this seemed to be because they either thought they would notice if they started to experience a symptom without having to ‘check’ for it, or it was because they were too involved in the tasks.

7.5.8.2 Symptom attribution

For those who had experienced side effects which they attributed to the tablet, I asked them why they made this connection with the tablet. The reasoning behind

participants' attribution of their symptoms to the tablet fell into three themes. The first and most common reason given by participants was because of the timing.

"As appeared after taking the tablet and I didn't experience them before" (P258)

The second reason participants gave was due to it being unusual for them to experience such symptoms.

"Wouldn't usually experience these symptoms so thought it must have been due to the tablet" (P112)

The final reason was due to the information they had read.

"Because it was on the leaflet and one of the more likely side effects" (P213)

7.5.8.3 Difference between the leaflets

Participants were asked what they thought the difference might have been between the two leaflets, i.e. how the leaflet they received might have been different to the other leaflet they could have been randomised to receive. Most participants were not sure what the difference could have been.

"Didn't occur to me what might have been changed" (P305)

Apart from being unsure the second most common aspect of the leaflet that participants thought might have been altered was the side effect section, such as the way side effects were presented.

"There could be different wording for likelihood of side effects, and the other one might not have used statistics" (P203)

As well as this participants thought one of the main differences could be the complexity of the leaflet.

"Thought my leaflet was quite simple, more in layman terms. The other one might be more complex or scientific" (P213)

Other differences proposed by participants included the way the leaflet was formatted and the precautions

“Maybe the information would be laid out horizontally and the order of the information might have been different” (P335)

“More things to consult the Dr about before you take it. More warnings and precautions in the other leaflet” (P226)

7.5.8.4 Changes to improve the risk information

Most participants thought that the risk information in the leaflet they read was clear and detailed enough.

“There was sufficient information about the risks and it was clear” (P334)

Some participants explained that too much information can be a bad thing.

“No, it wasn't super lengthy but it was enough. Too much information becomes cloudy” (P276)

Some participants thought the side effect information could be clearer.

“Could be more specific about what actually is 'more than 1 in 10', e.g. is it 8 in 10 or 2 in 10”? (P259)

In addition some of those participants that got the intervention leaflet noted that it was too focused on the uncommon side effects.

“It was unusual it started at '80% won't get...', thought it might have missed out some of the more common side effects” (P170)

Other participants wanted more specific information about potential long term use effect, and general precautions before taking the tablet.

“More information on frequent usage - what could be the problem with prolonged use” (P181)

“Could have included information about potential interactions between medicines, e.g. warning if you are taking the pill. Also there was no guidance on age, e.g. is it ok for under 12s”? (P265)

Lastly some participants also mentioned more information about side effects in general would be helpful.

“More clear instructions about what are side effects, need more information rather than just list them. E.g. why could it give you headaches, and what happens in event of overdose” (P151)

7.5.8.5 Taking the tablet again

Most participants were happy to take the tablet again provided they needed it or it was to be recommended to them by their doctor or pharmacist.

“If I found out what the tablet was I would take again if suggested by my pharmacist” (P131)

For others there seemed to be a trade-off between their perceived need and their concerns about side effects.

“Depends, if the symptom or illness was a lot worse than the side effects then I would take it” (P299)

Some participants were put off from wanting to take it again due to their experience of side effects.

“No it is too powerful, makes you dizzy/tired. Also there are too many side effects that could happen” (P102)

Whereas others were put off from taking it as they did not experience any effects from the tablet.

“No, because not experienced side effects wouldn't think it would be strong enough to treat anything” (P106)

7.6 Discussion

7.6.1 Summary of main results

The results from this study show that positive framing of side effect information reduces the risk of participants experiencing symptoms which they attribute to a recently taken tablet. This reduction is clearly linked to the phrasing used in the leaflet – it applies only to those symptoms described in the leaflet and not to others. As such it also supports the role that expectations have in triggering nocebo effects (Hahn, 1997), supporting the findings in Chapter 2. The study also supports previous work showing the effectiveness of positive framing of side effect information in reducing side effect reporting following influenza vaccination (O'Connor et al., 1996). Importantly, despite previous claims that positive framing might be viewed with suspicion by patients (MHRA, 2005), there was no difference in participant satisfaction for the two leaflets or their perceived credibility, suggesting that the intervention could be straightforward to adopt in routine practice.

No difference was found for the total number or severity of symptoms attributed to the tablet. It seems that positively framing side effect information stopped people attributing symptoms to the tablet in the first place, however once a person did attribute a symptom to the tablet it did not help to limit the number or severity of the symptoms they attributed to the tablet.

Despite previous studies showing an interaction with anxiety (Witthöft & Rubin, 2013), no interaction was found between baseline anxiety and leaflet type. This was surprising as anxiety could play a part in nocebo effects in two ways, either directly, through misattributing the physical symptoms that feeling anxious generates (Kirsch, 1997b; Stewart-Williams, 2004), or through expectations as a result of symptom apprehension. It is possible that a lack of interaction could be explained by participants' low anxiety at baseline, and hence why re-analysing the interaction without participants

who guessed the tablet was placebo, showed a slight effect. Alternatively, given that in Chapter 2 anxiety did not come out as strong predictor of nocebo effects, it is possible that it is not be as important in predicting nocebo effects as originally thought.

7.6.2 Limitations

This was a well-controlled and adequately powered study, with both the participants and researcher blind to the experimental condition. However, one limitation inherent in the design was that participants were more focussed on monitoring themselves for symptoms than they might have been in daily life after taking a tablet. Although I attempted to reduce this effect by occupying participants with cognitive tasks after taking the tablet, the qualitative feedback did note that many participants were nonetheless monitoring how they were feeling during the tasks. This effect is likely to have raised levels of symptom reporting in both experimental conditions. In addition, it is possible that completing the filler tasks could have themselves caused symptoms, e.g. concentrating on the tasks may have encouraged headaches/fatigue. Alternatively, it is possible that some of the symptoms participants experienced could have been due to natural variation, and were not triggered by the sham pill. Future studies should address this limitation by including a control group who do not receive a pill.

Similarly to the pilot study, I also had more than one primary outcome. To guard against accusations of “cherry picking” significant results, the protocol for the trial including the three primary outcomes listed in order of importance was pre-registered on a publicly accessible database prior to the recruitment of the first participant. For future trials, to avoid this concern entirely, I will select only one primary outcome for the pre-registered protocol.

Other limitations include the fact that the sample was not representative of the general public, in particular being well-educated, with 65% having a higher education

qualification, and young, with a mean age of 27. Recruitment also took place via online platforms, which further increased the selectivity of the participants recruited. A less well-educated sample would have potentially been more or less susceptible to placebo effects. Also, as participants volunteered knowing that I was investigating side effects to a tablet, it is possible that those who volunteered were people who were generally trusting of medications or medical science. This can be seen by the low mean score in anxiety at baseline and also in participants' low perceived sensitivity to medicine. Given that all of these factors may reduce the likelihood of placebo effects occurring, the number of participants who attributed symptoms to the tablet, and the number and severity of these attributed symptoms is likely to be an underrepresentation compared to the general public.

Another limitation concerns the fact that I altered two parts of the side effect information in the intervention PIL – the numeric and verbal risk information. This was to produce the most effective intervention; however, it means I cannot tell if only one part is causing the effect or if there is a cumulative effect of the numeric and verbal information. Further study is needed to explore this.

Finally, in this study we chose to minimise the amount of deception required by informing participants that we would not tell them the identity of the tablet until after the study was completed, rather than providing them with a false cover story about the identity of the tablet. This procedure aligns with the principles of authorised deception (Miller et al., 2005) and, as the results demonstrate, is an effective way of triggering the placebo response. One additional positive feature of this procedure is that the results were not influenced by participants' idiosyncratic preconceived perceptions about the risks and benefits of any one specific medicine, while symptom expectations were kept uniform across participants by providing them with a PIL containing the essential details about their tablet. In real life, of course, patients usually are aware of the

medication they have taken, and the impact of the variables I assessed may not be as clear-cut.

7.6.3 Impact of deception

Although ethical issues are raised through the use of deception to elicit symptoms in participants, the information I gave to participants was accurate, in that it correctly conveyed what is known about placebo and nocebo effects. In addition I made participants aware that information was being withheld from them, thereby using an ‘authorised deception’ approach to consent. The method was well received by participants. At the end of data collection participants were emailed a debrief explaining the aims of the study and that the tablet was in fact inert. Sixteen participants replied and each expressed their thanks for receiving the debrief email. Their reaction to finding out the tablet was a placebo was positive, with participants surprised to find this out but still interested in the aim of the study. For example one participant said *“That is such an interesting study aim!! I laughed out loud when I learned I'd been given a placebo. Brilliant.”* And another exclaimed *“I have to say I was absolutely surprised by the fact that the pill I was given was actually a placebo! It was a very useful lesson for me as well as I have realised how powerful a placebo mechanism could be.”*

In addition participants were still keen to receive the final report once I had finished analysing the data and wished me luck with the rest of study, for example one participant said *“It sounds like fascinating research you’re doing – best of luck with analysing the results, I’d love to see the findings in due course.”* Not only this, participants were still happy to participate again in future studies with one participant saying *“Thank you very much for the opportunity of taking part in this study. I’m happy to participate again if it’s needed.”* No negative feedback was received.

7.6.4 Implications for clinical practice

The findings suggest that framing the risk of side effects in PILs positively in terms of those who will remain side effect free has the potential to reduce the risk of nocebo induced side effects that patients experience to their medications. There would be little financial cost to implementing the intervention, which could be easily introduced throughout the healthcare system. Importantly, as no information is withheld in positively framed leaflets, the intervention does not infringe a participants' ability to give fully informed consent, something which has been a concern about previous proposed interventions (Wells & Kaptchuk, 2012).

As evidenced from the qualitative feedback however, it is clear that some participants thought that the leaflet they read had missed out the more common side effects. These participants had obviously received the positively framed leaflet. To address this, perhaps leaflets using positive framing of side effects should also include a statement noting that it is common for patients not to experience any side effects. It is also important to note that although the intervention does reduce the chance of participants experiencing symptoms which they attribute to the tablet, in some instances it may be helpful for patients to attribute symptoms to their medication, for example when they have an allergic reaction or a genuine specific side effect that requires medical attention. In these cases it is important for patients to attribute these symptoms to their medication and seek medical attention. To encourage this, PILs should warn patients of specific side effects that would require them to seek medical attention.

7.6.5 Future research

Although this study provides good evidence for the efficacy of positive framing, additional research is still required to test the effectiveness of it in a more realistic situation, for example with patients prescribed a new medication. Two issues in particular require further attention. First, does positive framing reduce the likelihood of

patients reporting severe side effects to their physician? This would be undesirable if so. Second, is the intervention only effective in the short term? It is possible, for example, that over a longer period of time patients will forget the information in the leaflet, reducing the impact of the positive framing. Or a longer period of time could mean patients may be more likely to experience unrelated physical symptoms and misattribute them to the tablet. This part of the study only looked at the effect of framing on placebo responses, however, as mentioned in Chapter 2 from the results of the systematic review, it is also important to look at predisposing factors e.g. psychosocial factors, which will be investigated in Chapter 8. In addition it is important for future research to understand how the public interpret the current way we communicate side effects, which will be investigated in Chapter 9 and 10, to see if a change in this information is justified.

7.7 Conclusions

Nocebo induced side effects attributed to medications result in a significant cost to the NHS and to patients' quality of life. Positive framing of side effect information in PILs appears to be a cheap, effective intervention to reduce the risk of this occurring, and does not affect patients' ability to give fully informed consent. Future work is needed to assess the effectiveness in a more realistic setting.

Chapter 8 Predicting attribution of symptoms to a sham medicine

8.1 Introduction

Previous research has implicated expectations (Bingel et al., 2011; Hahn, 1997), learning (Van den Bergh et al., 1995; Vogtle et al., 2013) and misattribution of coincidental symptoms (Petrie et al., 2005; Petrie et al., 2004) as being important in explaining the occurrence of placebo effects. However, whether some people are particularly predisposed to experiencing a placebo effect remains unclear.

Several potential predisposing factors were reviewed in Chapter 2 including gender, anxiety, somatisation, somatosensory amplification, low optimism and baseline symptoms. The results of that review highlighted inconsistent findings with regards to the importance of these factors in predicting placebo responses.

There is a growing literature, however, concerning other potential predictors relating to medicine-related beliefs. These include people's beliefs about the necessity, harm and use of medicines, their perceptions of their own sensitivity to medicines, and their worries about the health effects of modern medicine, which can all work to increase people's expectations of side effects (Faasse & Petrie, 2013). These factors have previously been shown to be associated with patients' choice of medicine (e.g. complementary vs. conventional, or generic vs. branded) (Andersson Sundell & Jönsson, 2016; Figueiras et al., 2010; Petrie et al., 2001), their adherence to their medication (Horne, Chapman, et al., 2013; Menckeborg et al., 2008; Phatak & Thomas, 2006), as well as their information seeking behaviour (Faasse, Grey, Horne, & Petrie, 2015) and side effect reporting (Heller et al., 2015; Kaptein et al., 2005; Nestoriuc et al., 2010; Petrie et al., 2004; Rief et al., 2012). Given how prevalent these beliefs are, and the importance they have over patients' decisions and experiences in medical settings, it would be useful to look at the ability of these factors to predict placebo responses.

In order to understand whether some people are particularly predisposed to experiencing a placebo effect, as part of the RCT I tested several potential predictors for their association with the attribution of symptoms by healthy participants to a sham medicine. Identifying associations between these variables and symptom attribution might enable clinicians to tailor their interactions and the way they address potential side effects with their patients. It may also suggest new areas for interventions designed to reduce the likelihood of placebo effects.

8.2 Aims

To test whether the following potential predictors were associated with the attribution of symptoms by healthy participants to a sham medicine: a) demographics (gender, age, ethnicity, education, employment), b) psychological factors (anxiety, optimism, somatisation, somatosensory amplification), c) medicine related beliefs (modern health worries, beliefs about medicines, perceived sensitivity to medicines, trust in medicines and pharmaceutical companies), and d) symptom factors (previous symptoms and expected side effects).

8.3 Method

To avoid repetition a brief overview of the methods are presented here, for full methodological details see Chapter 7.

8.3.1 Design

This was a short prospective cohort study which formed part of the RCT as detailed in Chapter 7. Participants completed a variety of measures to see if these predicted whether they attributed symptoms to the tablet. This study was approved by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee at King's College London University (Reference number: PNM 14/15-62).

8.3.2 Participants

All participants who took part in the RCT were included in the analysis.

8.3.3 Sample size

The sample size calculation was based on identifying an effect on symptom attribution from the intervention tested in the RCT. The associations tested here are therefore exploratory.

8.3.4 Measures

For a copy of the full questionnaire and wording used see Appendix H.

8.3.4.1 Pre-tablet

8.3.4.1.1 Demographics

Participants were asked their age, gender, ethnicity, highest level of education and employment status.

8.3.4.1.2 Psychological factors

Somatosensory amplification was assessed using the Somatosensory Amplification Scale (Barsky, Goodson, Lane, & Cleary, 1988). This is a 10-item scale that measures the tendency to experience somatic sensations as intense, noxious, and disturbing. Participants rated the degree to which each statement is characteristic of them in general on a five point scale ranging from 1 to 5. The scores range from 10-50 with higher scores indicating greater somatosensory amplification.

Somatization was assessed using the Patient Health Questionnaire Somatic Symptom Severity Scale (Kroenke et al., 2002). This is a 15-item scale designed to measure the prevalence of the most common bodily symptoms (e.g. headache, nausea) experienced in the last four weeks. Participants rated each item on a three point scale ranging from 0 “not bothered at all” to 2 “bothered a lot.” The scores range from 0-30 with higher scores indicating greater somatization.

Dispositional optimism was assessed using the Revised Life Orientation Test (LOT-R) (Scheier, Carver, & Bridges, 1994). The LOT-R consists of six items (plus four filler items) which measures where participants lie on the pessimism-optimism

scale. Participants rated each item on a 5 point scale ranging from 1 “strongly disagree” to 5 “strongly agree.” The scores range from 6-30, with higher scores indicating greater optimism.

Anxiety was assessed using the state anxiety inventory – short version (Marteau & Bekker, 1992). This includes six items which participants rated on a four point scale ranging from 1 “not at all” to 4 “very much.” The scores range from 6-24 with higher scores indicating greater anxiety.

8.3.4.1.3 Medicine-related beliefs

Participant general beliefs about medicines were assessed using the overuse and harm general subscales of the Beliefs about Medicines Questionnaire (BMQ) (Horne et al., 1999). This included eight items (four relating to harm, and four relating to overuse) which participants’ measured on a 5 point scale, ranging from 1 “strongly disagree” to 5 “strongly agree.” The scores range from 4-20 with higher scores indicating greater perceived harm or overuse.

Perceived sensitivity to medicines was assessed using the perceived sensitivity to medicines scale (Horne, Faasse, et al., 2013). The scale includes 5 items assessing the extent to which people felt that they were sensitive to different aspects of medication rated on a five point scale ranging from 1 “strongly disagree” to 5 “strongly agree.” The scores range from 5-25 with higher scores indicating greater perceived sensitivity.

Worries about modernity was assessed using the 32 item modern health worries scale (Petrie et al., 2001) which assesses how concerned participants are about the effects of different aspects of modernity on their personal health. Such aspects include “overuse of antibiotics,” “cell phone towers.” Participants rated each item on a five point scale, ranging from 0 “no concern” to 4 “extreme concern.” The scores range from 0 to 128 with higher scores indicating greater worries about modernity.

8.3.4.1.4 Symptoms

A modified version of the generic assessment of side effects scale (GASE) (Rief et al., 2009) was used to assess participants' symptom experience in the past 24 hours. The GASE is used to assess side effects in clinical trials and supports the early detection of drug-induced adverse events. The side effects listed in the modified version were those commonly reported during a nocebo response (14 items) (Wells & Kaptchuk, 2012) or which were already listed on the GASE, detectable within an hour of taking the tablet, and not too serious (e.g. we removed "hair loss" from the list) (9 items). Participants rated each symptom on a four point scale ranging from 0 "not present" to 3 "severe." Scores range from 0-23 for the number of previous symptoms, and 0-69 for the severity of previous symptoms.

Symptom expectations were also assessed with a modified version of the GASE (Rief et al., 2009). The side effects listed were the same, however in this case participants were asked to state how likely they thought they were to experience the symptom in the hour after taking the tablet. Each symptom was rated on a 4 point scale ranging from 0 "not at all likely" to 3 "very likely." Scores range from 0-69 with higher scores indicating greater expectations of symptoms.

8.3.4.2 *Post-tablet*

8.3.4.2.1 Psychological factors

Anxiety was assessed again as before with the state anxiety inventory short version (Marteau & Bekker, 1992).

8.3.4.2.2 Medicine-related beliefs

Trust in medicine was assessed using three items regarding how much participants trusted the current process in which medicines were developed, tested and approved for use, rating each statement on a five point scale from 1 "strongly disagree" to 5 "strongly agree." The scores range from 3-15 with higher scores indicating greater

trust in medicine. Trust in pharmaceutical companies was assessed using two items concerning whether participants believed pharmaceutical companies acted in patients' best interests and if they are only interested in making money (reverse scored). Participants rated each statement on a five point scale from 1 "strongly disagree" to 5 "strongly agree." The scores ranged from 2-10 with higher scores indicating greater trust in pharmaceutical companies.

8.3.4.2.3 Symptom reports

This was assessed with the modified version of the GASE (Rief et al., 2009). This time, participants rated each of the 23 symptoms on a four point scale ranging from 0 "not present" to 3 "severe" and were asked if any symptom they experienced was related to taking the tablet – "yes" or "no." Scores range from 0-23 for the number of symptoms attributed to the tablet, and 0-69 for the severity of symptoms attributed to the tablet.

8.3.4.2.4 Guess at tablet identity.

Participants were asked to give their best guess at what the tablet was and rate how confident they were from 1 "not at all confident" to 5 "completely confident" about their answer.

8.3.5 Procedure

Questionnaires were completed during the course of the RCT reported in Chapter 7. After providing consent, participants answered questions about their demographic characteristics, recent symptoms, modern health worries, tendency for somatosensory amplification, belief about medicines, somatization, optimism, perceived sensitivity to medicines, and anxiety. Participants were then randomised to receive one of two leaflets about the tablet which they read immediately (as detailed in the previous Chapter). After reading the leaflet, participants completed questions about their anxiety and expectations of side effects. They then took the tablet with water and an hour later

completed questions about their anxiety, symptom experience, trust in medicine and pharmaceutical companies, and what they thought the tablet was. A summary of the procedure can be seen in Figure 8-1.

8.3.6 Outcomes

My primary outcomes included whether participants attributed one or more symptoms to the sham medicine and the number of symptoms participants attributed to the sham medicine.

Although I also considered analysing symptom severity as a third outcome, in practice this was not feasible. The severity data did not meet the assumptions for negative binomial regression analyses as it was not based on count data, nor did it meet the assumptions for linear regression due to its non-normal distribution. Whereas analysing severity data for the RCT involved simply comparing between two groups with a Mann-Whitney U test (with issues about confounding largely resolved by the use of randomisation), for the current analyses it would have been important to adjust for multiple demographic variables which is not feasible for a Mann-Whitney U. Moreover, the data on severity were very highly correlated with the number of symptoms participants reported and were therefore unlikely to have produced any additional insightful results. Given the high complexity and redundancy of the analysis, I did not analyse severity as an outcome.

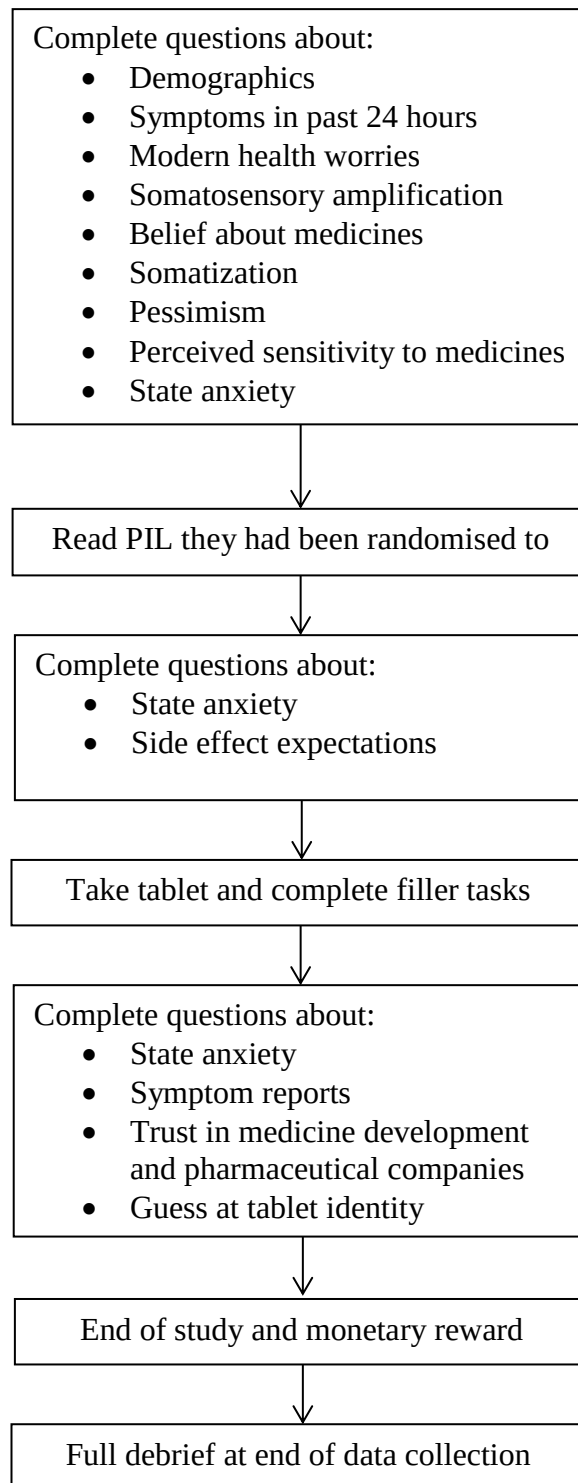


Figure 8-1 Participation procedure.

8.3.7 Analysis

I used a hurdle model fitted to the dependent variable of the number of symptoms attributed to the tablet (see Section 7.4.9.2 for a description of this approach). These analyses adjusted for gender, age, ethnicity, employment status, highest level of education and condition participants were randomised to. These variables were

controlled for due to suggestions in the literature that they can influence placebo responses (Bavbek et al., 2015; Hahn, 1997; Papadopoulos & Mitsikostas, 2012). Analyses were carried out using Stata 15.

8.4 Results

8.4.1 Participant Characteristics

The final sample contained 203 participants, 65 of whom were male, and 138 who were female (see Figure 7-2 in previous Chapter for a diagram of participant flow through the study). The mean age of the sample was 27.15 years with the majority of the sample being of White ethnicity (59.6%). For full baseline characteristics of the sample see Table 8-1.

Table 8-1 Baseline characteristics of the sample.

Variable	Total sample (N = 203)
Age	27.15 (8.63)
Number of baseline symptoms	2.60 (2.70)
Severity of baseline symptoms	2.95 (3.29)
Baseline anxiety	9.60 (2.71)
Gender	
Male	65 (32.0%)
Female	138 (68.0%)
Ethnicity	
White	121 (59.6%)
Other	82 (40.4%)
Education	
Secondary school	71 (35.0%)
Higher education	132 (65.0%)
Employment	
Working	78 (38.4%)
Not working	125 (61.6%)

Note: Data are mean (SD), or n (%)

8.4.2 Symptom attribution rates

Almost half of the participants (n = 95, 46.8%) attributed one or more symptoms to the tablet. The mean number of symptoms attributed to the tablet was 1.03 (SD = 1.49).

8.4.3 Primary outcomes: Associations with symptom attribution

Table 8-2 shows the association between the measures and whether participants attributed one or more symptoms to the tablet, and the number of symptoms they went on to attribute.

8.4.3.1 Demographics

Men had a 52% increase in the odds of attributing symptoms to the tablet compared to women. Older participants were less likely to attribute symptoms, with each increase of 1 year in age resulting in a 3% decrease in the odds of participants attributing symptoms to the tablet. There was no association between ethnicity, employment status or education level and attributing symptoms to the tablet. There was no association between any of the demographic variables measured and the number of symptoms attributed to the tablet.

8.4.3.2 Psychological factors

There was no effect of anxiety, optimism, somatisation or somatosensory amplification on the odds of symptom attribution. With regards to the number of symptoms attributed only anxiety scores after reading the PIL showed a significant effect with each increase in anxiety score being associated with a 6% increase in the rate of symptoms attributed to the tablet.

8.4.3.3 Symptoms

For baseline symptoms, each increase in the number of symptoms in the previous 24 hours was associated with a 7% increase in the odds of attributing symptoms to the tablet. There was no effect of the severity of baseline symptoms on the odds of symptom attribution. For each increase in participants' likelihood of expected symptoms there was a 6% increase in the odds of attributing symptoms to the tablet. Both number and severity of previous symptoms, and expected likelihood of symptoms was associated with the number of symptoms participants go on to attribute to the tablet.

Each one point increase in these variables was associated with a 4%, 4% and 3% increase in the rate of symptoms attributed to the tablet respectively.

8.4.3.4 *Medicine-related beliefs*

Each increase in modern health worries, belief that medicines cause harm and perceived sensitivity to medicine score was associated with a 2%, 10% and 9% increase in the odds, respectively, of participants attributing symptoms to the tablet. For each increase in participants' level of trust in medicine development and pharmaceutical companies there was a 9% and 12% decrease in the odds of participants attributing symptoms to the tablet respectively. There was no effect of these variables on the number of symptoms participants go on to attribute to the tablet, apart from modern health worries, which was associated with a 1% increase in the rate of symptoms attributed to the tablet.

8.4.4 Guess at tablet identity & sensitivity analyses

Re-running the analyses without the nine participants who guessed the tablet was a placebo (see Section 7.5.6) did not change any of the results from the adjusted analyses. See Appendix M for full results of the sensitivity analyses.

Table 8-2 Predictors of attributing one or more symptoms to the sham medicine, and the number of symptoms which are subsequently attributed.

Variable	No (%) or Mean (SD)	Symptom attribution		Number of attributed symptoms	
		Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
<u>Demographics</u>					
Gender					
Male	65 (32.0)	1.37 (0.94-1.99)	1.52 (1.02-2.25)	0.90 (0.71-1.16)	0.85 (0.66-1.09)
Female	138 (68.0)	†	†	†	†
Age	27.15 (8.63)	0.98 (0.96-1.00)	0.97 (0.95-0.99)	1.00 (0.99-1.02)	1.01 (0.99-1.02)
Ethnicity					
Other	82 (40.4)	0.93 (0.66-1.32)	0.91 (0.63-1.31)	0.89 (0.70-1.14)	0.89 (0.69-1.13)
White	121 (59.6)	†	†	†	†
Employment					
Working	78 (38.4)	0.97 (0.68-1.39)	1.16 (0.77-1.76)	1.11 (0.86-1.42)	1.16 (0.89-1.52)
Not working	125 (61.6)	†	†	†	†
Education					
School qualifications	71 (35.0)	1.23 (0.85-1.76)	1.11 (0.76-1.63)	1.05 (0.83-1.35)	1.15 (0.88-1.49)
University degree	132 (65.0)	†	†	†	†
<u>Experimental condition</u>					
Control leaflet	101 (49.8)	1.47 (1.04-2.08)	1.47 (1.03-2.10)	0.82 (0.64-1.01)	0.76 (0.60-0.97)
Positively framed	102 (50.2)	†	†	†	†
<u>Psychological factors</u>					
Anxiety before leaflet	9.60 (2.71)	1.01 (0.94-1.07)	1.01 (0.95-1.08)	1.03 (0.99-1.08)	1.03 (0.98-1.08)
Anxiety after leaflet	9.57 (2.51)	1.04 (0.97-1.12)	1.06 (0.99-1.14)	1.06 (1.02-1.11)	1.06 (1.01-1.11)
Anxiety 1 hour after taking tablet	9.14 (2.62)	1.04 (0.97-1.11)	1.05 (0.98-1.12)	1.03 (0.99-1.08)	1.03 (0.99-1.08)
Change in anxiety	-0.46 (2.34)	1.04 (0.96-1.12)	1.04 (0.96-1.12)	1.00 (0.96-1.05)	1.01 (0.97-1.05)
Optimism	14.80 (3.68)	1.02 (0.97-1.07)	1.02 (0.97-1.07)	0.99 (0.96-1.03)	1.00 (0.96-1.03)
Somatisation	4.18 (3.25)	1.04 (0.98-1.09)	1.05 (0.99-1.11)	1.03 (0.99-1.07)	1.02 (0.99-1.07)

Somatosensory amplification	23.52 (6.16)	1.02 (0.99-1.04)	1.03 (1.00-1.06)	0.99 (0.98-1.01)	0.99 (0.97-1.01)
<u>Symptoms</u>					
Number of symptoms in previous 24 hours	2.60 (2.70)	1.06 (0.99-1.13)	1.07 (1.00-1.15)	1.05 (1.01-1.10)	1.04 (1.00-1.09)
Severity of symptoms in previous 24 hours	2.95 (3.29)	1.04 (0.98-1.09)	1.05 (0.99-1.11)	1.05 (1.01-1.08)	1.04 (1.00-1.08)
Expected likelihood of symptoms	5.42 (6.03)	1.06 (1.03-1.10)	1.06 (1.02-1.09)	1.03 (1.01-1.05)	1.03 (1.01-1.05)
<u>Medicine-related beliefs</u>					
Modern health worries	25.82 (20.37)	1.01 (1.00-1.02)	1.02 (1.01-1.03)	1.01 (1.00-1.01)	1.01 (1.00-1.01)
BMQ overuse	10.91 (3.28)	1.01 (0.96-1.07)	1.03 (0.97-1.09)	1.02 (0.98-1.06)	1.01 (0.98-1.05)
BMQ harm	7.94 (2.68)	1.06 (0.99-1.07)	1.10 (1.02-1.08)	1.01 (0.97-1.05)	1.00 (0.95-1.05)
Perceived sensitivity to medicines	7.26 (2.81)	1.07 (1.00-1.14)	1.09 (1.02-1.17)	1.01 (0.97-1.04)	0.99 (0.96-1.03)
Trust in medicine development	11.72 (2.10)	0.92 (0.85-1.00)	0.91 (0.83-0.99)	0.96 (0.91-1.01)	0.97 (0.92-1.02)
Trust in pharmaceutical companies	5.42 (1.63)	0.87 (0.78-0.98)	0.88 (0.79-0.98)	0.92 (0.85-1.00)	0.93 (0.86-1.01)

Note: * Controlling for gender, age, ethnicity, employment, education and experimental condition using logistic regression, OR = Odds ratio, RR = Rate ratio, BMQ = belief about medicines questionnaire, † = Reference category, bold = significant at p<.05

8.5 Discussion

8.5.1 Summary of main results

This study suggests that several factors may predispose people towards experiencing a placebo effect after taking a new medication. In terms of demographic predictors, men were more likely to attribute symptoms to the tablet than women. This is despite previous findings from the systematic review in Chapter 2 suggesting no robust evidence for an effect of gender on placebo responses. This might have been due to the way that placebo effects were induced. It may be that men are specifically susceptible to placebo effects induced through information which alters expectancies, something which has been shown previously by Klosterhalfen et al. (2009). In addition, despite previous evidence in the systematic review showing no effect of age in predicting placebo effects, this study found older participants had decreased odds of experiencing placebo effects than younger participants. It is unclear why this should be so, particularly as the age range was not very large ($SD=8.63$). Interestingly gender and age did not affect the number of symptoms participants go on to attribute to the tablet, suggesting they play more of a 'predisposing' role rather than affecting the intensity of a placebo response. Other demographic factors such as education or employment status showed no effect, supporting the results from the review.

In terms of psychological characteristics, there was only an association between anxiety scores after reading the PIL and the number of attributed symptoms, similar to previous findings in Chapter 2 showing a weak effect of anxiety. It is surprising that anxiety levels only affected the number of symptoms attributed and not the odds of participants attributing symptoms to the tablet. It is possible however, that in this case the lack of an association with anxiety and the odds of symptom attribution reflected the generally low levels of state anxiety seen in this sample, which in turn probably reflected the voluntary nature of the experiment. Higher levels of anxiety, and a

different pattern of results, might be seen among patients for whom a medication is necessary, rather than voluntary.

More general personality characteristics such as optimism, somatisation and somatosensory amplification did not show any significant associations supporting the inconsistent effects seen for these factors in Chapter 2. However, beliefs that directly concerned medication such as a belief that medicines cause harm, modern health worries, perceived sensitivity to medicines, trust in medicine development, and trust in pharmaceutical companies were associated with the odds of symptom attribution. Attempts to predict and prevent nocebo responses might therefore be better directed at attitudes related to medicine rather than on more dispositional factors. It is interesting that these factors (apart from modern health worries) did not affect the number of symptoms attributed. This may be because they do not have much weight in affecting the intensity of a nocebo response, or it could be because my sample consisted of healthy individuals who are unlike most people that take medications. This reduces the ability to detect the influence of potential psychological predictors which may show more variation in less healthy samples.

The fact that participants with more symptoms at baseline were more likely to attribute symptoms to the tablet, and then go on to attribute a higher number of symptoms to the tablet adds support to the theory that many nocebo effects could be due to misattribution of coincidental symptoms (Faasse & Petrie, 2013; Petrie et al., 2004). The more symptoms a participant has at baseline the more opportunity there is for one of these symptoms to be misattributed as a symptom caused by the tablet. In addition participants with higher expectations of developing side effects from the tablet were more likely to attribute symptoms to the tablet, and then attribute a higher number of symptoms to the tablet, supporting the role that negative expectations play in generating nocebo effects (Barsky et al., 2002; Hahn, 1997).

8.5.2 Limitations

Many of the limitations of this study have been discussed in Chapter 7. For the results reported here there are some additional limitations. Firstly, the sample size calculation for this study was based on the requirements of the linked RCT, rather than the ability to assess associations between baseline measures and symptom attribution. This is, however, one of the largest studies to date to have examined these effects on symptom attribution, as previously noted from the results of the systematic review in Chapter 2. It is also useful as an exploratory piece of research to get an understanding of what is important in predicting nocebo responses to allow future research to expand on.

Secondly, the sample had very unequal numbers of male and female participants, and the age distribution was limited. Because of this it is harder to reliably interpret the effect of these factors on symptom reporting. Future studies ideally need to be more representative of the general public in terms of the proportion of males and females, and age distribution.

Thirdly, trust in medicine and pharmaceutical companies was measured after participants had taken the pill. As such the results for these variables in particular should be interpreted with caution.

8.5.3 Implications for clinical practice

Although many predictors only showed small effect sizes, given how common nocebo induced side effects can be, any way to reduce them may result in a large impact at a population level. Patients with high expectations of side effects, negative beliefs about medicines, low trust in pharmaceutical companies or the way in which medicines are developed, or high perceived sensitivity to medicines may particularly benefit from reassurance by clinicians or interventions aimed at correcting any unrealistic beliefs or expectations they may have about their medication. This has previously been shown to be feasible by Petrie, Perry, Broadbent, and Weinman (2012) who sent individually

tailored text messages to asthma patients based on their illness and medication beliefs. They found that compared to a control group the test message intervention increased their perceived necessity of preventer medication, their belief in the long-term nature of their asthma, and their perceived control over their asthma (Petrie et al., 2012).

8.5.4 Future research

To allow clinicians to identify patients at risk of side effects, it is important for future research to replicate the investigation of baseline predictors of placebo effects preferably in a patient sample to confirm if the factors found in this study are important in predicting the attribution of non-specific symptoms to a real medication. This would also be useful to shed more light on whether there are different factors that affect someone being a placebo responder or not in a given situation, or the intensity of a placebo response. It is also important for future research to try and establish what the nature of the role of gender is in placebo effects. Due to the extensive literature on gender differences in symptom reporting (van Wijk & Kolk, 1997), it has often been assumed that women are more susceptible to placebo effects than men. However my review found no evidence for this and the trial actually showed men were more susceptible. It may be that women are more susceptible to placebo effects that are generated through social mechanisms such as social observation, as is supported in the literature (Faasse, Grey, Jordan, et al., 2015; Lorber et al., 2007), whereas men may be more susceptible to placebo effects which are generated through information which can alter expectations through more cognitive mechanisms (Klosterhalfen et al., 2009), such as PILs. Further research is needed to decipher this relationship.

In addition future research can use these findings to help develop different interventions. For example as low trust in medicine and pharmacy is a problem, an intervention to improve patients trust in this area could be beneficial to reduce the risk of placebo responses to medicines. As well as this as current symptoms can be readily

misattributed to medicines, interventions designed to talk about current symptoms, getting patients to acknowledge them e.g. through a symptom diary and warn of misattribution could be useful too.

8.6 Conclusions

The results from this study suggest that it is hard to predict who is at risk of developing placebo responses to their medicines just from their general demographics or personality. Instead the results suggest we should be looking at more specific factors relating to their beliefs about the supposed exposure. In addition we should also take into account the number of symptoms they are experiencing before they are exposed and their side effect expectations. Future work is needed to investigate these factors in a patient sample and to decipher the relationship between gender and placebo effects.

Chapter 9 People's understanding of verbal risk descriptors in patient information leaflets

9.1 Introduction

The RCT reported in Chapter 7 showed that positive framing of side effect information can help reduce nocebo effects. However, as this involves changing the way we communicate side effect risk in PILs it was important to understand whether such changes are fully justified. While changes to the wording in order to reduce nocebo effects might be worthwhile, if the current wording is well understood by patients, changing it might arguably be seen as too risky by the MHRA, EC and pharmaceutical industry. In the study described in this Chapter, I investigated how people interpret the current verbal risk descriptors used in PILs, as well as alternatives, to see how well members of the public understand current descriptors, or alternatives to them, based on the same basic approach.

Medicines are the most common form of healthcare intervention, therefore providing patients with information that allows them to make an informed choice about their treatment is important, as addressed in the National Plan for the NHS (2000). Of this information, that relating to side effects has been found to be the most important for patients and has the most influence on their decisions regarding whether or not to take a medicine (Grime, Blenkinsopp, Raynor, Pollock, & Knapp, 2007). As such, Europe's medicine legislation in 1992, overseen by the European Medicines Agency stipulated that all medicines prescribed in each of the 27 member states must be distributed with a comprehensive PIL, supplied as a package insert, which is required to present the risk of potential side effects in "clear and understandable terms for the patient" (EC, 1992).

An EC guideline in 1998 suggested grouping adverse effects within a PIL according to five frequency bands, each described using one of five verbal terms (EC, 1998). This way of quantifying the risk of adverse reactions was originally suggested by

the Council for International Organizations of Medical Sciences Working Group III (1995), and therefore is also applicable outside the European Union.

These five terms were:

- Very common (More than 1 in 10)
- Common (Up to 1 in 10)
- Uncommon (Up to 1 in 100)
- Rare (Up to 1 in 1000)
- Very rare (Up to 1 in 10,000)

However, it is important to note that the EC recommended risk expressions were not based on systematic empirical evidence (Knapp et al., 2015). This is a concern as there are large individual differences in people's interpretation of terms used to describe risk probability (Mazur & Merz, 1994; Reagan, Mosteller, & Youtz, 1989). If patients incorrectly interpret the EC recommended verbal risk descriptors, they may misjudge the risk associated with a medicine, affecting their decision whether to take the treatment (Berry, Raynor, Knapp, & Bersellini, 2003).

Since these guidelines were published many studies have set out to evaluate the usefulness of the EC guideline descriptors, and as anticipated they have proved to be problematic (Büchter et al., 2014; Zipkin et al., 2014). In a sample of 268 students from Reading University, participants were asked to estimate the percentage of the population (or the number of people out of 10 000) for each of the five verbal risk descriptors. The results showed that the students massively overestimated the risk associated with each of the five descriptors. On average, very common was given the percentage 64%, common – 45%, uncommon – 18%, rare – 8%, and very rare – 4% (Berry, Raynor, & Knapp, 2003). A similar study with the general population has been carried out just looking at the verbal risk descriptor 'very common' (Berry et al., 2002) and again showed this to be associated with a risk of 64%, as opposed to the EC intended

probability of 10%. In another study in the UK looking at the verbal risk descriptors ‘common’ and ‘rare,’ only 7 out of 180 participants provided probability estimates that fell within the correct EC guidelines frequency range (Berry, Raynor, & Knapp, 2003). In part, estimations seem to depend on side effect type with ‘mild’ side effects given higher estimations than ‘severe’ side effects when described as ‘common’ or ‘rare’ (Berry, Raynor, & Knapp, 2003).

Although these results have all come from studies examining hypothetical situations, studies with patients (Berry, Raynor, Knapp, et al., 2003; Knapp, Berry, & Raynor, 2001) and parents presented with verbal descriptors for the side effect risk of the child flu vaccine (Smith et al., 2017) have resulted in similar findings. And it is not only patients or members of the public who overestimate the probability estimates for verbal risk descriptors. Research with doctors, pharmacists and lawyers (Berry, Holden, & Bersellini, 2004; Ziegler, Hadlak, Mehlbeer, & Konig, 2013) show that they overestimate the risk of verbal risk descriptors too, although not to the same extent as non-medically trained participants. For example, doctors generally assume that 46% of patients will experience a ‘common’ side effect, as opposed to 65% as assumed by participants with no medical training (Berry et al., 2004).

These studies have limitations, often being based on small samples which are not representative of the general population. No study so far has used a national representative sample. Nonetheless, in reaction to these studies, in 2009 the EC updated its guidelines and now recommends that risks are conveyed by combining each of the five verbal terms with a numerical frequency to form combined expressions, e.g. ‘very common, (more than 1 in 10 people)’ (EC, 2009). The MHRA also suggests this approach in their recommendations to medicine license holders (MHRA, 2005).

However, again this guidance for the use of a combined risk expression is not evidenced based, and there is concern that inclusion of a verbal term may still lead to

overestimation (Knapp et al., 2015). In a sample of 339 people visiting the Cancer Help UK website, Knapp et al. (2015) evaluated the full range of combined verbal and numerical risk expressions recommended in the EC guidance and demonstrated that they can lead to significant risk overestimations when compared to numerical frequency bands alone. In addition Knapp, Raynor, et al. (2009) in sample of 187 participants from the Cancer Research UK website revealed that the combined format did not lead to more accurate side effect risk estimates than the verbal format in four of the six instances where participants were asked to estimate the risk of side effects.

Therefore, it might be argued that it is preferable to represent side effect risk in terms of numerical frequencies only rather than combining verbal and frequency band descriptors. And indeed, the draft revision of the 1998 guidelines no longer makes reference to the use of verbal risk descriptors (EC, 2006). However, verbal risk descriptors may still have a place in the presentation of side effect risk; they can break up long lists of side effects into more manageable sections based on occurrence frequency, they can convey the uncertainty of risk, and some people are more comfortable with verbal rather than numerical information (Knapp, Gardner, et al., 2009). It is possible, that the problem is simply in identifying the right verbal descriptors.

9.2 Aims

The aim of this research was to carry out the first study in this area that is demographically representative of the English population to find out how they interpret the current verbal risk descriptors used in PILs, as well as two sets of alternative verbal risk descriptors. I also sought to identify whether there are demographic or psychological factors that make individuals more likely to estimate the numerical risk represented by these descriptors in accordance with the EC frequency bands. Psychological characteristics such as beliefs about medicines, optimism or perceived

sensitivity to medicines are associated with medicine side effect expectations (Faasse & Petrie, 2013; Geers, Helfer, et al., 2005) and may also affect how people perceive the risk information about medication.

In this study, I used a large cross-sectional survey of a representative sample of 18 to 65 year olds in England in order to:

1. Assess how people interpret the risk associated with the EC recommended verbal risk descriptors and two sets of alternative verbal risk descriptors.
2. Investigate if people interpret the risk associated with verbal risk descriptors differently depending on whether they describe a mild or severe side effect.
3. Determine whether demographic and/or psychological factors are associated with correctly interpreting the risk implied by the EC recommended verbal risk descriptors.

9.3 Method

9.3.1 Design

The market research company Ipsos MORI was commissioned to conduct an online survey of adults aged between 18 and 65 living in England. Data collection took place between 18th March and 1st April 2016. This study was approved by the Psychiatry, Nursing and Midwifery Research Ethics Committee at King's College London (ref: HR-15/16-2104), see Appendix N for a copy of ethical approval.

9.3.2 Participants

Ipsos MORI recruited participants from an existing panel of people willing to take part in internet surveys living in England (approximate n=160,000). I excluded over 65s due to the strong likelihood of bias within the responses of participants in this age group. Older adults who are members of an internet survey panel are not representative of the general population of older adults. Only 71% of individuals aged 65- 74, and 33% of those over 75 are frequent internet users as noted by the Office for

National Statistics (2015). This compares to 87% to 99% for younger age groups. As a result, older adults who do use the internet regularly and sign up for online survey panels show greater bias in their responses than participants in other age groups (Pew Research Center, 2015).

9.3.3 Sample size

Quotas based on participant age and gender (interlocked), location, and working status were used to ensure that the sample reflected the known demographic profile of adults aged 18-65 in England, according to data from the National Readership Survey (2015). I intended to recruit 1,000 participants to provide a sample error of about plus or minus 3% at the total sample level.

9.3.4 Questionnaire development

Where possible, I included or adapted items that had been previously developed and tested for their reliability and validity, and that have been widely used in the literature. Using opportunity sampling I piloted all items with five members of the general public who read through the questionnaire with me and identified anything that was not clear. I rephrased items where necessary to improve clarity. The full wording for all items used in the survey, are given in the Appendix N.

9.3.5 Measures

9.3.5.1 Verbal risk descriptor probability estimates

I included several items to assess participant understanding of risk descriptors. These asked people to consider a PIL for an unnamed drug which stated, for example, that “nausea is common.” Items then asked participants to estimate how many out of 10,000 people who take the drug would develop that side effect. I chose a consistent denominator for each item to prevent confusion among participants had denominators changed in each question. To prevent the need for participants to give responses of less than 1, I decided that a denominator of 10,000 would be needed. This choice to get

participants to use numbers is supported by (Schwartz & Woloshin, 2013) who argue that despite concerns people do not understand the use of numbers, representative populations are competent in using numbers as a decision aid for choosing between two drugs (Schwartz, Woloshin, & Welch, 2009).

Participants were asked about either mild side effects ('headache' or 'nausea') or severe side effects ('seizure' or 'difficulty breathing') depending on which condition they had been assigned to. I used the EC recommended descriptors 'very common,' 'common,' 'uncommon,' 'rare' and 'very rare' supplemented with the terms 'very uncommon' and 'extremely rare.' I also included other terms used in the risk communication literature (Beyth-Marom, 1982; Johnson, 1973; Lichtenstein & Newman, 1967) which could be combined into similar scales based on likelihood (very likely, likely, somewhat unlikely, fairly unlikely, very unlikely, extremely unlikely) and chance (very high chance, high chance, fair chance, low chance, very low chance, extremely low chance). Verbal risk descriptors were presented in a random order to participants.

9.3.5.2 Demographic factors

I asked participants about their: age, gender, ethnicity, highest level of education, employment status and whether they or anyone in their household had a long-standing illness, disability or infirmity.

9.3.5.3 Psychological factors

I adapted the single item literacy screener (Morris, MacLean, Chew, & Littenberg, 2006) assessing health literacy and asked participants to rate how often they needed help reading PILs, and included one item which asked how often they read PILs when taking a new medication. Both were rated from 1 "never" to 5 "always". I used one item from the health anxiety inventory (Salkovskis, Rimes, Warwick, & Clark, 2002) to assess health anxiety which asked participants to select one of four statements

describing their feelings over the past six months. These ranged from 1 “I do not worry about my health” to 4 “I spend most of my time worrying about my health.”

I assessed optimism using the LOT-R (Scheier et al., 1994) which consists of six items (plus four filler items) giving a total score from 6 to 30 with higher scores indicating higher optimism.

Participant general beliefs about medicines were assessed using the overuse and harm general subscales of the BMQ (Horne et al., 1999), providing scores from 4 to 20 for each subscale, with higher scores indicating higher perceived overuse or harm.

Finally, how sensitive participants thought they were to medicines was assessed using the Perceived Sensitivity to Medicines scale (Horne, Faasse, et al., 2013), giving a score from 5 to 25 with higher scores indicating higher perceived sensitivity.

9.3.6 Procedure

Potential participants were emailed a link to the survey. After providing informed consent and clicking through to begin the survey, participants were allocated to receive questions about either mild or severe side effects. This was decided by the survey software based on which condition had the lowest number of completed responses at that time. Panel participants typically receive points for every survey they complete: for my survey, participants received points equivalent to 75 pence. See Appendix P for a copy of the information sheet and consent.

9.3.7 Outcomes

The primary outcome was participants’ probability estimates for each of the verbal risk descriptors.

The secondary outcomes included the effect of side effect type, demographic psychological factors on participants’ probability estimates.

9.3.8 Analysis

I grouped participant side effect frequency estimates into the same bands as those suggested for use by the EC guidelines (EC, 1998) and produced histograms to show the frequency with which each band was selected for each verbal risk descriptor.

I carried out a series of Mann-Whitney U tests to test if participants' median estimates differed between mild and severe side effects.

I used a series of multinomial logistic regressions to test if any demographic or psychological characteristics were associated with participants under, over or correctly estimating the numerical risk associated with the EC recommended verbal risk descriptors. Participants' numerical risk estimates were first recoded as an under, over or correct estimate for each descriptor. For the verbal risk descriptors of very common and very rare (where it is not possible to overestimate or underestimate respectively), binary logistic regressions were carried out instead. For each of the regressions, all demographic variables and side effect type (mild or severe) were added to the regression in one block, and each psychological variable was added on its own, controlling for the previously entered variables.

For all analyses, answers of 'don't know' or 'prefer not to say' were excluded. A maximum of 3% of participants answered 'don't know' for any one question where this was an option, and 1% for 'prefer not to say.' All analyses were carried out using SPSS 22. Because the frequency of participants' side effect numerical estimates for each of the verbal risk descriptors did not change by more than 0.2% when using data weighted by age, gender, region and working status, I used unweighted data for the analyses.

9.4 Results

9.4.1 Sample characteristics

1003 participants completed the survey and were included in the final sample (see Figure 9-1 for response rates). Demographic information for the participants is given in Table 9-2.

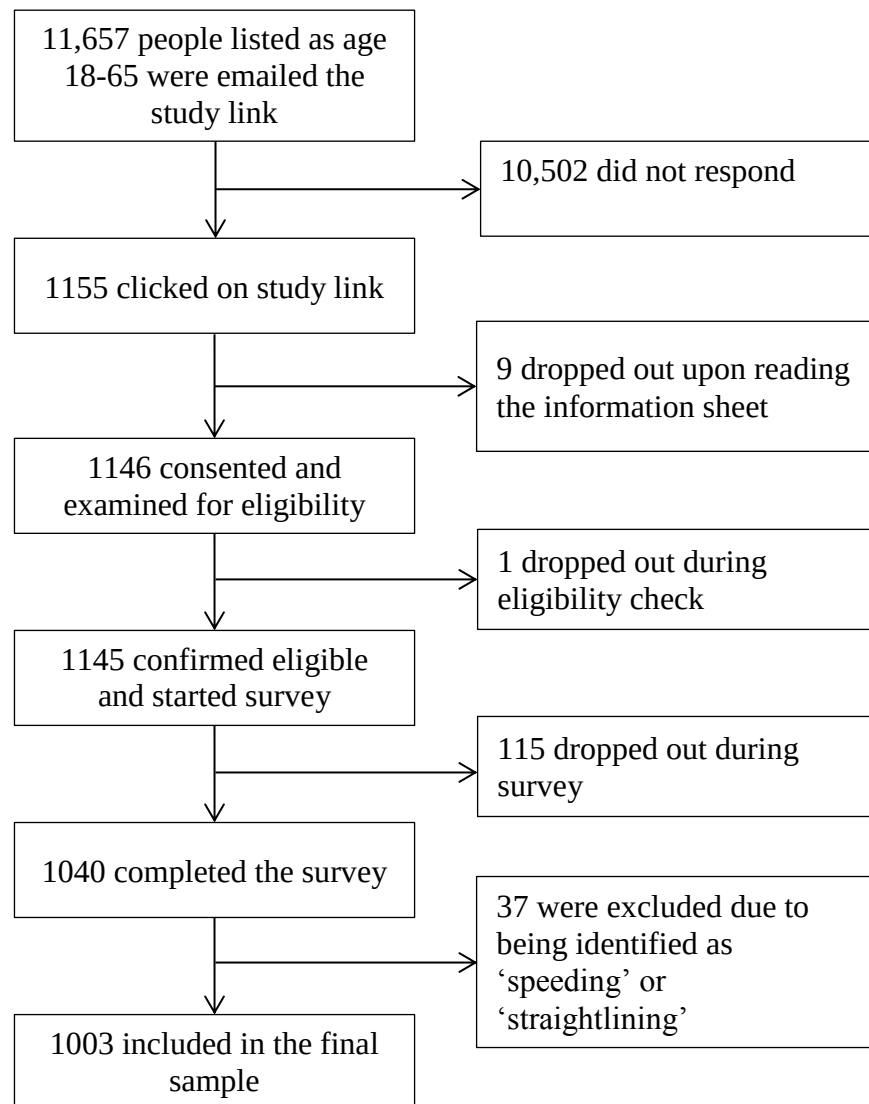


Figure 9-1 Participant flow through the survey.

Note: Eligibility check was used to confirm participants' age in case this had changed since they were emailed the link

* Completing the survey too quickly to have given genuine, considered answers, or providing identical answers to five or more consecutive questions where this was possible.

9.4.2 Primary outcome: People's interpretation of the different verbal risk descriptors

Figure 9-2 shows the frequency of participants' numerical risk estimates for each verbal risk descriptor. Two distinct distributions were apparent; those for 'high risk' verbal descriptors which portrayed a side effect as 'very common, common, very likely, likely, very high chance, high chance, or fair chance' and those for 'low risk' verbal descriptors which portrayed a side effect as 'uncommon, rare, unlikely' and so on. Within these two groups, the distributions were near to identical regardless of what adjective (e.g. common, likely, chance) or adverb (e.g. very, high, fair) was used.

For the high risk verbal descriptors, most participants (84.4% and 81.2%, respectively) thought 'very common' and 'common' meant a risk of 1,001-10,000 per 10,000 patients (ie more than 1 in 10) for mild side effects, with similar percentages seen for 'very likely' (83.8%), 'likely' (83.2%), 'very high chance' (85.2%), 'high chance' (84.0%), and 'fair chance' (74.7%). This pattern repeated itself for severe side effects, with the majority (56.3 to 71.2%) of participants giving estimates that corresponded to a risk of 1,001-10,000 (more than 1 in 10). For low risk verbal descriptors, the majority (61.8 to 76.7%) of participants provided estimates of 101-1,000 (up to 1 in 10) or 11-100 (up to 1 in 100) for mild side effects, with this dropping to 43.5 to 70.6% for severe side effects. See Table 9-1 for full breakdown of participants' estimates.

Table 9-1 Frequency of how many people provided numerical risk estimates that were correct or incorrect according to the corresponding EC frequency bands.

Verbal risk descriptor	Guess	Mild, n (%)	Severe, n (%)	Total, n (%)
Very Common	Correct	427 (84.4)	354 (71.2)	781 (77.9)
	Incorrect (under)	79 (15.6)	143 (28.8)	222 (22.1)
Common	Under	31 (6.1)	82 (16.5)	113 (11.3)
	Correct	64 (12.6)	93 (18.7)	157 (15.7)
	Over	411 (81.2)	322 (64.8)	733 (73.1)
Uncommon	Under	71 (14.0)	125 (25.2)	196 (19.5)
	Correct	162 (32.0)	163 (32.8)	325 (32.4)
	Over	273 (54.0)	209 (42.1)	482 (48.1)
Rare	Under	27 (5.3)	57 (11.5)	84 (8.4)
	Correct	86 (17.0)	135 (27.2)	221 (22.0)
	Over	393 (77.7)	305 (61.4)	698 (69.6)
Very Rare	Correct	44 (8.7)	72 (14.5)	116 (11.6)
	Incorrect (over)	462 (91.3)	425 (85.5)	887 (88.4)

9.4.3 Secondary outcome: The effect of side effect severity on people's

interpretation of the verbal risk descriptors

Participants' numerical risk estimates were lower for each verbal risk descriptor when it described severe side effects compared to mild side effects (all p values <0.001, see Figure 9-3).

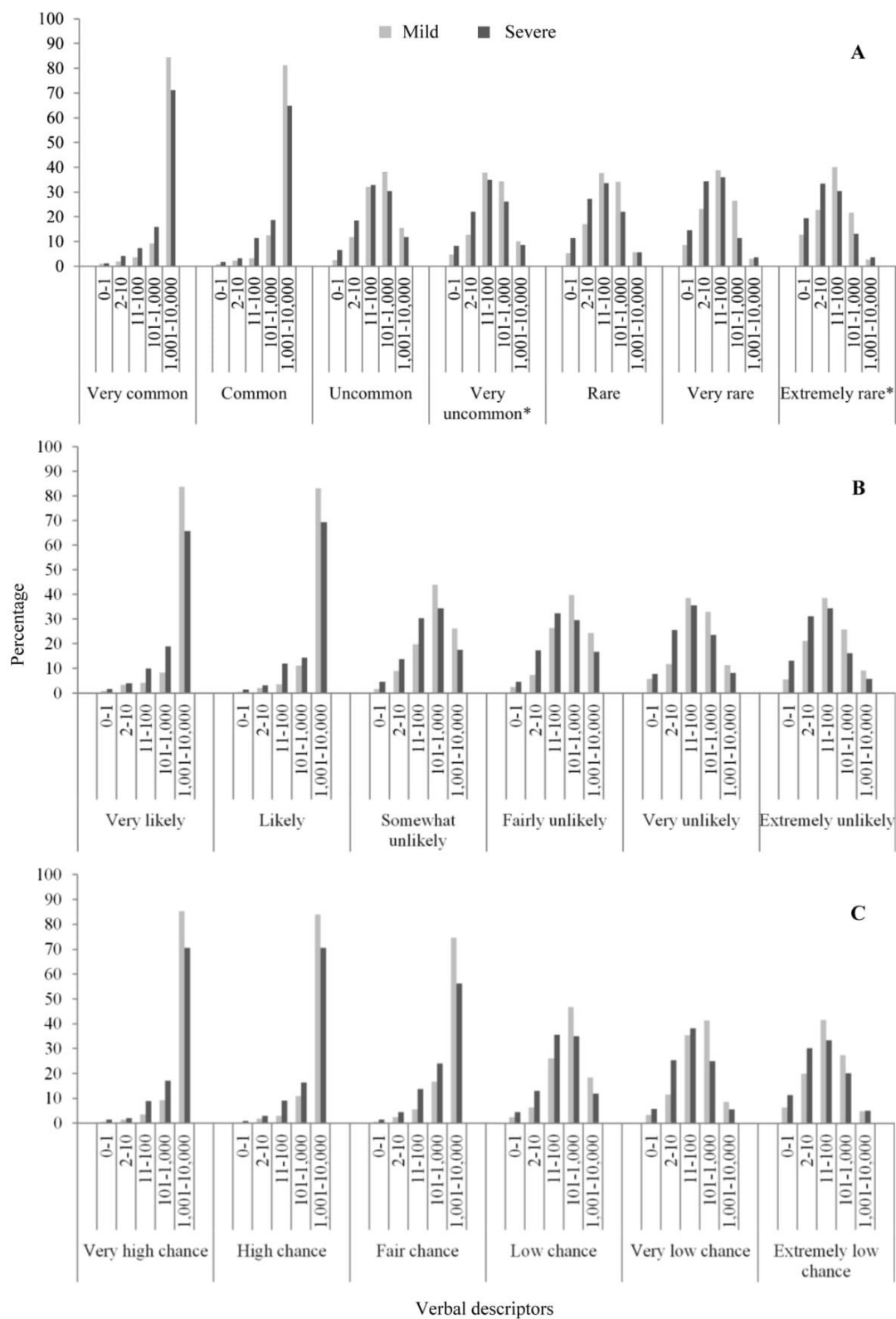


Figure 9-2 Participants' estimates of the meaning for each verbal risk descriptor.
 Note: A = European Commission recommended verbal descriptors, B = Likely verbal descriptors, C = Chance verbal descriptors, *Added in for this study

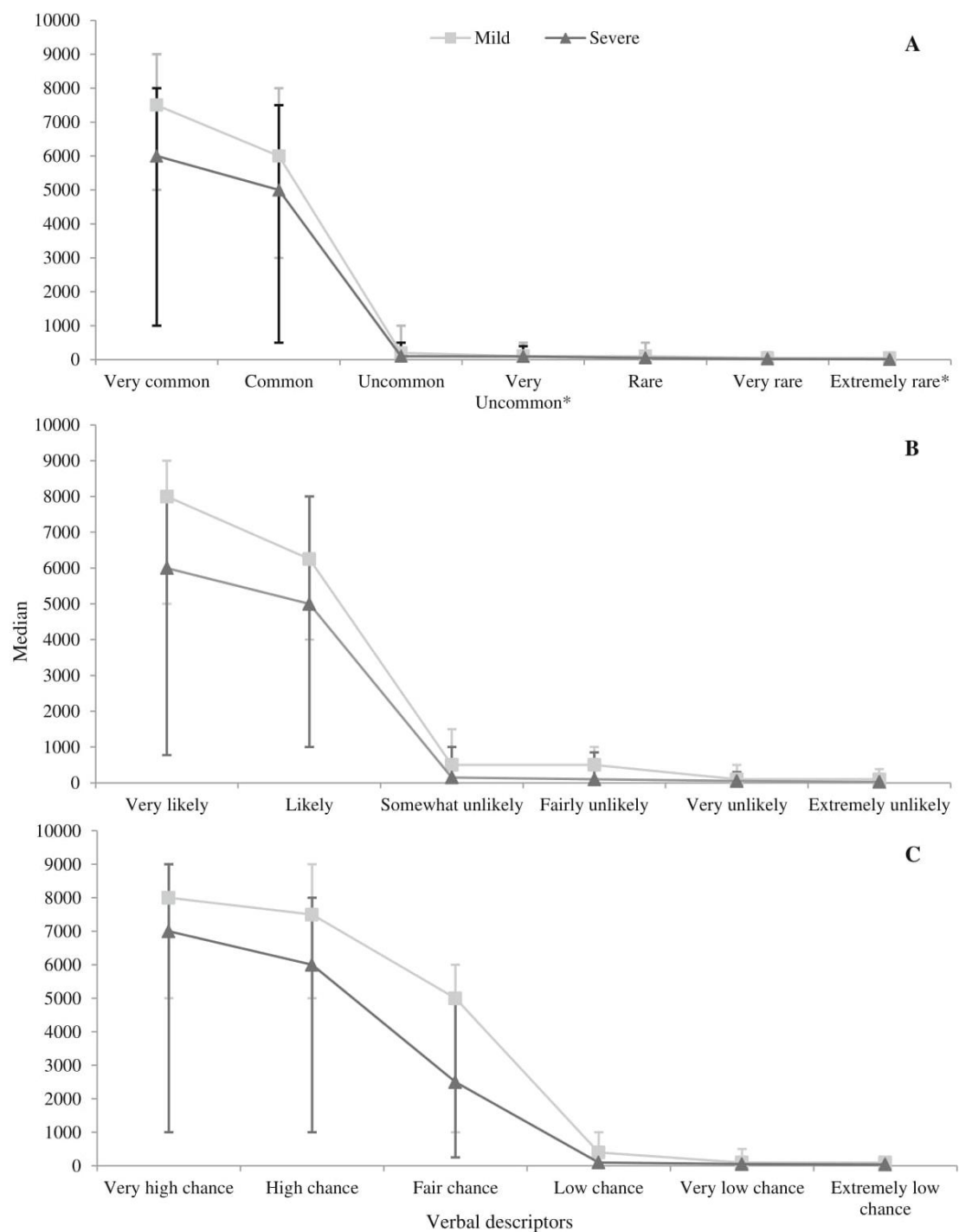


Figure 9-3 Median estimates out of 10,000 given for each verbal risk descriptor.
 Note: A = European Commission recommended verbal descriptors, B = Likely verbal descriptors, C = Chance verbal descriptors, *Added in for this study. Bars represent the Interquartile range.

9.4.4 Secondary outcome: The association between demographic and psychological factors on people's numerical estimates for the EC recommended verbal risk descriptors

Table 9-2 shows the association between demographic and psychological variables with participants' numerical estimates. Older participants and those from

ethnic minorities were generally less likely to overestimate the numerical risk of the verbal risk descriptors. Participants with no academic qualifications were 63% less likely than participants with university degrees to give correct estimates for ‘very common,’ and 56% less likely than participants with degrees to overestimate ‘common.’ Participants who had someone in their household with a long-term illness or disability were 129% more likely than those without to underestimate ‘rare.’ By far the most influential factor was whether the descriptor related to mild or severe side effects. In general, mild side effects were more likely to be overestimated than severe side effects.

Most psychological characteristics had no association with whether participants estimated the numerical risk in accordance with the EC frequency bands. Optimism showed a small but significant effect for two verbal risk descriptors, with each 1 point increase in optimism resulting in participants being 4% less likely to overestimate ‘uncommon’ and 6% less likely to underestimate ‘rare’ descriptors. Belief about the harm of medicines also showed a small but significant effect for the ‘very common’ descriptor, with each 1 point increase in harm score resulting in participants being 6% less likely to give correct estimates. Finally for each 1 point increase in health illiteracy, participants were 24% less likely to provide a correct estimate for ‘Very common’ compared to underestimate it. Similarly for each 1 point increase in health illiteracy, participants were 27% less likely to overestimate ‘common’ compared to estimating it in accordance with the EC frequency bands.

9.4.5 Post-hoc analyses

As an additional analysis, I tested how much variance could be explained by entering the predictors altogether in one model. For predicting correct or incorrect estimates for the verbal risk descriptors ‘very common’ and ‘very rare’ using binary logistic regression, both models were a good fit for the data with both Hosmer and Lemeshow tests being non-significant ($p > 0.068$). However, using Nagelkerke’s R^2 the

models only explained 10.3% of the variance in estimates for 'very common,' and 3.1% of the variance in estimates for 'very rare.' Similarly for predicting correct, over or under estimates for the verbal risk descriptors 'common,' 'uncommon' and 'rare' using multinomial logistic regressions, the models were a good fit for the data with all χ^2 tests being non-significant (p s > 0.232). Again, however, using Nagelkerke's R^2 the models only explained 12.3% of the variance in estimates for 'common,' 10.6 % of the variance in estimates for 'uncommon,' and 8.7% of the variance for 'rare' outcomes.

Table 9-2 Demographic and psychological factors associated with how well participants guessed the numerical risk estimate for very common, common, uncommon, rare and very rare.

Variable	No (%) or mean (SD)	Verbal risk descriptors							
		Very common, correct, aOR (95% CI)	Common, underestimated, aOR (95% CI)	Common, overestimated, aOR (95% CI)	Uncommon, underestimated, aOR (95% CI)	Uncommon, overestimated, aOR (95% CI)	Rare, underestimated, aOR (95% CI)	Rare, overestimated, aOR (95% CI)	Very rare, correct, aOR (95% CI)
Demographic									
Gender ^a									
Male	492 (49.1%)	0.97 (0.71-1.32)	1.00 (0.61-1.64)	1.12 (0.78-1.60)	0.74 (0.52-1.07)	1.15 (0.86-1.54)	1.32 (0.79-2.21)	1.33 (0.97-1.82)	0.71 (0.48-1.07)
Female	511 (50.9%)	†	†	†	†	†	†	†	†
Age ^a	41.56 (13.13)	0.99 (0.97-0.99)	1.01 (0.99-1.03)	0.99 (0.98-1.01)	1.01 (0.99-1.02)	0.97 (0.96-0.98)	0.99 (0.97-1.01)	0.98 (0.97-0.99)	1.00 (0.98-1.02)
Ethnicity ^a									
Ethnic minorities	107 (10.7%)	0.60 (0.37-0.97)	0.72 (0.33-1.55)	0.50 (0.30-0.84)	0.87 (0.48-1.59)	0.75 (0.46-1.19)	0.98 (0.44-2.20)	0.84 (0.51-1.41)	1.19 (0.64-2.20)
White	886 (88.3%)	†	†	†	†	†	†	†	†
Employment ^a									
Not working	280 (27.9%)	0.98 (0.67-1.39)	0.81 (0.46-1.41)	0.83 (0.56-1.24)	0.89 (0.59-1.34)	0.77 (0.55-1.07)	0.74 (0.40-1.35)	0.88 (0.61-1.25)	0.94 (0.59-1.51)
Working	723 (72.1%)	†	†	†	†	†	†	†	†
Education ^a									
No qualifications	44 (4.4%)	0.37 (0.19-0.74)	0.60 (0.19-1.89)	0.44 (0.21-0.93)	0.63 (0.25-1.62)	0.97 (0.47-1.97)	0.94 (0.18-4.88)	2.16 (0.91-5.18)	0.76 (0.25-2.26)
School qualifications	387 (38.6%)	0.84 (0.60-1.16)	1.49 (0.88-2.52)	0.98 (0.67-1.44)	0.94 (0.64-1.37)	0.91 (0.67-1.24)	1.13 (0.66-1.94)	1.20 (0.87-1.68)	0.70 (0.45-1.08)
University degree	565 (56.3%)	†	†	†	†	†	†	†	†
Household illness ^a									
Yes - me	290 (28.9%)	0.88 (0.61-1.26)	0.82 (0.46-1.47)	0.87 (0.58-1.30)	0.91 (0.59-1.38)	1.25 (0.89-1.77)	0.96 (0.51-1.80)	0.98 (0.68-1.41)	0.89 (0.55-1.43)
Yes - someone else	128 (12.9%)	0.88 (0.51-1.30)	1.40 (0.66-2.99)	1.12 (0.63-1.99)	0.72 (0.40-1.30)	1.04 (0.67-1.62)	2.29 (1.13-4.68)	1.12 (0.67-1.88)	0.88 (0.47-1.66)
No	571 (56.9%)	†	†	†	†	†	†	†	†
Experimental									
Side effect type ^a									
Mild	506 (50.4%)	2.16 (1.57-2.96)	0.54 (0.32-0.92)	1.81 (1.26-2.58)	0.57 (0.40-0.83)	1.32 (0.99-1.77)	0.75 (0.44-1.28)	2.02 (1.47-2.76)	0.59 (0.39-0.88)
Severe	497 (49.6%)	†	†	†	†	†	†	†	†
Psychological									
Optimism ^b	18.72 (4.53)	1.00 (0.97-1.04)	0.97 (0.92-1.03)	0.99 (0.95-1.03)	0.98 (0.94-1.02)	0.96 (0.93-0.99)	0.94 (0.89-0.99)	0.97 (0.94-1.01)	0.99 (0.95-1.04)
PS to medicines ^b	11.02 (4.19)	0.99 (0.96-1.04)	0.99 (0.93-1.05)	1.01 (0.96-1.05)	1.02 (0.98-1.07)	1.04 (1.00-1.07)	0.95 (0.89-1.01)	1.00 (0.96-1.04)	1.00 (0.95-1.05)
BMQ overuse ^b	12.19 (3.00)	0.99 (0.94-1.04)	0.99 (0.91-1.08)	1.02 (0.96-1.08)	1.03 (0.97-1.10)	1.04 (0.99-1.10)	0.99 (0.91-1.08)	0.99 (0.94-1.04)	0.99 (0.92-1.06)
BMQ harm ^b	9.71 (2.82)	0.94 (0.89-0.99)	1.01 (0.92-1.10)	0.96 (0.90-1.02)	1.00 (0.94-1.07)	1.01 (0.95-1.06)	1.01 (0.92-1.11)	0.98 (0.93-1.04)	1.01 (0.94-1.09)
Healthy anxiety ^b	2.02 (0.61)	1.03 (0.79-1.34)	0.99 (0.64-1.52)	1.10 (0.81-1.49)	0.90 (0.65-1.25)	1.28 (0.99-1.65)	1.16 (0.74-1.82)	1.07 (0.82-1.41)	0.99 (0.70-1.40)
Health illiteracy ^b	1.57 (0.96)	0.76 (0.65-0.89)	0.96 (0.76-1.22)	0.73 (0.61-0.87)	1.13 (0.94-1.37)	0.94 (0.80-1.10)	0.97 (0.74-1.27)	0.91 (0.77-1.07)	1.03 (0.83-1.27)
PIL reading frequency ^b	3.83 (1.18)	1.12 (0.98-1.28)	1.05 (0.85-1.31)	1.12 (0.96-1.30)	0.98 (0.84-1.14)	1.07 (0.94-1.22)	0.83 (0.66-1.03)	0.95 (0.83-1.10)	0.99 (0.83-1.18)

Note: Adjusted odd ratios for those who provided correct estimates for Very common and Very rare, and over/underestimated Common, Uncommon, and Rare compared to those who gave correct estimates. Variables without a reference category were treated as continuous and odds ratios represent the result of a 1 point increase in these variables. ^a Controlled for each other, ^b Controlled for demographic, and experimental variables, aOR = adjusted odds ratio, † = Reference category, PS = Perceived sensitivity, BMQ = Belief about medicines, PIL = Patient information leaflet, SD = Standard deviation, CI = Confidence interval, **bold** = p < .05, N ≠ 1003 due to excluding 'don't know' or 'prefer not to say'.

9.5 Discussion

9.5.1 Summary of main results

There are several key findings from this work. First, the verbal risk descriptors recommended by the EC and commonly used in PILs are not accurately interpreted by members of the public as meaning the same things as the associated numerical expression. As shown in previous studies (Berry et al., 2004; Berry et al., 2002; Berry, Raynor, & Knapp, 2003; Ziegler et al., 2013) people widely overestimate what they mean in terms of frequencies. This overestimation of risk is important, making people less inclined to take their medication (Berry et al., 2002; Woodward, Bereznicki, Westbury, & Bereznicki, 2016) and leading to potentially self-fulfilling expectations of symptoms (Barsky et al., 2002). This overestimation generalises to other verbal risk descriptors not recommended by the EC: simply tweaking the wording of the verbal risk descriptors in use seems unlikely to resolve this problem. Instead, the issue may be a fundamental mismatch between how we are attempting to communicate (with five different divisions of frequency) and how people understand risk. The data suggest people view verbal risk descriptors as meaning either ‘likely’ or ‘not likely’ – all descriptors are mentally reinterpreted as one of those two versions.

Second, it is hard to establish who will interpret the risk information in accordance with the corresponding EC frequency bands. Even combining all the predictors into one model did little to explain the variance in estimates across the different verbal risk descriptors. Only age and side effect type showed a consistent effect. This follows previous research that has shown that older people have lower perceptions of risk in general (Savage, 1993). The finding that mild side effects were particularly likely to be overestimated has also been shown previously (Berry, Raynor, & Knapp, 2003) and may reflect the influence of the availability heuristic (Tversky & Kahneman, 1973): given that people will have had more experience with headaches

than seizures, it seems likely that people will find it easier to recall an example of a headache, elevating their perceived likelihood. Ethnicity, education and health illiteracy did have an effect but only for the higher verbal risk descriptors. White participants, participants with academic qualifications and those who were more health literate were more likely to overestimate these high verbal risk descriptors. It is possible that White participants are more likely to overestimate than participants from ethnic minorities as it has been shown that they are prescribed more medications (Horne et al., 2004) and may have more experience with medication side effects. It is surprising that participants with academic qualifications and those with higher health literacy were more likely to overestimate and I am unsure why this might be.

9.5.2 Limitations

This study is strengthened by its large sample size and the fact that it was demographically representative of 18 to 65 year olds in the English population. While it is possible to question the validity of the data as it is unknown if online participants read the questions properly or whether they were distracted with other tasks whilst completing the study (Gosling, Vazire, Srivastava, & John, 2004), this issue may not be as big as suspected, however (Ramsey, Thompson, McKenzie, & Rosenbaum, 2016), and was partly offset by the exclusion of participants for ‘straightlining’ or ‘speeding.’ It is limited however in terms of selection bias, as I do not know whether members of market research panels are psychologically representative of the general population in terms of attitudes to medicines and their risk of side effects. In addition, only 10% of those invited to participate actually responded. It is plausible that this group were not psychologically or behaviourally representative of the general population.

It is also possible that the finding that psychological variables predict poorly on participants’ estimates might be due a lack of quality in the measures used capturing these variables. This is unlikely for optimism, belief and medicines, and perceived

sensitivity to medicines which were measured using well validated scales, however health anxiety, health literacy and PIL reading behaviour were assessed by modifying validated scales and creating bespoke items for this study.

The response mode I chose for participants when estimating the numerical risk of the verbal risk descriptors also could have affected the results. Participants were asked to give a number out of 10,000 however past research has suggested that open ended questions such as this are more susceptible to risk overestimation compared to questions which require selecting an answer from a few different response options (Woloshin, Schwartz, Black, & Welch, 1999). I chose this method to make it easier for participants to express small probabilities, and to allow participants to give their exact thoughts rather than having to choose from select options covering a broad range of answers.

In addition, many of the questions used in the survey were hypothetical, for example asking participants to estimate the risk of side effects to an imagined drug. It is possible that patients prescribed a real medication would have a different understanding of the risks associated with that medication and might answer these questions differently. I assessed this possibility, in a recent survey of 1,001 parents whose children were eligible for the flu vaccine. In this survey I included similar measures to those reported here in order assess how parents understand the verbal descriptors used to describe the risk of side effects from the vaccine in the accompanying PIL. This survey is not reported in detail in this thesis, but full details are available in Smith et al. (2017). In the parent sample, the median estimates were that out of 10,000 vaccinated children, a 'very common' side effect would affect 5,000 children (i.e. 50%), a 'common' side effect would affect 2,000 (20%), an 'uncommon' side effect would affect 199 (2%) and a 'very rare' side effect with affect 50 (0.5%) (Smith et al., 2017).

These results are similar to those reported in this chapter, albeit with a slightly lower median figure for the ‘common’ descriptor.

I also excluded over 65s due to concerns of how representative they are in online surveys. However over 65s are the heaviest medication consumers as noted by the Health and Social Care Information Centre (2013), therefore the results may be different for this population.

9.5.3 Implications for clinical practice and policy

Verbal risk descriptors have long been favoured for the presentation of side effect risk on the basis that they can break up long lists of side effects into more manageable sections based on frequency, convey the uncertainty of risk, and because some people are more comfortable with verbal than numerical information (Knapp, Gardner, et al., 2009). Current guidelines suggest PILs should combine the verbal risk descriptors with the numerical expressions (EC, 2009), however I argue this is not enough as it still leads to overestimation (Knapp et al., 2015; Knapp, Raynor, et al., 2009). If combined expressions are used, it remains important to use the correct verbal risk descriptor which is interpreted by people in the same way as the numerical expression that is associated with it. However, this survey has shown that verbal risk descriptors as a whole mislead rather than inform, leading readers to greatly overestimate their risk of side effects. I suggest that PILs should abandon the use of these verbal risk descriptors and instead side effect risk should be grouped under numerical frequency bands only. Alternatively, because the current system needs revising anyway, positively framing the risk of side effects could be trialled as a different way to improve the public’s understanding of the way we communicate side effect risk. As well as having implications for PILs, the results of this survey also point out the need for clinicians to reassure patients that side effects are much less likely than patients think. In addition as mild side effects were overestimated more than severe I

suggest that practitioners may wish to focus in particular on correcting misperceptions about the likelihood of mild side effects.

9.5.4 Future research

It would be interesting for future research to see how the results differ by comparing different type of response options for estimating the numerical risk of verbal descriptors. It is also important to replicate this study with patients given a newly prescribed medication to remove any limitations relating to the hypothetical scenario used in the survey. These findings should also be extended to over 65s who are the heaviest medication users, to see if the extent of this overestimation is still present in this group. Research should also examine whether use of numerical, rather than verbal, descriptors produces more realistic risk estimates among participants. As with verbal risk descriptors, different numerical formats are possible (e.g. reframing the risk in terms of the number/proportion of people who remain side effect free). Identifying the best way of presenting this information remains an important goal.

9.6 Conclusions

Members of the public commonly overestimate the risk associated with verbal risk descriptors. It may be difficult, if not impossible, to find the perfect verbal risk descriptors that are interpreted by the public in line with the different levels of side effect risk. Although they are helpful in breaking up long lists and conveying uncertainty for those uncomfortable with numbers, the risks of overestimation outweighs these benefits. It may be that PILs should abandon the use of verbal risk descriptors altogether. This will limit the opportunity people have to overestimate the likelihood of side effects allowing patients to make informed decisions about their medication and reducing the occurrence of side effects brought on from negative expectations.

Chapter 10 The influence of the current side effect risk information in patient information leaflets on people's side effect expectations

10.1 Introduction

Current guidelines suggest combining verbal risk descriptors with their corresponding numerical expression when describing side effect risk. However this still leads to overestimation. It is suggested that this is because the current verbal risk descriptors are flawed as people's interpretation of them are still at odds with the corresponding numerical expression. As discussed in Chapter 9, I found that the general public systematically overestimate the current verbal risk descriptors used to communicate side effect risk in PILs, however I also found this was still the case with all other verbal risk descriptors that I tested. It seems it may be a near impossible task to find verbal risk descriptors that are interpreted in line with their corresponding numerical expression.

Although previous studies have looked at how verbal descriptors and side effect type affect people's numerical estimation of side effects (Berry et al., 2004; Berry et al., 2002; Berry, Raynor, & Knapp, 2003; Berry, Raynor, Knapp, et al., 2003; Knapp et al., 2001; Knapp, Raynor, & Berry, 2004), they have not looked at how side effect information in PILs and the type of side effect they are describing affects people's subsequent personal expectations of side effects. The two issues are linked, but not identical. It is possible for an optimistic patient to believe that symptoms are common but unlikely to affect them personally, and vice versa. One of the main ways that patients can generate these negative expectations of their medication is by reading the accompanying PIL. This is important as it is these expectations that may trigger a nocebo response.

From my systematic review in Chapter 2 and the results from the predictors of symptom attribution in Chapter 8, I know that expectations such as those generated

from verbal suggestions of what symptoms to expect are one of the strongest factors affecting the development of placebo effects. Expectations have also been found to contribute to the side effects that patients experience from their medications (Mondaini et al., 2007; Myers et al., 1987).

Previous research has suggested that factors such as belief about medicines and perceived sensitivity to medicines are associated with medicine side effect expectations (Faasse & Petrie, 2013) and they have also been implicated in the placebo response as shown from the results in Chapter 8. Therefore, it would be useful to gain more of an understanding of what influences people's side effect expectations as targeting these factors is a potential way of reducing expectations and therefore placebo responses to medicines.

10.2 Aims

This study set out to investigate people's expectations of side effects when described using the EC recommended combined descriptors and to determine what affects these expectations.

The specific aims were to:

1. Assess people's expectations of side effects when described using the EC recommended combined risk descriptors.
2. Investigate if these expectations differ depending on whether they relate to mild or severe side effects.
3. Determine whether demographic factors and/or psychological factors are associated with the expectation of experiencing a side effect after taking a medicine labelled with one of the EC recommended combined risk descriptors.
4. Determine if participants' understanding of what the verbal descriptors mean is associated with their subsequent expectations of side effects.

10.3 Method

10.3.1 Design

Data for these analyses were drawn from the same survey reported in Chapter 9. This study was approved by the Psychiatry, Nursing and Midwifery Research Ethics Committee at King's College London (ref: HR-15/16-2104), for a copy of ethical approval see Appendix N.

10.3.2 Participants

All participants who took part in the study reported in Chapter 9 also contributed data for the analyses reported in this Chapter.

10.3.3 Sample size

IPSOS Mori used quotas based on the National Readership Survey (2015) to ensure that the sample reflected the demographic profile of 18 to 65 year olds in England. This is standard method for this form of research to ensure samples are representative of the adult English population. I intended to recruit 1,000 participants to provide us with a sample error of about plus or minus 3% at the total sample level.

10.3.4 Questionnaire development

Where possible I used or adapted items that had been previously developed and tested for their reliability and validity. I piloted all items with them and rephrased items where necessary to improve clarity. The full wording for all items used in the survey, are given in the Appendix O.

10.3.5 Measures

10.3.5.1 Side effect expectations

Five items were used to assess participant expectations of side effects. Depending on which condition they had been assigned to, participants were told that a new drug had been developed with either 'dizziness' or 'kidney failure' as one of its side effects. The side effect was described using each of the five EC recommended

combined verbal and frequency expressions (e.g. very common, may affect more than 1 in 10 people) which were presented in a random order. Participants were asked to rate how likely they were to experience dizziness or kidney failure if they took the drug on a five point scale ranging from ‘very unlikely to very likely.’

10.3.5.2 Demographic factors

I asked participants about their: age, gender, ethnicity, highest level of education, employment status and whether they or anyone in their household had a long-standing illness, disability or infirmity.

10.3.5.3 Psychological factors

I adapted the single item literacy screener (Morris et al., 2006) to assess health literacy and included one item which asked how often they read PILs when taking a new medication. I used one item from the health anxiety inventory (Salkovskis et al., 2002) to assess health anxiety. The LOT-R (Scheier et al., 1994) was used to assess optimism, and participants’ general beliefs about medicines were assessed using the overuse and harm general subscales of the BMQ (Horne et al., 1999). Finally, how sensitive participants thought they were to medicines was assessed using the Perceived Sensitivity to Medicines scale (Horne, Faasse, et al., 2013).

10.3.6 Procedure

Potential participants were emailed a link to the survey. After providing informed consent and clicking through to begin the survey, participants were allocated to receive questions about either mild or severe side effects. This was decided by the survey software based on which condition had the lowest number of completed responses at that time. Panel participants received points equivalent to 75 pence for taking part.

10.3.7 Outcomes

The primary outcome was participants' side effect expectations after reading the EC recommended combined verbal and frequency expressions.

The secondary outcomes included the effect of side effect type, demographic and psychological factors, and how well participants estimated the EC recommended verbal descriptors on participants' side effect expectations

10.3.8 Analysis

Participants' expectations were grouped by likelihood to see the frequency that each likelihood statement was selected for the different risk descriptors. I carried out a series of chi-squared tests to see if participant expectations differed between mild and severe side effects. For occurrences where the expected cell count was below 5, Fisher's exact test was used instead.

Ordinal regressions were carried out to identify if any demographic or psychological characteristics, or how well participants estimated the EC recommended descriptors, were associated with expectations of personally experiencing side effects. The dependent variable for each regression was participants' scores on the likelihood scale for each verbal descriptor. For each regression, all demographic variables and side effect type (mild or severe) were added in one block, and each psychological variable was added on its own, controlling for the previously entered variables.

For all analyses, answers of 'don't know' or 'prefer not to say' were excluded. Only 3% of participants answered 'don't know,' and 1% answered 'prefer not to say' for any question where this was an option. Analyses were carried out using SPSS 22. As participant expectations did not change by more than 0.2% when using data weighted by age, gender, region and working status, I used unweighted data in the analyses.

10.4 Results

10.4.1 Sample characteristics

1003 participants completed the survey and were included in the final sample (see Figure 9-1 in Chapter 9 for response rates). Demographic information for the participants is given in Table 10-2.

10.4.2 Primary outcome: The influence of the EC recommended combined risk descriptors on side effect expectations

Table 10-1 shows participant expectations of side effects for each of the descriptors. Expectations of side effects varied widely for each descriptor, however the majority of participants thought that ‘Very common’ and ‘Common’ side effects were very likely or likely to happen to them (51.9% and 45% respectively) despite these terms only being intended to represent a risk of around 1 in 10 patients being affected. Expectations of side effects dropped substantially for ‘Uncommon,’ ‘Rare’ and ‘Very rare’ with 8.1%, 5.8 % and 4.1% of participants thinking there were very likely or likely to experience the side effects respectively.

10.4.3 Secondary outcome: The effect of side effect severity on side effect expectations

The difference in expectations between mild and severe side effects is shown in Table 10-1. There was no difference in expected likelihood between mild and severe side effects except for side effects described as ‘rare’ in which expectations were lower for mild versus severe side effects, $p = .003$.

Table 10-1 Expected likelihood of mild (dizziness) and severe (kidney failure) side effects from an imagined new drug using the EC recommended combined descriptors.

Current guidelines	Expectancy	Mild, n (%)	Severe, n (%)	Total, n (%)
Very Common (more than 1 in 10)	Very likely	115 (22.7)	106 (21.3)	221 (22.0)
	Likely	152 (30.0)	148 (29.8)	300 (29.9)
	About as likely as not	118 (23.3)	128 (25.8)	246 (24.6)
	Unlikely	91 (18.0)	79 (15.9)	170 (16.9)
	Very unlikely	20 (4.0)	20 (4.0)	40 (4.0)
	Don't know	10 (2.0)	16 (3.2)	26 (2.6)
	Chi square test	$\chi^2 = 1.443, p = .837$		
Common (up to 1 in 10)	Very likely	58 (11.5)	63 (12.7)	121 (12.1)
	Likely	175 (34.6)	155 (31.2)	330 (32.9)
	About as likely as not	122 (24.1)	132 (26.6)	254 (25.3)
	Unlikely	121 (23.9)	114 (22.9)	235 (23.4)
	Very unlikely	20 (4.0)	19 (3.8)	39 (3.9)
	Don't know	10 (2.0)	14 (2.8)	24 (2.4)
	Chi square test	$\chi^2 = 1.874, p = .759$		
Uncommon (up to 1 in 100)	Very likely	7 (1.4)	10 (2.0)	17 (1.7)
	Likely	32 (6.3)	32 (6.4)	64 (6.4)
	About as likely as not	92 (18.2)	103 (20.7)	195 (19.4)
	Unlikely	215 (42.5)	217 (43.7)	432 (43.1)
	Very unlikely	154 (30.4)	121 (24.3)	275 (27.4)
	Don't know	6 (1.2)	14 (2.8)	20 (2.0)
	Chi square test	$\chi^2 = 4.827, p = .306$		
Rare (up to 1 in 1,000)	Very likely	3 (0.6)	7 (1.4)	10 (1.0)
	Likely	28 (5.5)	20 (4.0)	48 (4.8)
	About as likely as not	56 (11.1)	72 (14.5)	128 (12.8)
	Unlikely	136 (26.9)	169 (34.0)	305 (30.4)
	Very unlikely	278 (54.9)	218 (43.9)	496 (49.5)
	Don't know	5 (1.0)	11 (2.2)	16 (1.6)
	Fisher's exact test*	$* = 15.452, p = .003$		
Very Rare (up to 1 in 10,000)	Very likely	5 (1.0)	6 (1.2)	11 (1.1)
	Likely	15 (3.0)	15 (3.0)	30 (3.0)
	About as likely as not	38 (7.5)	51 (10.3)	89 (8.9)
	Unlikely	65 (12.8)	70 (14.1)	135 (13.5)
	Very unlikely	375 (74.1)	342 (68.8)	717 (71.5)
	Don't know	8 (1.6)	13 (2.6)	21 (2.1)
	Chi square test	$\chi^2 = 3.495, p = .481$		

Note: Chi-square analyses did not include participants who answered 'Don't know'

* One cell had an expected cell count of less than 5 so Fisher's exact was used instead

10.4.4 Secondary outcome: The association between demographic and psychological factors on participants' side effect expectations

Table 10-2 shows the association between demographic variables and perceived likelihood of experiencing side effects, with all demographic variables controlled for each other. Men were 31% less likely than women to have higher expectations of side effects described as being 'very common' or 'common.' Participants from ethnic minorities were more likely to have higher expectation of side effects being as 'common, uncommon, rare and very rare.' Compared to those with a university degree, participants with no academic qualifications were more likely to have a higher expectation of side effects described as 'uncommon, rare and very rare.' Similarly compared to having a university degree, participants with school qualifications were more likely to have a higher expectation of side effects described as 'uncommon, rare and very rare.' Having an illness or an illness in the household increased expectations of side effects compared to having no household illness but this was only significant for some of the descriptors ('very common,' 'common,' and 'uncommon').

Table 10-2 also shows the association between psychological variables and perceived likelihood of experiencing side effects, controlling for demographic characteristics. People with a higher perceived sensitivity to medicines were 5 to 10% more likely to have higher expectations of side effects described using each of the descriptors compared to those with a lower perceived sensitivity to medicines. Participants who thought medicines were overused or caused harm were 5 to 10%, and 7 to 20% respectively more likely to have higher expectations of side effects described as 'common,' 'uncommon,' 'rare' or 'very rare.' Participants scoring higher on health anxiety were 25% more likely to have higher expectations of side effects described as 'very common' compared to those with lower health anxiety. Participants who needed help reading PILs were 14 to 49% more likely to have higher expectations of side

effects described as ‘common,’ ‘uncommon,’ ‘rare’ and ‘very rare.’ Participants who read PILs more often were 12% less likely to have higher expectations of side effects described as ‘very rare’ compared to those who read PILs less often. There was no effect of optimism on participants’ side effect expectations.

10.4.5 Secondary outcome: The association between participants’ numerical risk estimates of the verbal risk descriptors and their subsequent side effect expectations

Whether participants estimated each of the EC recommended descriptors in accordance with the corresponding EC frequency band had little effect on their side effect expectations, apart from the descriptor ‘very rare’ and ‘uncommon.’ Participants who overestimated the number of patients likely to experience a ‘very rare’ side effect were 45% less likely to have higher expectations of ‘very rare’ side effects, and participants who underestimated the intended meaning of ‘uncommon’ were 54% more likely to have higher expectations of uncommon side effects. Full results of participants’ estimations are provided in Chapter 9.

Table 10-2 Demographic and psychological factors associated with participant expectations that very common, common, uncommon, rare and very rare side effects would personally affect them.

Variable	No (%) or mean (SD)	Verbal risk descriptors				
		Very common, aOR (95% CI)	Common, aOR (95% CI)	Uncommon, aOR (95% CI)	Rare, aOR (95% CI)	Very rare, aOR (95% CI)
<u>Demographics</u>						
Gender ^a						
Male	492 (49.1%)	0.69 (0.46-0.92)	0.69 (0.55-0.87)	1.05 (0.83-1.33)	0.88 (0.69-1.12)	0.94 (0.70-1.25)
Female	511 (50.9%)	†	†	†	†	†
Age ^a	41.56 (13.13)	0.99 (0.98-1.00)	1.00 (0.99-1.01)	0.99 (0.98-1.00)	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Ethnicity ^a						
Ethnic minorities	107 (10.7%)	1.25 (0.86-1.83)	1.49 (1.02-2.18)	2.09 (1.42-3.07)	2.06 (1.41-3.03)	2.33 (1.53-3.56)
White	886 (88.3%)	†	†	†	†	†
Employment ^a						
Not working	280 (27.9%)	1.07 (0.81-1.39)	1.01 (0.78-1.32)	1.02 (0.78-1.33)	0.90 (0.68-1.19)	0.79 (0.56-1.10)
Working	723 (72.1%)	†	†	†	†	†
Education ^a						
No academic qualifications	44 (4.4%)	0.82 (0.47-1.46)	1.23 (0.69-2.20)	3.06 (1.70-5.51)	2.73 (1.52-4.92)	4.88 (2.62-9.06)
School qualifications	387 (38.6%)	0.94 (0.74-1.19)	0.99 (0.77-1.25)	1.42 (1.11-1.81)	1.52 (1.18-1.96)	1.55 (1.14-2.10)
University degree	565 (56.3%)	†	†	†	†	†
Household illness ^a						
Yes - me	290 (28.9%)	1.27 (0.97-1.66)	1.40 (1.07-1.83)	1.42 (1.07-1.87)	1.13 (0.85-1.50)	1.23 (0.88-1.71)
Yes- someone else	128 (12.9%)	1.47 (1.04-2.10)	1.78 (1.25-2.54)	1.85 (1.29-2.65)	1.17 (0.81-1.70)	1.06 (0.68-1.65)
No	571 (56.9%)	†	†	†	†	†
<u>Experimental</u>						
Side effect type ^a						
Mild	506 (50.4%)	1.03 (0.82-1.29)	1.00 (0.80-1.26)	0.80 (0.63-1.12)	0.70 (0.55-0.89)	0.77 (0.58-1.03)
Severe	497 (49.6%)	†	†	†	†	†
<u>Estimates</u>						
Very common, Very rare ^b						

Incorrect	-	0.83 (0.63-1.10)	-	-	-	0.55 (0.37-0.83)
Correct	-	†	-	-	-	†
Common, Uncommon, Rare ^b						
Under	-	-	0.94 (0.60-1.48)	1.54 (1.10-2.16)	1.29 (0.79-2.09)	-
Over	-	-	0.96 (0.70-1.33)	1.25 (0.95-1.64)	1.08 (0.80-1.46)	-
Correct	-	-	†	†	†	-
<u>Psychological</u>						
Optimism ^b	18.72 (4.53)	0.98 (0.95-1.00)	0.98 (0.96-1.01)	0.97 (0.95-1.00)	0.98 (0.95-1.00)	0.98 (0.95-1.02)
PS to medicines ^b	11.02 (4.19)	1.05 (1.02-1.08)	1.05 (1.02-1.08)	1.07 (1.04-1.10)	1.10 (1.07-1.14)	1.10 (1.07-1.14)
BMQ overused ^b	12.19 (3.00)	1.04 (1.00-1.08)	1.05 (1.01-1.09)	1.08 (1.04-1.12)	1.05 (1.01-1.09)	1.08 (1.03-1.14)
BMQ harm ^b	9.71 (2.82)	1.04 (1.00-1.08)	1.07 (1.03-1.12)	1.14 (1.10-1.19)	1.17 (1.12-1.22)	1.20 (1.13-1.26)
Healthy anxiety ^b	2.02 (0.61)	1.25 (1.02-1.53)	1.13 (0.93-1.39)	1.14 (0.93-1.40)	0.98 (0.79-1.20)	1.07 (0.84-1.37)
Health illiteracy ^b	1.57 (0.96)	1.06 (0.94-1.20)	1.14 (1.00-1.29)	1.44 (1.27-1.63)	1.49 (1.31-1.69)	1.47 (1.28-1.68)
PIL reading frequency ^b	3.83 (1.18)	1.00 (0.91-1.11)	0.97 (0.87-1.07)	0.96 (0.86-1.06)	0.96 (0.86-1.07)	0.88 (0.78-0.99)

Note: Variables without a reference category were treated as continuous and therefore the odds ratios represent the result of a 1 point increase in these variables.

a Controlled for each other, b Controlled for demographic and experimental variables, aOR = adjusted odds ratio, † = Reference category, PS = Perceived sensitivity, BMQ = Belief about medicines, PIL = Patient information leaflet, SD = Standard deviation, CI = Confidence interval, **bold** = p < .05.

N ≠ 1003 due to excluding 'don't know' or 'prefer not to say' responses.

10.5 Discussion

10.5.1 Summary of main results

There are several key findings from this work. First, when presented with the standard format of side effect risk information that is currently used in PILs, people form high expectations about their personal likelihood of experiencing symptoms, with the majority of people thinking ‘very common’ or ‘common’ side effects are likely to happen to them, despite those descriptors only representing a risk of around 1 in 10 people being affected. However, these expectations are formed independently from probability estimates. Under, over or correctly estimating the numerical meaning of a side effect risk descriptor had little bearing on whether a patient felt that they, personally, would experience it. These high side effect expectations are problematic, as they can be an important precursor to the development of actual side effects, as a result of a nocebo effect, as shown in Chapter 2 and 8. Although reading about side effects does not always cause someone to experience a side effect (Howland, Baker, & Poe, 1990; Myers & Calvert, 1973), in some situations it can (Mondaini et al., 2007; Myers et al., 1987). Therefore it is important to reduce any unrealistically high side effect expectations that PILs produce.

Second, similar to the nocebo literature reviewed in Chapter 2, participants’ expectation of side effects described using the current guidelines do show associations with demographic and psychological factors. This will allow clinicians to be aware of those patients more at risk of developing nocebo induced side effects to their medications as a result of high side effect expectations. Women are more likely to expect higher risk side effects compared to men, and people from ethnic minorities are more likely to expect side effects than people who are White. This supports previous research that has shown women and people from ethnic minorities have more dread of potential risks/hazards in general (Savage, 1993). Participants with no academic

qualifications and those with school qualifications are more likely to expect a lower risk of side effects than those with university degrees. This may be because these participants are less familiar with and have difficulty interpreting the terms ‘1 in 1000’ and ‘1 in 10,000’ that accompanied the verbal descriptors in these questions and therefore misinterpret what it means in terms of their personal side effect expectations. Similarly higher health illiteracy was associated with higher expectations of side effects. Having a household illness increased expectations of side effects compared to not having a household illness, possibly due to the availability heuristic (Tversky & Kahneman, 1973) as symptoms are more likely to be present if there is a household illness. Interestingly, despite being implicated in the literature on people’s numerical estimates of the descriptors (Berry, Raynor, & Knapp, 2003), I found side effect type had little effect on participants’ expectations. Similarly whether participants provided correct or incorrect risk estimates for the descriptors had little effect on expectations. There are two possible explanations for this. First the verbal risk descriptors do not influence expectations. Or second, the inclusion of the numerical expression draws people’s attention away from the verbal risk descriptor. Either way the verbal risk descriptors are ineffective at influencing people’s expectations. These support the view that participants form independent expectations of side effects from any generalised, numerical risk estimates.

In terms of the psychological factors, perceived sensitivity to medicines showed the strongest association with expectation; participants with a higher perceived sensitivity were more likely to expect side effects than those with a lower perceived sensitivity. In addition a stronger belief that medicines are overused and cause harm increased the expected likelihood of side effects. This supports previous research showing negative views about medicines translate into negative expectations (Faasse & Petrie, 2013). Perceived sensitivity to medicines and negative belief about medicines

have also been found to determine side effect reporting to vaccinations and new medication (Nestoriuc et al., 2010; Petrie et al., 2004). It is likely that the relationship between these factors and symptom reporting is mediated by negative expectations. It may be important to combat these negative medication beliefs in the first instance to reduce patients experiencing nocebo induced side effects as a result of negative expectations.

10.5.2 Limitations

The limitations regarding the representativeness of market research panels, the hypothetical nature of the study and excluding over 65s have been discussed in the previous Chapter. Additional limitations for this part of the study include that fact I chose to use different side effects to assess participants' understanding of the descriptors than those used in the primary side effect expectations outcome. This was because I was interested in participants' perceptions of verbal descriptors rather than side effects, and also to avoid confusing participants when they came to answer the primary outcome questions. It is plausible that had I used the same symptom in the estimation measure I would have identified stronger associations with the primary outcome.

Also due to the hypothetical nature, despite Chapter 2 showing there is some evidence that previous experience influences nocebo effects, I could not assess participants' previous experience with this imaginary drug. I did include the perceived sensitivity to medicines measure which assessed participants' past reactions to medicines in general, and which therefore acted as a proxy measure of participants' experience of side effects in the past. It would be useful for future research in this area to take patients' past side effect experience into consideration

10.5.3 Implications for clinical practice

Verbal descriptors have long been favoured for the presentation of side effect risk information (Knapp, Gardner, et al., 2009). However, previous research including the results in the previous Chapter, has shown that verbal descriptors mislead rather than inform, leading readers to greatly overestimate the risk of side effects. Given that the findings suggest that participant estimations of the currently used descriptors also have little if any impact on patient expectations of their own likelihood of experiencing side effects, the rationale for using them appears to be weak. As well as having implications for PILs, the results also highlight the need for clinicians to assess patients' understanding of the side effect information and the risk of side effects occurring, before explaining the likelihood of side effects based on information in PILs and providing reassurance to patients if necessary. This is particularly important for patients with risk factors for over-estimating their likelihood of developing side effects, namely: women, those with lower educational attainment, those with a household illness, those who seem to have difficulty reading health-related literature, those with a perceived sensitivity to medicine, and negative beliefs about the overuse and harm of medicine.

10.5.4 Future research

Future research could usefully build on this study by testing whether the findings hold true for patients given a newly prescribed medication as the situation studied here was hypothetical. It may also be useful for future research to break down ethnicity into more than two categories, to see if any further differences lie within the 'ethnic minority' category. Not only this there is a possibility that risk information also affects the perceived benefits, as well as side effects of a medication, so future work in these field should consider both forms of outcome.

Finally I suggest that future research should continue to explore ways of reducing participant expectations of side effects. I have attempted to achieve this with

altering the framing of side effect risk, however there may be other ways of communicating side effect risk which lowers side effect expectations. For example figurative risk representations that visually display the risk of side effects has been shown to improve comprehension and accuracy of side effect risk interpretation when displayed alongside numerical risk formats (Zipkin et al., 2014).

10.6 Conclusions

Members of the public commonly overestimate their own personal likelihood of developing the side effects referred to in PILs using the current risk descriptors. This is especially true for women, ethnic minorities, those less educated, those with a household illness and those who have a higher perceived sensitivity to medicines, and negative beliefs about medicines. Interestingly, however, how someone interprets a risk descriptor has little bearing on whether they expect to develop side effects themselves. These findings add weight to the suggestion that PILs should abandon the use of verbal risk descriptors altogether, as ineffective and liable to misinterpretation. In the meantime health care professionals should take care to correct any unrealistic expectations patients may have about medication side effects to allow patients to make properly informed decisions about medication and to reduce the likelihood of nocebo effects.

Chapter 11 Discussion

Nocebo effects are often dubbed as the ‘evil twin’ to the placebo, and result in the experience of noxious symptoms in response to an inert exposure (Barsky et al., 2002). More recently the term has been used to describe the experience of non-specific symptoms that patients attribute to their medications (Faasse & Petrie, 2013). For example evidence suggests that between 38% and 100% of medication side effects are caused by factors associated with the treatment context such as finding out about the potential side effect and the doctor-patient interaction, rather than by the active ingredients in the medication itself (Mahr et al., 2017). For example, studies have suggested that many of the muscular symptoms that patients attribute to their statin medication are actually the product of a nocebo effect (Tobert & Newman, 2016), generated through negative expectations as a result of the adverse media coverage this medication has received in recent years (Horton, 2016). This is a problem as any type of side effect, whether related to the pharmacological action of the drug or not, reduces patients’ quality of life and can be enough to make the patient stop taking their medication (Ammassari et al., 2001; Kardas et al., 2013), resulting in avoidable costs to health services (National Institute For Health and Clinical Excellence, 2009).

This PhD set out to understand more about nocebo responses to medications and what we can do to prevent them by answering the following research questions.

- 1) What predicts whether someone will experience a nocebo response?
- 2) Can altering communication about side effect risk reduce the occurrence of nocebo responses?
- 3) Do the English population misinterpret the current wording used to communicate side effect risk?

I will address each of these research questions in turn highlighting the main findings and discussing the overall implications these have on our understanding of placebo responses to medicines and what we can do to prevent them.

11.1 Summary of main results

11.1.1 What predicts whether someone will experience a placebo effect?

It is important to understand what the strongest predictors of placebo effects are in order to develop and administer an effective intervention to reduce them. Current literature suggests there are three main theoretical mechanisms for explaining how placebo effects occur: misattribution, expectation and learning. The misattribution theory suggests that people may misattribute pre-existing symptoms or those that occur co-incidentally to the effects of a new exposure (Petrie et al., 2005; Petrie et al., 2004). The expectation theory suggests that negative expectations can either make an individual more likely to attend to new or current sensations and attribute them to the exposure (Barsky et al., 2002), or else act directly, for example by triggering emotional states such as anxiety (Kirsch, 1997a, 1997b). Lastly, learning can elicit placebo effects through association or social observation, for example if an inert stimulus has been previously paired with a symptom inducing stimulus (Van den Bergh et al., 1995), or through observing someone else experience symptoms to the same exposure (Vogtle et al., 2013). In Chapter 2, I carried out a systematic review to identify the strongest predictors of placebo effects and assess whether these provide support for the mechanisms suggested in the literature. Using the results from the systematic review I then developed an intervention that could target one of these mechanisms.

My systematic review of 89 studies looked at different factors in terms of their ability to predict participants' reporting of symptoms to an inert exposure. The review revealed 14 different categories of risk factor that had been tested in the literature. Out of these categories, the strongest predictors of participants experiencing placebo effects

were having a higher perceived dose of exposure, receiving explicit suggestions that the exposure triggers certain symptoms, observing people experiencing symptoms from the exposure, and having higher baseline expectations of symptoms. There was some evidence for the role of participants' personality in predicting placebo effects; however due to inconsistent results it was hard to identify which facets of personality are more strongly linked with placebo effects. In addition, although not strong predictors on their own, learning through the process of classical conditioning, suggestions about the likelihood of receiving an inert or real exposure, self-awareness and negative affect consistently interacted with other risk factors.

As well as investigating predictors from the systematic review, I also assessed them in my RCT. These focused on the ability of participants' characteristics, baseline symptoms and symptom expectations to predict the risk of participants attributing symptoms to the tablet. Surprisingly, in this study men had increased odds of attributing symptoms to the tablet compared to women, despite the previous systematic review findings in Chapter 2 showing no overall evidence for the effect of gender in placebo effects. This might have due to the way that placebo effects were induced. Previous research has shown that men are more susceptible to placebo effects which are induced through information designed to change expectancies (Klosterhalfen et al., 2009). It may be that men are susceptible to placebo effects induced this way, and women are more susceptible to other ways that can be used to induce placebo effects such as social modelling (Faasse, Grey, Jordan, et al., 2015; Lorber et al., 2007; Vambheim & Flaten, 2017). In addition, despite finding no effect of age in generating placebo effects in Chapter 2, I found older people had decreased odds of attributing symptoms to the tablet than those younger than them. Again, this finding may be specific to the situation being studied. Older people might have more experience with medicines and how their body reacts. Therefore they may be better able to detect when a symptom is or is not a result

of a medication. Gender and age did not affect the number of symptoms participants go on to attribute to the tablet. This suggests they may play more of a ‘predisposing’ role rather than affecting the intensity of a placebo response. Other demographic factors such as education or employment status showed no effect, supporting the results from the review in Chapter 2. Also studying the effect of ethnicity, I found no association with symptom attribution.

In terms of the other predictors, participants with more symptoms at baseline and higher expectation of side effects had an increase in the odds of attributing symptoms to the tablet, and attributed a higher number of symptoms to the tablet, highlighting the importance of these factors in predicting placebo responses. Anxiety, optimism, somatisation and somatosensory amplification had no effect on the odds of symptom attribution. Instead measures that addressed medicine-related beliefs seemed to be more important. Belief that medicines cause harm, modern health worries, and perceived sensitivity to medicines were all associated with increased odds of symptom attribution. Similarly I also found that trust in medicine development and pharmaceutical companies were associated with a substantial decrease in the odds of symptom attribution. This tallies in with past research showing that a more general distrust in modern medicine is associated with symptom reporting (Eriksen et al., 2004; Kaptein et al., 2005; Petrie et al., 2001; Rief et al., 2012). However it is something that to my knowledge has not been considered specifically in the literature before but warrants further investigation as a potential way for clinicians to identify those at risk of placebo effects.

These factors identified as predictors of placebo effects both from the systematic review and RCT lend support to the different mechanisms that have been suggested to explain placebo effects. For example, the expectation mechanism is supported by the risk factors of symptom suggestions and perceived dose identified in the systematic

review, as well as by the influence of symptom expectations and medicine-related beliefs on symptom attribution in the RCT. The learning mechanism is supported by the evidence found for social observation and classical condition in contributing to placebo effects in the systematic review. Finally, the misattribution mechanism is supported by evidence for self-awareness identified in the systematic review and the influence of participants' symptom experience at baseline in the RCT.

Given the support found for the different mechanisms of placebo effects, as has been suggested in reference to the placebo literature (Stewart-Williams, 2004), it is probably inappropriate to lump all placebo effects together. Although they are often considered as competing mechanisms, they may in fact highlight the fact that there are many different aspects of placebo effects and to label them as one phenomenon is inappropriate.

11.1.2 Can altering communication about side effects reduce the occurrence of placebo responses?

By far the most supported mechanism of placebo identified in the systematic review was that of expectations due to the strong influence that verbal suggestions, dose and participants' baseline expectations had on symptom reporting in response to an inert exposure. Intervening in participants' expectations therefore seemed to be the best way to reduce placebo responses to medications. PILs provide an excellent opportunity to deliver such an intervention as they are already required to be distributed with every prescribed and OTC medication (MHRA, 2010). Between 35-70% of patients read the accompanying PILs for their medication at some point, and information about side effects is the most commonly read section (Harris, Dickinson, Raynor, MacDonald, & Knapp, 2015; Raynor et al., 2007). I therefore extended previous findings looking at the influence of side effect communication on symptom reporting to the influenza vaccine

(O'Connor et al., 1996) and tested the effectiveness of positively framing side effect risk information to reduce symptom reporting to an inert tablet.

Piloting the effectiveness of positively framed side effect risk information on symptom expectations showed the intervention was successful at reducing symptom expectations and therefore should be effective at reducing actual symptom reporting. Undertaking an RCT I tested the effect of using positively framed side effect risk information (e.g. uncommon, 90% of people will not be affected) on symptom reporting to an inert tablet compared to current wording used in PILs (e.g. common, 1 in 10 people will be affected). Due to the ethical issues surrounding placebo research as discussed in Chapter 4, any information given to participants was as truthful as possible and where deception was needed I used an authorised deceptive approach in order to reduce the amount of deception and any negative impacts this could have. The results from this large, methodologically rigorous study showed that positive framing of side effect information significantly reduced the likelihood of participants attributing symptoms to an inert tablet. However, I found no effect of positively framing side effect risk information on the total number or severity of symptoms attributed to the tablet. It therefore seems that positively framing side effect risk does well in stopping participants attributing any symptoms they experience to the tablet in the first place, but once participants have attributed symptoms it does not affect the number of symptoms they go on to attribute to the tablet or the severity of those symptoms. The results of the intervention are still encouraging however, as it could be argued that stopping participants attributing symptoms to the tablet at all is the most important outcome. It is better to have fewer people experiencing placebo responses rather than the same amount of people experiencing fewer placebo related symptoms each.

In addition, I found that despite previous concerns from the MHRA that positively framing side effects could be seen as a “marketing ploy” (MHRA, 2005),

positive framing had no effect on participants' satisfaction with the leaflet, its perceived credibility or their anxiety after reading the leaflet. The results suggest that altering the communication of side effects by using positive framing is received no differently to the current form of communication. Positively framing side effect risk information therefore shows promise as a potential intervention to reduce patient nocebo responses to their medication.

It is important to note there are other ways which have been discussed in the literature to reduce nocebo responses to medications by reducing expectations of side effects, however these have been met with concerns. Under the Hippocratic Oath, the primary aim of physicians is the principle of 'do no harm.' At the same time, modern bioethics requires physicians to obtain informed consent, respect their patient's autonomy and be transparent (Gillon, 2003). Colloca and Miller (2011) note that physicians have an obligation to express truthful information to their patients so they can make informed decisions about their medical care, however at the same time they face a challenge of how they can communicate this in a way that keeps nocebo responses to a minimum but is still consistent with informed consent. This responsibility to provide informed consent is in conflict with the responsibility to minimise the harm to patients, and as such many of the suggestions to reduce nocebo responses to medications are met with concerns about their ability to uphold patient informed consent and their paternalistic nature, reducing patient autonomy.

For example, in one of the first articles to discuss the clinical implications of nocebo research Colloca and Miller (2011) suggest the use of authorised concealment. In this approach patients would be asked if they are willing to agree not to receive information about certain types of side effects for a particular medicine they have been prescribed (Colloca & Miller, 2011). However not knowing about all the side effects can be harmful, especially if one of the concealed side effects, if disclosed, would

influence patients' decisions to take the medication or not (Colloca & Miller, 2011). As a result, failing to disclose all the risks (whether agreed to or not by patients) compromises informed consent.

Alfano (2015) proposed a similar concept to authorised concealment but also suggests physicians could provide patients with what he calls a 'bad fortune cookie,' a list of potential side effects concealed in a sealed envelope for the patient to open if they experienced any unexpected health outcomes. Blease (2015) however argues that these proposals to reduce nocebo responses could in fact aggravate them rather than prevent them from occurring. For example she suggests that patients who are aware that some of the risk information has been concealed may be more tempted to search for every possible side effect of their treatment (Blease, 2015). Similarly Roeser (2015) expressed concern that the concealment of side effects promotes uncertainty which could in itself create worse side effects due to the anxiety that is caused by not knowing. The request by physicians to conceal information from their patients might also have a knock on effect on the doctor-patient relationship (Meynen & Widdershoven, 2015; Roeser, 2015). For example patients may question why their physician would intentionally keep information from them or lie to them. This loss of trust may affect the physician's attempt to reduce nocebo responses but could also even reduce the positive placebo response (Meynen & Widdershoven, 2015), since trust between patients and physicians is an important factor in the generation of placebo effects (Bystad, Bystad, & Wynn, 2015; Meynen, Swaab, & Widdershoven, 2012). This concern is supported by the findings from Chapter 8: in my study, higher trust in different attributes of the medical and pharmaceutical industry was associated with a lower chance of attributing symptoms to the inert tablet.

In an attempt to balance the need for informed consent and do no harm, Wells and Kaptchuk (2012) proposed the idea of contextualised informed consent. This

involves the physician taking into account the possible side effects of the prescribed treatment, the person being treated and the disease, and tailoring the information they provide about the side effects in order to give the most transparency but with the least potential harm (Wells & Kaptchuk, 2012). Fortunato, Wasserman, and Menkes (2017) propose a similar idea but suggest that on top of this, patients should be encouraged to report any side effects promptly and should then receive appropriate follow-up disclosure through a phone call or appointment. Not surprisingly the idea of tailoring side effect information depending on the patient being treated has come under fire due to its highly paternalistic nature. Preventing patient autonomy to promote patient well-being risks creating a paternalistic approach where physicians feel authorized to control the disclosure of information without permission from their patients, influencing the decision-making processes, and preventing a therapeutic alliance with their patient (Brody & Colloca, 2013). In addition, similar to the authorised concealment approach, some of the side effects withheld from patients could be an important factor in their decision to take the medication or not (Colloca & Miller, 2011).

Not only do the above approaches carry concerns regarding informed consent and patient autonomy, they also neglect an important source of information that patients can access and which they may even use as their primary source of medical information, the internet. In this current age, the use of smart phones means it is possible for patients to learn about all the side effects of their treatment before they get home from the doctor's, even after agreeing for the side effects to be concealed. Many patients will look for side effect information on the internet (McMullan, 2006), therefore even if physicians do withhold this information, it is still available on the internet for nocebo effects to be induced (Meynen et al., 2012).

The use of positive framing however does not withhold any information about side effects, therefore it does not infringe informed consent, patient autonomy or

encourage patients to seek further information on the internet. This approach is an example of libertarian paternalism (Thaler & Sunstein, 2008), in which the goal is to “influence the choices of affected parties in a way that will make those parties better off,” often by using ‘nudge’ techniques which shape decision making but importantly do not withhold any information. Positively framing side effect risk in PILs is therefore one of the more appealing and suitable interventions that could be used to reduce nocebo responses to medications. Especially since the UK Supreme Court recently ruled that Doctors are obliged to tell patients about every risk of their treatment, and should not have the power to decide what information a patient should be given (Dyer, 2015).

11.1.3 How do people understand and interpret the current wording used in PILs to communicate side effect risk?

As my intervention to reduce nocebo responses to medications involves changing the way we communicate side effect risk in PILs it was important to test whether such changes are justified. While changes to the wording in order to reduce nocebo effects might be justified, if the current wording is well understood by patients, changing it might justifiably be seen as too risky by the MHRA, EC and pharmaceutical industry. Previous research has suggested that the risks implied by the current verbal risk descriptors used in PILs are overestimated (Berry et al., 2004; Berry et al., 2002; Berry, Raynor, & Knapp, 2003). In addition despite EC guidelines attempting to overcome this overestimation by recommending that verbal risk descriptors are presented alongside their numerical risk frequency, this still leads to overestimation (Knapp et al., 2015; Knapp, Raynor, et al., 2009). It seems this is because people’s interpretations of the verbal risk descriptors are at odds with their corresponding numerical frequency bands. However existing studies researching this are flawed, often being based on small student populations. I wanted to test people’s interpretation of the

current verbal risk descriptors used in PILs in the first study in this area that is representative of England.

The results from the survey showed that the general public do not accurately interpret the verbal risk descriptors recommended by the EC, and widely overestimate what they mean in terms of frequencies. This overestimation generalised to other verbal descriptors I tested which are not used in PILs. Closer analysis of the data suggested that there may be a fundamental mismatch between how we are attempting to communicate (with five different divisions of frequency) and how people understand risk. The data suggests people view descriptors as meaning either ‘likely’ or ‘not likely’ – all descriptors are mentally reinterpreted as one of those two versions.

I also investigated how the general public interpret the combined expressions and found that these lead to high expectations about their personal likelihood of experiencing symptoms. The majority of people thought that side effects which were ‘very common, more than 1 in 10’ or ‘common, up to 1 in 10’ were at least likely if not very likely to happen to them personally. These high expectations are a problem as I have highlighted previously that expectations are an important predictor of placebo responses to medications. It is important that if PILs are going to use this combined expression that they use the correct verbal risk descriptors which people interpret in line with the corresponding numerical expression. However, my research suggests this may not be possible (changing the verbal risk descriptors or tweaking the wording does little to affect people’s estimations).

I also found that participants’ side effect expectations to the current combined expressions are formed independently from their probability estimates of the verbal risk descriptors. Underestimating the current verbal risk descriptors does not necessarily mean that people will have lower side effect expectations. This further calls into question why PILs use verbal risk descriptors if participants’ estimations of what that

means for people's risk in general has little impact on their own risk expectations. It may be better to abandon the use of verbal risk descriptors entirely in PILs.

As expectations are important in the experience of nocebo responses I examined associations between participant characteristics and their side effect expectations. I found that participants who were female, from ethnic minorities, who were less well educated, had a household illness or were health illiterate, were more likely to have higher expectations of side effects. It was interesting to find here that demographic characteristics such as ethnicity and education were associated with side effect expectations, despite finding no relationship previously with nocebo responding. This could have been due to the small sample being studied in the RCT compared to the survey which contained many more educated and ethnically diverse participants. It is also interesting that here women have higher side effect expectations, yet I found no effect of gender on nocebo responses in the systematic review, and the RCT found men were more susceptible to the nocebo response. Further work is needed to decipher the nocebo-gender relationship. Similar to associations I found with nocebo responses however, participants with higher perceived sensitivity to medicines and negative beliefs about medicines were more likely to have higher expectation of side effects, whereas optimism and health anxiety showed no associations. It is possible therefore that the associations between perceived sensitivity to medicines, negative beliefs about medicines and nocebo responding is mediated by side effect expectations.

In summary, the results from the survey of a representative sample of England therefore justify the need for a change in the current way we communicate side effect risk in PILs. It is important to communicate side effects in a way that patients will correctly understand and interpret making sure they do not overestimate the risk to others and also themselves. Positively framing side effect risk information reduces side

effect expectations and the likelihood of nocebo responses and could be a way of communicating side effect risk that is better understood by patients.

11.2 Limitations

A general limitation of the research conducted in this PhD is the focus on analogues to genuine medications, rather than responses to active medication itself. There is evidence to suggest that active placebos (which mimic the side effects of the actual drug) have more impact than passive placebos (Moncrieff, 2003). This might also be true for nocebo effects, with active nocebos perhaps inducing stronger nocebo effects. In the review, for instance, I only included studies that looked at symptom reporting following an inert exposure, with most studies carried out in a laboratory or experimental setting. Similarly the RCT took place at a purpose built clinical research facility within a hospital and used an unnamed tablet. Clearly this does not reflect what happens in normal situations where people take medications at home while carrying out their daily activities. In addition, the cross-sectional survey asked participants to think about hypothetical scenarios rather than asking them about a medication that they were genuinely taking. On the one hand, this artificiality may limit the generalisability of the results. It could be that the impact of the intervention or perceptions about the risks of a drug will be less clear cut in the real world. On the other hand ensuring the stimuli in the RCT and systematic review where genuinely inert allowed me to test factors influencing nocebo effects more clearly. In addition the cross-sectional survey allowed the generic issues relating to the wording of side effects in PILs to be identified, uncontaminated by specific issues relating to media reporting around any one particular medicine.

Another limitation is the fact that the sample of participants included in the RCT, survey and in the majority of the studies included in the systematic review were healthy people between the ages of 18 and 65. Older adults are the largest consumers of

prescription medications (Catlin, Cowan, Hartman, & Heffler, 2008) and the most at risk of medication side effects (Gurwitz et al., 2003). Therefore it is older adults who are most prone to experience nocebo effects to their medications, rather than those studied in this PhD. In addition, the sample of participants included in the RCT were not representative of the general public, and due to the voluntary nature of the study were not overly worried or concerned about taking part or medicines in general. This can be seen by their scores for PIL reading behaviour, perceived sensitivity to medicines, beliefs that medicines cause harm and beliefs that medicines are overused, all of which were higher on average for the representative sample used in the online survey compared to the sample used for the RCT. Replication of the findings in a broader group of participants will be an important next step.

11.3 Implications

I believe the implications of the research carried out for my PhD to understand and prevent nocebo responses to medications are three-fold.

First, the current way that we are communicating side effect information in PILs does not work. The general public drastically overestimate the intended statistical risk of the verbal risk descriptors used in PILs. In addition, the EC's suggestion of combining the verbal risk descriptors with their corresponding numerical expression still leads to people forming high expectations about their own likelihood of getting the side effects. This begs the question as to why we are using these verbal descriptors at all if a) people do not understand them and b) they cause people to have unrealistic expectations about their own likelihood of getting side effects.

Second, one way that we could change the way we communicate side effect risk in PILs is by using positive framing. Framing side effect risk in terms of the number of people who remain side effect free has shown promising results by reducing side effect expectations and significantly reducing the likelihood of participants experiencing

nocebo responses to an inert tablet. Not only has this been shown to be effective as a potential way to reduce nocebo responses to medicines, it is also ethically viable as it does not raise concerns regarding paternalism, patient autonomy or informed consent. There are still gaps (listed below) that require further research before this can be recommended and rolled out across clinical practice with confidence, but the initial results presented in thesis appear promising.

Finally, it may be possible to predict, to some degree, who is more likely to experience nocebo responses to their medications. As evidenced by the systematic review and RCT, my results suggest we should not be overly concerned about patients' demographic characteristics or personality features such as anxiety, optimism, somatisation or somatosensory amplification as these have shown inconsistent effects. Instead, as well as patients' current symptoms and side effect expectations, my results suggest we should also be aware of patients' medicine-related beliefs, such as any negative beliefs about medications, a high perceived sensitivity to medications and low trust in medicine development and pharmaceutical companies. It is important for physicians to take the time to address and correct any of such beliefs or expectations if they are unrealistically negative. These are much stronger predictors of nocebo responses to medications than more dispositional factors and play a part in the formation of side effect expectations, an important precursor to nocebo responses.

11.4 Future research

Future research should focus on developing the most effective form of positively framed side effect risk information and ensuring it is better understood by patients than the risk information currently in use. For example, testing whether it is better to use frequencies (e.g. 9 in 10 people will not be affected) as opposed to percentages (e.g. 90% of people will not be affected), and if either are more effective without accompanying verbal descriptors, would be of value. In addition, it is important to test

the effectiveness of positively framing side effect risk in a more realistic setting, for example a patient population prescribed a medication for the first time. This will enable us to see if this intervention works outside of a laboratory setting before being confident in rolling it out across clinical practice. Relatedly, positive framing may not necessarily be beneficial in all circumstances. Many medications have serious, though rare, side effects which require medical attention; not attributing them to the medication could be detrimental to the wellbeing of the patient. This potential risk is something which future research will need to explore.

Similarly, to allow clinicians to identify patients at risk of side effects, it is important to investigate the predictors of nocebo effects in a patient sample to confirm if the factors that are important in predicting the attribution of symptoms to a sham medication are the same as those that predict the attribution of symptoms to a real medication. Also future research needs to decipher the relationship between gender and nocebo effects to see if there is something about the way that nocebo effects are induced which affects genders differently. We know that expectations are a major gateway to nocebo effects, but we do not know the best way to change these expectations. In this thesis, I have focused on the way side effects are communicated by altering the current wording in PILs. However, there might be other ways to influence side effect expectations and reduce nocebo responses to medications, for example through the use of figurative risk representations which allow people to visualise the risk of side effects (Zipkin et al., 2014).

Finally, on a separate note, it may be time for future research to start using less deceptive approaches to study nocebo effects. As noted in Chapter 4 despite evidence suggesting that deception in the field of psychology does not produce severe negative effects, deceptive research is not risk free. Researchers should be wary of any potential deleterious effects from deceiving their participants. As studying nocebo effects

requires some form of deception whether by deliberate misinformation or withholding information there are various approaches researchers can take as precautions. In my RCT I chose to minimise the amount of deception required by informing participants that I would not tell them the identity of the tablet until after the study was completed, rather than providing them with a false cover story about the identity of the tablet. This procedure aligns with the principles of authorised deception (Miller et al., 2005) and, as the results demonstrate, was an effective way of triggering the nocebo response.

11.5 Concluding remarks

Nocebo effects can explain many of the non-specific side effects that patients attribute to their medications. Not only is this a problem on an individual level, affecting adherence and health outcomes resulting in costs to the NHS, but it can also cause serious problems on a population wide level during public health emergencies.

Evidence from the studies reported here support the fact that nocebo effects can be explained by many different mechanisms, and the suggestion that there may be not just one nocebo effect, but rather a range of nocebo effects each brought about by different mechanisms. As my systematic review provided substantial evidence for the role that the expectation mechanism plays in nocebo effects, this is a good place to intervene to try to reduce nocebo responses. In terms of medications, one of the primary places where patients can develop these expectations is from what they read in the accompanying PIL. Not only are PILs readily amenable to change, a change in how we communicate side effect risk in PILs is also justified given how poorly they are currently understood by the general public. Positive framing of side effect risk in PILs significantly reduces the likelihood of participants attributing symptoms to a supposed medication. As such positive framing is a promising intervention to reduce the likelihood of patients attributing symptoms to their medication which are the result of a nocebo effect. In addition, compared to many other interventions that have been

suggested in the literature, positive framing does not withhold any information, and therefore does not infringe on informed consent or patient autonomy. More research is needed to assess the effectiveness in a patient population and to see if the intervention prevents patients attributing genuine, severe, side effects to their medication.

Finally, medicine-related beliefs seem to play a more important role in predicting placebo responses to a sham medicine than demographics or personality characteristics. Future work is needed to assess these factors in a patient sample attributing symptoms to a real medication, and to decipher the relationship between gender and placebo responses.

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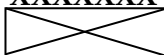
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Appendix A. Initial patient information leaflet design

Standard worded patient information leaflet

Package Leaflet: Information for the user

XXXXXXX 480 mg hard tablets



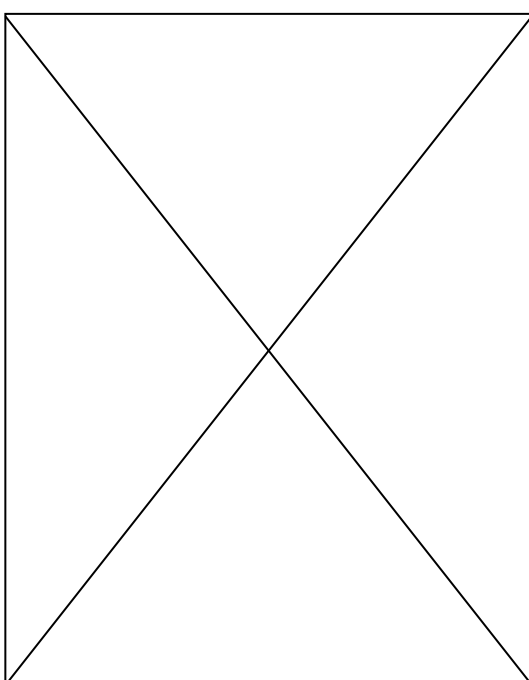
Read this leaflet carefully because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What XXXXXXX is and what it is used for
2. What you need to know before you take XXXXXXX
3. How to take XXXXXXX
4. Possible side effects
5. How to store XXXXXXX
6. Contents of the pack and other information

1. What XXXXXXX is and what it is used for



2. What you need to know before you take XXXXXXX

Do not take XXXXXXX:

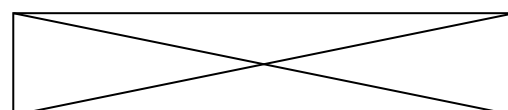
- if you are **allergic** to any of the ingredients of XXXXXXX listed in section 6.

Warnings and precautions:

Before you take XXXXXXX, talk to your doctor

- if you are **allergic to other over-the-counter tablets**
- If you have **diabetes**
- if you have a **severe medical condition**, which may require immediate hospitalisation

Other tablets and XXXXXXX



Pregnancy and breast-feeding

XXXXXXX has no known effect on pregnant women, women trying to conceive or on breast-fed infants.

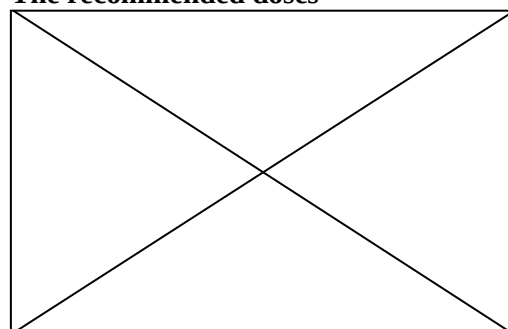
Driving and using machines

XXXXXXX has been known to have an effect on your ability to drive or use machines due to the occurrence of possible side effects.

3. How to take XXXXXXX

Take this tablet exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses



Method of administration

Swallow the tablet whole with water. Do not break or chew the tablet. XXXXXXXX can be taken with or without food. But it is recommended to be taken without food to achieve the greatest effect.

If you take more XXXXXXXX than you should

Stop taking XXXXXXXX.

In most cases of overdose, people have reported an increased number and severity of side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.

If you forget to take XXXXXXXX

Take the next tablet as soon as you remember.

4. Possible side effects

Like all tablets, this tablet can cause side effects, although not everybody gets them. These side effects mostly occur within one hour after taking the first tablet and will usually stop as you continue to take them.

Very common side effects

(More than 1 in 10 people will be affected)

- Headache
- Nausea

Common side effects

(1 in 10 people will be affected)

- Cough
- Dizziness
- Pain in limb
- Runny nose
- Sore throat
- Stomach ache
- Tiredness
- Bloating

Uncommon side effects

(1 in 100 people will be affected)

- Itchy skin

Rare side effects

(1 in 1,000 people will be affected)

- Confusion
- Agitation
- Anxiety

Reporting of side effects

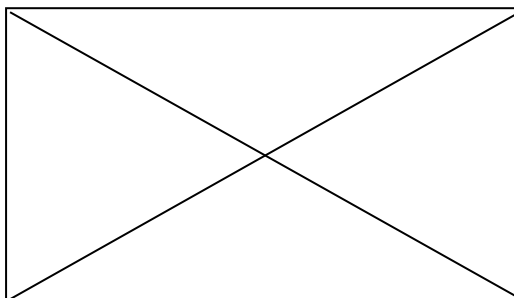
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

5. How to store XXXXXXXX

Keep out of the sight and reach of children. Do not use this tablet after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25 ° C.

Do not throw away any tablets via wastewater or household waste. Ask your pharmacist how to throw away tablets you no longer use. These measures will help protect the environment.

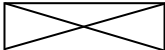
6. Contents of the pack and other information**What XXXXXXXX contains****What XXXXXXXX looks like**

The tablets have a round white opaque body.

This leaflet was last revised in 11/2014

Package Leaflet: Information for the user

XXXXXXX 480 mg hard tablets



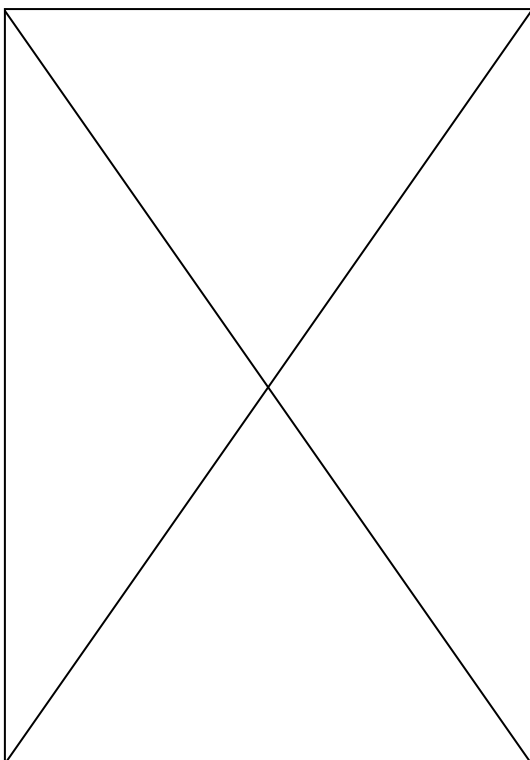
Read this leaflet carefully because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

7. What XXXXXXXX is and what it is used for
8. What you need to know before you take XXXXXXXX
9. How to take XXXXXXXX
10. Possible side effects
11. How to store XXXXXXXX
12. Contents of the pack and other information

1. What XXXXXXXX is and what it is used for



2. What you need to know before you take XXXXXXXX

Do not take XXXXXXXX:

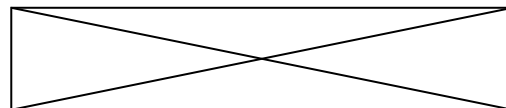
- if you are **allergic** to any of the ingredients of XXXXXXXX listed in section 6.

Warnings and precautions:

Before you take XXXXXXXX, talk to your doctor

- if you are **allergic to other over-the-counter tablets**
- If you have **diabetes**
- if you have a **severe medical condition**, which may require immediate hospitalisation

Other tablets and XXXXXXXX



Pregnancy and breast-feeding

XXXXXXX has no known effect on pregnant women, women trying to conceive or on breast-fed infants.

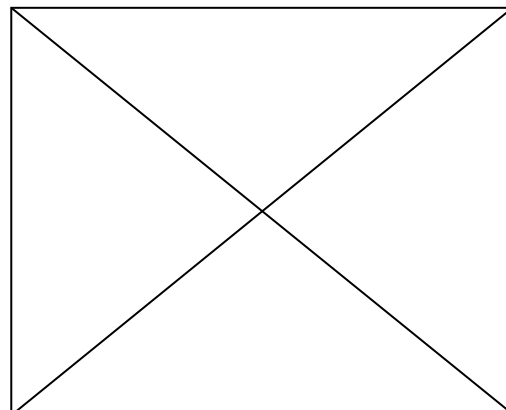
Driving and using machines

XXXXXXX has been known to have an effect on your ability to drive or use machines due to the occurrence of possible side effects.

3. How to take XXXXXXXX

Take this tablet exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses



Method of administration

Swallow the tablet whole with water. Do not break or chew the tablet. XXXXXXXX can be taken with or without food. But it is recommended to be taken without food to achieve the greatest effect.

If you take more XXXXXXXX than you should

Stop taking XXXXXXXX.

In most cases of overdose, people have reported an increased number and severity of side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.

If you forget to take XXXXXXXX

Take the next tablet as soon as you remember.

4. Possible side effects

Like all tablets, this tablet can cause side effects, although not everybody gets them. These side effects mostly occur within one hour after taking the first tablet and will usually stop as you continue to take them.

Uncommon side effects

(80% of people will not be affected)

- Headache
- Nausea

Very uncommon side effects

(90% of people will not be affected)

- Cough
- Dizziness
- Pain in limb
- Runny nose
- Sore throat
- Stomach ache
- Tiredness
- Bloating

Rare side effects

(99% of people will not be affected)

- Itchy skin

Very rare side effects

(99.9% of people will not be affected)

- Confusion
- Agitation
- Anxiety

Reporting of side effects

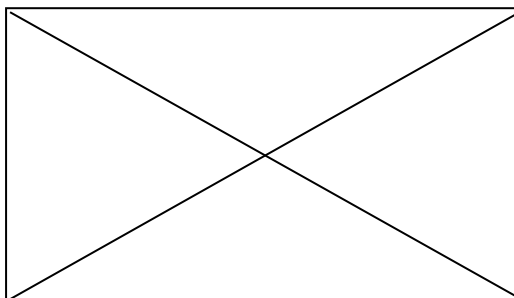
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

5. How to store XXXXXXXX

Keep out of the sight and reach of children. Do not use this tablet after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25 ° C.

Do not throw away any tablets via wastewater or household waste. Ask your pharmacist how to throw away tablets you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information**What XXXXXXXX contains****What XXXXXXXX looks like**

The tablets have a round white opaque body.

This leaflet was last revised in 11/2014

Appendix B. Original ethical approval for pilot and randomised controlled trial

Rebecca Orme
Department of Psychology
King's College London
5th Floor, Bermondsey Wing
Guy's Hospital
London
SE1 9RT

15 December 2014

Dear Rebecca,

PNM/14/15-62 Preventing the Nocebo Effect

Review Outcome: Full Approval

Thank you for submitting your application for ethical approval. This was reviewed by the PNM RESC on 9th December 2014. As a result, the Committee have granted full ethical approval for your study.

Provisos

Your approval is based on the following provisos being met:

1. Section 2.7: Please ensure that evidence of R&D approval can be made available upon request.
2. Section 7.1: The Committee recommends that participants are allowed at least 24 hours to consider whether to take part after reading the Information Sheet.
3. Section 7.3: The Committee recommends you should consider debriefing the participants after their individual session, rather than at the end of data collection.
4. Information Sheet: Specify an exact date as the deadline for withdrawal of participant data.
5. Consent Form: Please ensure that the text and the tick-boxes are aligned.
6. Questionnaire: Please use UK Census 2011 categories of ethnicity.

You are not required to provide evidence to the Committee that these provisos have been met, but your ethical approval is only valid if these changes are made. You must not commence your research until these provisos have been met.

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (<http://www.kcl.ac.uk/college/policyzone/index.php?id=247>).

For your information ethical approval is granted until 15 December 2015. If you need approval beyond this point you will need to apply for an extension to approval at least two weeks prior to this explaining why the extension is needed, (please note however that a full re-application will not be necessary unless the protocol has changed). You should also note that if your approval is for one year, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the duration of the research study, up to the conclusion of the research. The conclusion of the research is defined as the final date or event detailed in the study description section of your approved application form (usually the end of data collection when all work with human participants will have been completed), not the completion of data analysis or publication of the results.

For projects that only involve the further analysis of pre-existing data, approval must cover any period during which the researcher will be accessing or evaluating individual sensitive and/or un-anonymised records.

Note that after the point at which ethical approval for your study is no longer required due to the study being complete (as per the above definitions), you will still need to ensure all research data/records management and storage procedures agreed to as part of your application are adhered to and carried out accordingly.

If you do not start the project within three months of this letter please contact the Research Ethics Office.

Should you wish to make a modification to the project or request an extension to approval you will need approval for this and should follow the guidance relating to modifying approved applications: <http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx>

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance

(<http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx>)

We wish you every success with this work.

Yours sincerely,

James Patterson - Senior Research Ethics Officer

For and on behalf of

Professor Gareth Barker, Chairman

Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM RESC)

Cc: James Rubin

Appendix C. Ethics modification approval for pilot and randomised controlled trial

Rebecca Orme
Department of Psychology
King's College London
5th Floor, Bermondsey Wing
Guy's Hospital
London SE1 9RT

30 March 2015

Dear Rebecca,

PNM/14/15-62 Preventing the Nocebo Effect

Thank you for submitting a modifications request for the above study. I am writing to confirm approval of these. The approved modifications are summarised broadly below:

1. Information Sheet: Minor amendments to wording in order to mitigate participant anxiety.
2. Symptom questionnaire: Clarification of some of the wording used.
3. Modern Health Concerns: 'Amalgam dental fillings' renamed as 'Mercury dental fillings'.
4. PHQ-15: Minor reordering of items to prevent confusion.
5. Anxiety questionnaires: Inclusion of anxiety measure a baseline.
6. Inclusion of open-ended question about the tablet identity at the end of the study.
7. Use of a 'filler' task.
8. Circulation of the debrief e-mail *after* data-collection.
9. Clarifications within debrief e-mail.

Please note these modifications are approved with the following proviso:

1. Section 4: Please provide the Research Ethics Office with details of the 'filler' task once these are determined. Approval has been granted on the understanding that the filler will not cause participants any undue anxiety or distress.

If you have any questions, please let me know.

Yours sincerely,

James Patterson – Senior Research Ethics Officer

Cc: James Rubin

Evaluating Patient Information Leaflets for a Well-known Tablet

Questionnaire Booklet

PART 1

Background Information

Please state your:

Name:

Date of birth (dd/mm/yyyy): _ _ / _ _ / _ _ _ _

The gender you identify yourself with:

- ☐ Male
- ☐ Female

Choose one section from A to E, then tick one box to best describe your ethnic group or background:

A White

- ☐ English/Welsh/Scottish/Northern Irish/British
- ☐ Irish
- ☐ Gypsy or Irish Traveller
- ☐ Any other white background (please specify):.....

B Mixed / Multiple ethnic groups

- ☐ White and Black Caribbean
- ☐ White and Black African
- ☐ White and Asian
- ☐ Any other Mixed/Multiple ethnic background (please specify):.....

C Asian / Asian British

- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Chinese
- ☐ Any other Asian background (please specify):.....

D Black / African / Caribbean / Black British

- ☐ African
- ☐ Caribbean
- ☐ Any other Black/African/Caribbean background (please specify):.....

E Other ethnic group

- ☐ Arab
- ☐ Any other ethnic group (please specify):.....

Highest level of education:

- ☐ Left school without qualifications
- ☐ Secondary education (O-level/GCSE/A-level)
- ☐ Higher education (BSc,BA/higher qualification)

Employment status:

- ☐ Full time
- ☐ Part time
- ☐ Sick leave
- ☐ Unemployed
- ☐ Student

**PLEASE MAKE SURE YOU HAVE ANSWERED ALL THE
QUESTIONS
YOU HAVE NOW FINISHED PART 1, PLEASE NOTIFY THE
RESEARCHER. YOU WILL NOW RECEIVE THE FIRST
PATIENT INFORMATION LEAFLET FOR XXXXXXXX**

PART 2 – COMPLETE AFTER YOU HAVE READ THE PATIENT INFORMATION LEAFLET

Questions about the patient information leaflet

From the information you have just read in the patient information leaflet, to what extent do you expect to experience any of the listed side effects in the hour following taking XXXXXXXX?

(0 = not at all likely to 3 = very likely)

	Not at all likely 0	1	2	Very likely 3
Anxiety				
Dizziness				
Sore throat				
Nausea				
Chest pain				
Confusion				
Headache				
Tiredness				
Stomach ache				
Cough				
Itchy skin				
Hot flushes				
Depressed mood				
Dry mouth				
Abnormal sweating				
Breathing problems				
Tremor				
Runny nose				
Bloating				
Agitation				
Pain in limb				
Palpitations				
Irritability				
Any other symptoms? (please name these)				
1.....				
2.....				
3.....				

Having read the patient information leaflet, please state how much you agree with the following statements.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The leaflet was clear					
The leaflet was easy to understand					
The leaflet contained words I did not understand					
The leaflet was similar to what I would expect to see for other tablets					
I felt there was enough information to make an informed choice as to whether to take the tablet or not					
The information was sufficient for me to understand the risks and benefits of XXXXXXXX					
Overall, I am satisfied with the information I have just read about XXXXXXXX					

The patient information leaflet is a possible source of information about side effects to this tablet. Considering what you know, please circle the number between the pair of words that best describes your feelings about the information from the patient information leaflet you have just read.

Can't be trusted	1	2	3	4	5	Can be trusted
Is inaccurate	1	2	3	4	5	Is accurate
Is unfair	1	2	3	4	5	Is fair
Doesn't tell the whole story	1	2	3	4	5	Tells the whole story
Is biased	1	2	3	4	5	Is unbiased

PLEASE MAKE SURE YOU HAVE ANSWERED ALL THE QUESTIONS

YOU HAVE NOW FINISHED PART 2, PLEASE NOTIFY THE RESEARCHER. YOU WILL NOW RECEIVE THE SECOND PATIENT INFORMATION LEAFLET.

PART 3 – COMPLETE AFTER YOU HAVE READ THE SECOND PATIENT INFORMATION LEAFLET

Questions about the patient information leaflet

From the information you have just read in the patient information leaflet, to what extent do you expect to experience any of the listed side effects in the hour following taking XXXXXXXX?

(0 = not at all likely to 3 = very likely)

	Not at all likely 0	1	2	Very likely 3
Anxiety				
Dizziness				
Sore throat				
Nausea				
Chest pain				
Confusion				
Headache				
Tiredness				
Stomach ache				
Cough				
Itchy skin				
Hot flushes				
Depressed mood				
Dry mouth				
Abnormal sweating				
Breathing problems				
Tremor				
Runny nose				
Bloating				
Agitation				
Pain in limb				
Palpitations				
Irritability				
Any other symptoms? (please name these)				
1.....				
2.....				
3.....				

Having read the patient information leaflet, please state how much you agree with the following statements.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The leaflet was clear					
The leaflet was easy to understand					
The leaflet contained words I did not understand					
The leaflet was similar to what I would expect to see for other tablets					
I felt there was enough information to make an informed choice as to whether to take the tablet or not					
The information was sufficient for me to understand the risks and benefits of XXXXXXX					
Overall, I am satisfied with the information I have just read about XXXXXXX					

The patient information leaflet is a possible source of information about side effects to this tablet. Considering what you know, please circle the number between the pair of words that best describes your feelings about the information from the patient information leaflet you have just read.

Can't be trusted	1	2	3	4	5	Can be trusted
Is inaccurate	1	2	3	4	5	Is accurate
Is unfair	1	2	3	4	5	Is fair
Doesn't tell the whole story	1	2	3	4	5	Tells the whole story
Is biased	1	2	3	4	5	Is unbiased

PLEASE MAKE SURE YOU HAVE ANSWERED ALL THE QUESTIONS

YOU HAVE NOW FINISHED PART 3, PLEASE GO TO PART 4

PART 4

Guess at tablet identity

What do you think the tablet is?

.....

How confident are you that this is the tablet? Please tick the appropriate box from 1 to 5.

Not at all confident 1	2	Somewhat confident 3	4	Completely confident 5

Any other feedback?

If you have any other feedback about the patient information leaflets or the study in general, please comment below.

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**PLEASE MAKE SURE YOU HAVE ANSWERED ALL THE
QUESTIONS**

**YOU HAVE NOW FINISHED THE STUDY, THANK YOU FOR
YOUR PARTICIPATION**

Appendix E. Pilot study participant information sheet

INFORMATION SHEET FOR PARTICIPANTS

REC Reference Number: PNM/14/15-62

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET



Evaluating patient information leaflets for a well-known tablet

Invitation paragraph

I would like to invite you to participate in this research project which forms part of my PhD research. You should only participate if you want to; choosing not to take part will not disadvantage you in anyway. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask me if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

The aim of this pilot study is to evaluate two different patient information leaflets that have been developed for a well-known tablet. We cannot tell you what the tablet is or what it is used for as we do not want to bias your views about it, but we can guarantee that you will have heard of it before. In the study we will refer to the tablet as XXXXXXXX.

Why have I been invited to take part?

I am inviting people over 18 years of age and who are English speakers and writers.

Do I have to take part?

Participation is voluntary. You do not have to take part. You should read this information sheet and if you have any questions you should ask the research team. You should not agree to take part in this research until you have had all your questions answered satisfactorily.

What will happen to me if I take part?

If you are interested in taking part you will be emailed this information sheet. If you decide to take part we will arrange a time for you to come to the testing room to take part. Here the researcher will go through the information sheet with you again and if you are happy to proceed, sign the consent form. At the start of the study you will receive one of the patient information leaflets to read first. Following this you will be asked questions about the information leaflet you just read. You will then receive the second patient information leaflet to read and be asked to answer the same questions about the leaflet again. There will also be an opportunity at the end to provide any additional feedback about the leaflets.

Average participation time is expected to be 1 hour.

Please note even if you have decided to take part, you are still free to cease your participation at any time and to have research data/information relating to you withdrawn data without giving any reason up to 31st May 2015.

Location

The study will take place at the Weston Education Centre at King's College London.

Incentives

For taking part in this study you will receive a £20.

What are the possible risks of taking part?

There are no expected risks of taking part; you will just be asked questions about the patient information leaflets for the tablet. You will NOT take the tablet.

What are the possible benefits of taking part?

There are no direct benefits to taking part. However, the information I get from the study will help to influence current practice in patient information leaflet development. Furthermore, I will provide you with a summary of a final report describing the main findings, including good practice and innovative initiatives.

Will my taking part be kept confidential?

All your data is strictly confidential and will be held securely until the research is finished. Your participation is entirely voluntary. If you change your mind, you are free to stop your participation and to have your data withdrawn without giving any reason up to 31st May 2015. All data for analysis will be anonymised. In reporting on the research findings, I will not reveal the names of any participants. At all times there will be no possibility of you as individuals being linked with the data.

The UK Data Protection Act 1998 will apply to all information gathered within the questionnaire booklet and held on password-locked computer files and locked cabinets within King's College London. No data will be accessed by anyone other than me; and anonymity of the material will be protected by using anonymous participant ID numbers. No data will be able to be linked back to any individual taking part in the study. You may withdraw your data from the project anytime up to 31st May 2015. All questionnaire booklets will be shredded after answers have been uploaded to password-locked computer files. If you ask me to withdraw your data at any time before 31st May 2015 I will remove all traces of it from the records.

How is the project being funded?

The NIHR Health Protection Research Unit and Institute of Psychiatry, Psychology and Neuroscience are funding this research. For further information visit: epr.hpru.nihr.ac.uk

The study has been approved by the King's College London Research Ethics Committee

What will happen to the results of the study?

I will produce a final report summarising the main findings, which will be sent to you. I also plan to disseminate the research findings through publication and conferences.

Who should I contact for further information?

If you have any questions or require more information about this study, please contact me using the following contact details:

Rebecca Orme
Department of Psychological Medicine
Institute of Psychiatry, Psychology and Neuroscience
King's College London
Denmark Hill Campus
Weston Education Centre
10 Cutcombe Road
London
SE5 9RJ
Rebecca.orme@kcl.ac.uk
Tel: 020 7848 5686

What if I have further questions, or if something goes wrong?

If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact King's College London using the details below for further advice and information:

Dr James Rubin,
Psychological Medicine Department
Weston Education Centre
10 Cutcombe Road
London
SE5 9RJ
gideon.rubin@kcl.ac.uk
Tel: 020 7848 5684

Thank you for reading this information sheet and for considering taking part in this research.

Appendix F. Pilot study participant consent form

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and listened to an explanation about the research.



Title of Study: Evaluating Patient Information Leaflets for a Well-known Tablet

King's College Research Ethics Committee Ref: PNM 14/15-62

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box I am consenting to this element of the study. I understand that it will be assumed that un-ticked/initialled boxes mean that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element I may be deemed ineligible for the study.

Please tick or initial

☐

1. I confirm that I have read and understood the information sheet dated, 13/11/14, version 1 for the above study. I have had the opportunity to consider the information and asked questions which have been answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. Furthermore, I understand that I will be able to withdraw my data up to 31st May 2015.
3. I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998.
4. I understand that my information may be subject to review by responsible individuals from the College for monitoring and audit purposes.
5. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications.

Please tick or initial

☐☐☐☐☐

6. I agree that the research team may use my data for future research and understand that any such use of identifiable data would be reviewed and approved by a research ethics committee. (In such cases, as with this project, data would not be identifiable in any report). ☐
7. I understand that the information I have submitted will be published as a report and I wish to receive a copy of it. ☐
8. I understand that I must not take part if I fall under the exclusion criteria as detailed in the information sheet, and explained to me by the researcher. ☐

Name of Participant

Date

Signature

Name of Researcher

Date

Signature

Appendix G. Ethics modification approval for randomised controlled trial

Rebecca Webster
Department of Psychology
King's College London
5th Floor, Bermondsey Wing
Guy's Hospital
London SE1 9RT

23 October 2015

Dear Rebecca,

PNM/14/15-62 Preventing the Nocebo Effect

Thank you for submitting a modifications request for the above study. These were reviewed by the Psychiatry, Nursing and Midwifery (PNM) Research Ethics Subcommittee (RESC), on 20th October 2015, and approved. The approved modifications are summarised very broadly below:

1. Extension of period of approval by one year until 9th December 2018.
2. Updating of screening questionnaire to fulfil the SLAM pharmacy requirements for the dispensing of placebos.
3. Updating of the control and intervention patient information leaflet to reflect changes resulting from the pilot.
4. Addition of cognitive tasks.
5. Changes to questions posed by the participants.

If you have any changes, please let me know.

Yours sincerely,

James Patterson – Senior Research Ethics Officer

Assessing the severity of short term side effects to a well-known tablet

Questionnaire

PART 1

Background Information

Please state your:

Name:

Date of birth (dd/mm/yyyy): _ _ / _ _ / _ _ _ _

The gender you identify yourself with:

- ☐ Male
- ☐ Female

Choose one section from A to E, then tick one box to best describe your ethnic group or background:

A White

- ☐ English/Welsh/Scottish/Northern Irish/British
- ☐ Irish
- ☐ Gypsy or Irish Traveller
- ☐ Any other white background (please specify):.....

B Mixed / Multiple ethnic groups

- ☐ White and Black Caribbean
- ☐ White and Black African
- ☐ White and Asian
- ☐ Any other Mixed/Multiple ethnic background (please specify):.....

C Asian / Asian British

- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Chinese
- ☐ Any other Asian background (please specify):.....

D Black / African / Caribbean / Black British

- ☐ African
- ☐ Caribbean
- ☐ Any other Black/African/Caribbean background (please specify):.....

E Other ethnic group

- ☐ Arab
- ☐ Any other ethnic group (please specify):.....

Highest level of education:

- ☐ Left school without qualifications
- ☐ Secondary education (O-level/GCSE/A-level)
- ☐ Higher education (BSc,BA/higher qualification)

Employment status:

- ☐ Full time
- ☐ Part time
- ☐ Sick leave
- ☐ Unemployed
- ☐ Student

Symptoms experienced in the last 24 hours

Please rate whether you experienced any of the following complaints during the last 24 hours by using the scale below.

0 = Complaint not present

1 = Mild: complaint causes mild distress or discomfort, but no impairment in daily functioning

2 = Moderate: complaint causes moderate distress or discomfort or at least some impairment in daily functioning

3 = Severe: complaint causes severe distress and discomfort, severe impairment in daily functioning, or acute danger to health

Please try to choose an answer even if you are not completely sure.

	Not present 0	Mild 1	Moderate 2	Severe 3
Anxiety				
Dizziness				
Sore throat				
Nausea				
Chest pain				
Confusion				
Headache				
Tiredness				
Stomach ache				
Cough				
Itchy skin				
Hot flushes				
Depressed mood				
Dry mouth				
Abnormal sweating				
Breathing problems				
Tremor				
Runny nose				
Bloating				
Agitation				
Pain in limb				
Palpitations				
Irritability				
Further symptoms: (please name these)				
1.....				
2.....				
3.....				

Modern Health Concerns

These days many people worry about the effects of different aspects of modern life on health. Please rate the following items for how much you are concerned about their effect on your *personal health*. Tick one box for each item.

	No concern	A little concern	Moderate concern	High concern	Extreme concern
Cell Phones					
Radio or Cell Phone Towers					
High Tension Power Lines					
Nuclear radiation					
Air pollution					
Noise pollution					
Depletion of the Ozone Layer					
Traffic fumes					
Other Environmental Pollution					
Pesticide spray					
Poor building ventilation					
Genetically modified food					
Additives in Food					
Pesticides in Food					
Antibiotics in Food					
Hormones in Food					
Mad cow disease					
Contaminated Water Supply					
Fluoridation of Water					
Vaccination Programmes					
Overuse of Antibiotics					
Toxic Chemicals in Household Products					
Leakage from Microwave Ovens					
Bacteria in Air Conditioning Systems					
Drug Resistant Bacteria					
Mercury dental fillings					
Medical and dental X- Rays					
Bio-terrorism (e.g. anthrax poisoning)					

Somatosensory Amplification Scale

Please rate the degree to which each of the following statement is characteristic of you in general on an ordinal scale of 1 to 5. A higher score indicates the statement is more characteristic of you.

	1	2	3	4	5
When someone else coughs, it makes me cough too					
I can't stand smoke, smog, or pollutants in the air					
I am often aware of various things happening within my body					
When I bruise myself, it stays noticeable for a long time					
Sudden loud noises really bother me					
I can sometimes hear my pulse or my heartbeat throbbing in my ear					
I hate to be too hot or too cold					
I am quick to sense the hunger contractions in my stomach					
Even something minor, like an insect bite or a splinter, really bothers me					
I have a low tolerance for pain					

Belief about medicines questionnaire – General subscale

We would like to ask you about your personal views about medicines in general. These are statements other people have made about medicines in general. Please indicate the extent to which you agree or disagree with them by ticking the appropriate box. There are no right or wrong answers. We are interested in your personal views.

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
Doctors use too many medicines					
People who take medicines should stop their treatment for a while every now and again					
Most medicines are addictive					
Natural remedies are safer than medicines					
Medicines do more harm than good					
All medicines are poisons					
Doctors place too much trust on medicines					
If doctors had more time with patients they would prescribe fewer medicines					

Revised Life Orientation Test

Please answer the following questions about yourself by indicating the extent of your agreement and ticking a response to the right of the statement. Be as honest as you can throughout, and try not to let your responses to one question influence your response to other questions. There are no right or wrong answers.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
In uncertain times, I usually expect the best					
It's easy for me to relax					
If something can go wrong for me, it will					
I'm always optimistic about my future					
I enjoy my friends a lot					
It's important for me to keep busy					
I hardly ever expect things to go my way					
I don't get upset too easily					
I rarely count on good things happening to me					
Overall, I expect more good things to happen to me than bad					

Patient Health Questionnaire -15

During the past four weeks, how much have you been bothered by any of the following problems. Please indicate by ticking the appropriate box.

	Not bothered at all	Bothered a little	Bothered a lot
Stomach pain			
Back pain			
Pain in your arms or legs or other joints			
Headaches			
Chest Pains			
Dizziness			
Fainting spells			
Feeling your heart pound or race			
Shortness of breath			
Pain or problems during sexual intercourse			
Constipation, loose bowels, or diarrhoea			
Nausea, gas, or indigestion			
Feeling tired, or having low energy			
Trouble sleeping			
Menstrual cramps or other problems with your periods (women only)			

Perceived Sensitivity to Medicines Scale

These are statements other people have made when prescribed medication during regularly scheduled and patient-requested visits. Please indicate the extent to which these statements apply to you by ticking the appropriate box. Higher scores indicate a higher applicability.

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
My body is very sensitive to medicines					
My body overreacts to medicines					
I usually have stronger reactions to medicines than most people					
I have had a bad reaction to medicines in the past					
Even very small amounts of medicines can upset my body					

State - Trait Anxiety Inventory - Short version

A number of statements which people have used to describe themselves are given below. Read each statement and then tick the most appropriate response to the right of the statement to indicate how you feel right now, at this moment.

There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately	Very much
I feel calm				
I am tense				
I feel upset				
I am relaxed				
I feel content				
I am worried				

PLEASE MAKE SURE YOU HAVE ANSWERED ALL THE QUESTIONS

YOU HAVE NOW FINISHED PART 1, PLEASE NOTIFY THE RESEARCHER. YOU WILL NOW RECEIVE THE PATIENT INFORMATION LEAFLET FOR XXXXXXXX.

PART 2 – COMPLETE AFTER YOU HAVE READ THE PATIENT INFORMATION LEAFLET

State - Trait Anxiety Inventory - Short version

A number of statements which people have used to describe themselves are given below. Read each statement and then tick the most appropriate response to the right of the statement to indicate how you feel right now, at this moment.
There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately	Very much
I feel calm				
I am tense				
I feel upset				
I am relaxed				
I feel content				
I am worried				

Questions about the patient information leaflet

From the information you have just read in the patient information leaflet, to what extent do you expect to experience any of the listed side effects in the hour following taking XXXXXXXX?

(0 = not at all likely to 3 = very likely)

	Not at all likely 0	1	2	Very likely 3
Anxiety				
Dizziness				
Sore throat				
Nausea				
Chest pain				
Confusion				
Headache				
Tiredness				
Stomach ache				
Cough				
Itchy skin				
Hot flushes				
Depressed mood				
Dry mouth				
Abnormal sweating				
Breathing problems				
Tremor				
Runny nose				
Bloating				
Agitation				
Pain in limb				
Palpitations				
Irritability				
Any other symptoms? (please name these)				
1.....				
2.....				
3.....				

Having read the patient information leaflet, please state how much you agree with the following statements.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The leaflet was clear					
The leaflet was easy to understand					
The leaflet contained words I did not understand					
The leaflet was similar to what I would expect to see for other tablets					
I felt there was enough information to make an informed choice as to whether to take the tablet or not					
The information was sufficient for me to understand the risks of XXXXXXX					
Overall, I am satisfied with the information I have just read about XXXXXXX					

The patient information leaflet is a possible source of information about side effects to this tablet. Considering what you know, please circle the number between the pair of words that best describes your feelings about the information from the patient information leaflet you have just read.

Can't be trusted	1	2	3	4	5	Can be trusted
Is inaccurate	1	2	3	4	5	Is accurate
Is unfair	1	2	3	4	5	Is fair
Doesn't tell the whole story	1	2	3	4	5	Tells the whole story
Is biased	1	2	3	4	5	Is unbiased

PLEASE MAKE SURE YOU HAVE ANSWERED ALL THE QUESTIONS

YOU HAVE NOW FINISHED PART 2, PLEASE NOTIFY THE RESEARCHER. YOU WILL NOW TAKE ONE TABLET OF XXXXXXX.

PART 3 – COMPLETE AN HOUR AFTER TAKING

XXXXXXX

State - Trait Anxiety Inventory - Short version

A number of statements which people have used to describe themselves are given below. Read each statement and then tick the most appropriate response to the right of the statement to indicate how you feel right now, at this moment.

There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately	Very much
I feel calm				
I am tense				
I feel upset				
I am relaxed				
I feel content				
I am worried				

Symptoms experienced following taking XXXXXXXX

Please rate whether you experienced any of the following complaints since taking XXXXXXXX by using the scale below. Please indicate by ticking yes or no whether you believe that these symptoms are related to taking XXXXXXXX.

0 = Complaint not present

1 = Mild: complaint causes mild distress or discomfort, but no impairment in daily functioning

2 = Moderate: complaint causes moderate distress or discomfort or at least some impairment in daily functioning

3 = Severe: complaint causes severe distress and discomfort, severe impairment in daily functioning, or acute danger to health

Please try to choose an answer even if you are not completely sure.

Complaints	Not present	Mild	Moderate	Severe	Is this complaint related to taking XXXXXXXX?	
	0	1	2	3	Yes	No
Anxiety						
Dizziness						
Sore throat						
Nausea						
Chest pain						
Confusion						
Headache						
Tiredness						
Stomach ache						
Cough						
Itchy skin						
Hot flushes						
Depressed mood						
Dry mouth						
Abnormal sweating						
Breathing problems						
Tremor						
Runny nose						
Bloating						
Agitation						
Pain in limb						
Palpitations						
Irritability						
Further symptoms: (please name these)						
1.....						
2.....						
3.....						

When you take new medications do you read the patient information leaflet accompanying them?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

Which sections of the patient information leaflet do you read? (Tick all that apply)

- ☐ What the medicine is and what it is used for
- ☐ What you need to know before you take the medicine
- ☐ How to take the medicine
- ☐ Possible side effects
- ☐ How to store the medicine
- ☐ Contents of the pack and other information

Please state how much do you agree with the following statements:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I trust the current process through which medicines are developed					
I trust the current process through which medicines are tested					
I trust the current process through which medicines are approved for use					
I trust pharmaceutical companies to act in patients' best interests					
Pharmaceutical companies are only interested in making money					

Guess at tablet identity

What do you think the tablet was?

.....

How confident are you that this is the tablet you took? Please tick the appropriate box from 1 to 5.

Not at all confident 1	2	Somewhat confident 3	4	Completely confident 5

**PLEASE MAKE SURE YOU HAVE ANSWERED ALL THE
QUESTIONS**

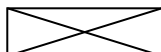
YOU HAVE NOW FINISHED THIS SECTION OF THE STUDY,
PLEASE AWAIT FURTHER INSTRUCTION

Appendix I. Patient information leaflets used in the randomised controlled trial

Standard worded patient information leaflet

Package Leaflet: Information for the user

XXXXXXX hard tablets



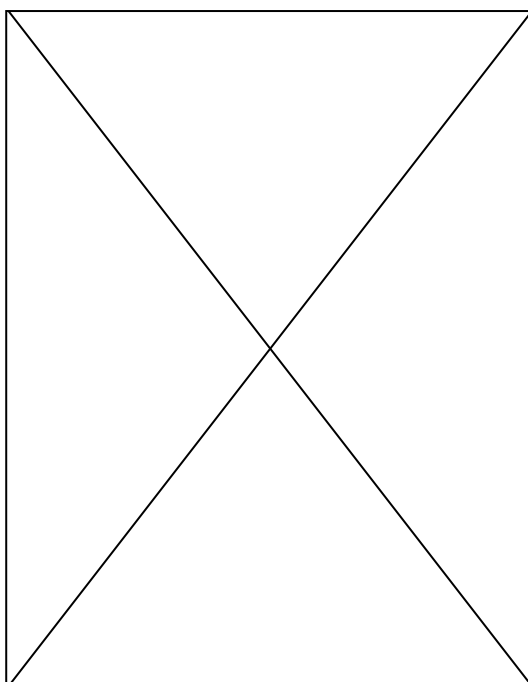
Read this leaflet carefully because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

13. What XXXXXXX is and what it is used for
14. What you need to know before you take XXXXXXX
15. How to take XXXXXXX
16. Possible side effects
17. How to store XXXXXXX
18. Contents of the pack and other information

1. What XXXXXXX is and what it is used for



2. What you need to know before you take XXXXXXX

Do not take XXXXXXX:

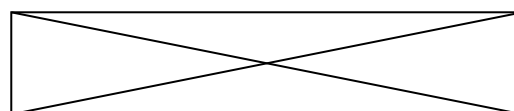
- if you are **allergic** to any of the ingredients of XXXXXXX listed in section 6.

Warnings and precautions:

Before you take XXXXXXX, talk to your doctor

- if you are **allergic to other over-the-counter tablets**
- If you have **diabetes**
- if you have a **severe medical condition**, which may require immediate hospitalisation

Other tablets and XXXXXXX



Pregnancy and breast-feeding

XXXXXXX has no known effect on pregnant women, women trying to conceive or on breast-fed infants.

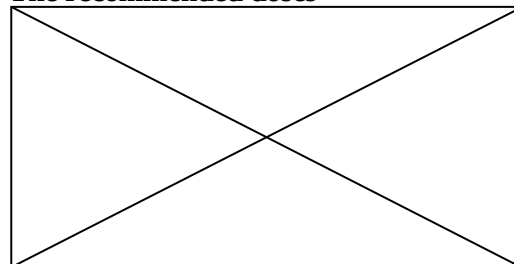
Driving and using machines

XXXXXXX has been known to have an effect on your ability to drive or use machines due to the occurrence of possible side effects. If you are affected do not drive or use machines until the side effects wear off.

3. How to take XXXXXXX

Take this tablet exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses



Method of administration

Swallow the tablet with water. The tablet can be divided into two equal halves. Do not chew the tablet. XXXXXXXX can be taken with or without food. But it is recommended to be taken without food to achieve the greatest effect.

If you take more XXXXXXXX than you should

Stop taking XXXXXXXX.

In most cases of overdose, people have reported an increased number and severity of side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.

If you forget to take XXXXXXXX

Take the next tablet as soon as you remember.

4. Possible side effects

Like all tablets, this tablet can cause side effects, although not everybody gets them. These side effects mostly occur within one hour after taking the first tablet and will usually stop as you continue to take them.

Very common side effects

(More than 1 in 10 people will be affected)

- Headache
- Nausea

Common side effects

(1 in 10 people will be affected)

- Cough
- Dizziness
- Pain in limb
- Runny nose
- Sore throat
- Stomach ache
- Tiredness
- Bloating

Uncommon side effects

(1 in 100 people will be affected)

- Itchy skin

Rare side effects

(1 in 1,000 people will be affected)

- Confusion
- Agitation
- Anxiety

Reporting of side effects

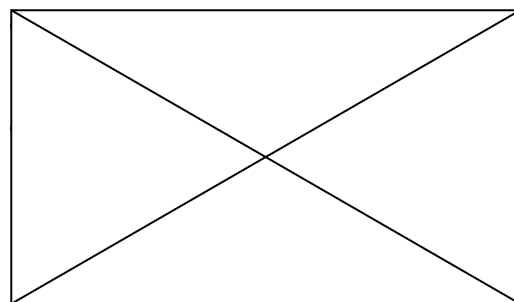
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

5. How to store XXXXXXXX

Keep out of the sight and reach of children. Do not use this tablet after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25 ° C.

Do not throw away any tablets via wastewater or household waste. Ask your pharmacist how to throw away tablets you no longer use. These measures will help protect the environment.

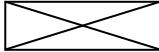
6. Contents of the pack and other information**What XXXXXXXX contains****What XXXXXXXX looks like**

The tablets have a round white opaque body with a breakline.

This leaflet was last revised in 08/2015

Package Leaflet: Information for the user

XXXXXXX hard tablets



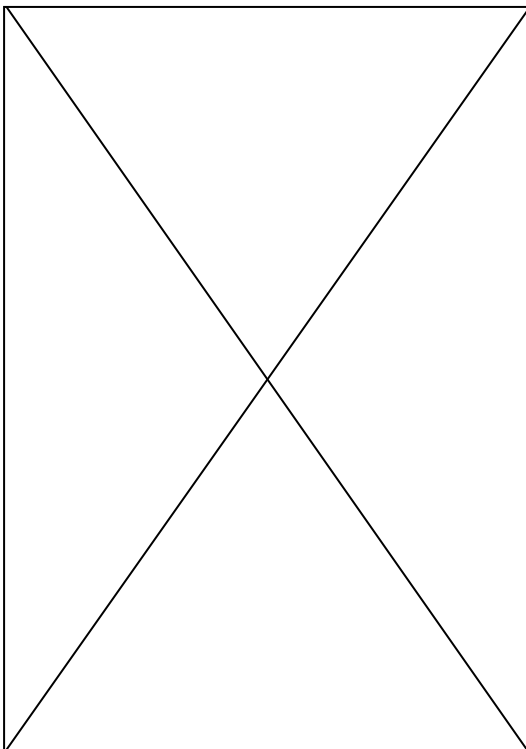
Read this leaflet carefully because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

19. What XXXXXXX is and what it is used for
20. What you need to know before you take XXXXXXX
21. How to take XXXXXXX
22. Possible side effects
23. How to store XXXXXXX
24. Contents of the pack and other information

1. What XXXXXXX is and what it is used for



2. What you need to know before you take XXXXXXX

Do not take XXXXXXX:

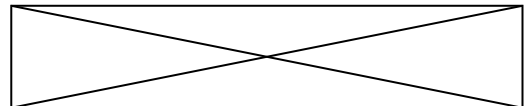
- if you are **allergic** to any of the ingredients of XXXXXXX listed in section 6.

Warnings and precautions:

Before you take XXXXXXX, talk to your doctor

- if you are **allergic to other over-the-counter tablets**
- If you have **diabetes**
- if you have a **severe medical condition**, which may require immediate hospitalisation

Other tablets and XXXXXXX



Pregnancy and breast-feeding

XXXXXXX has no known effect on pregnant women, women trying to conceive or on breast-fed infants.

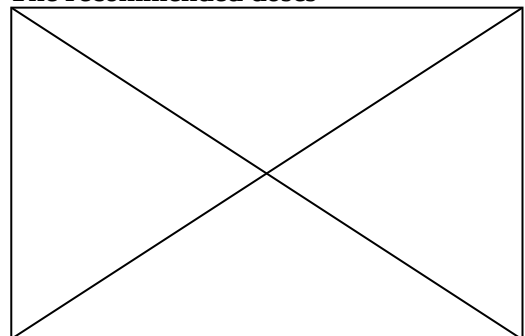
Driving and using machines

XXXXXXX has been known to have an effect on your ability to drive or use machines due to the occurrence of possible side effects. If you are affected do not drive or use machines until the side effects wear off.

3. How to take XXXXXXX

Take this tablet exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses



Method of administration

Swallow the tablet with water. The tablet can be divided into two equal halves. Do not chew the tablet. XXXXXXXX can be taken with or without food. But it is recommended to be taken without food to achieve the greatest effect.

If you take more XXXXXXXX than you should

Stop taking XXXXXXXX.

In most cases of overdose, people have reported an increased number and severity of side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.

If you forget to take XXXXXXXX

Take the next tablet as soon as you remember.

4. Possible side effects

Like all tablets, this tablet can cause side effects, although not everybody gets them. These side effects mostly occur within one hour after taking the first tablet and will usually stop as you continue to take them.

Uncommon side effects

(80% of people will not be affected)

- Headache
- Nausea

Very uncommon side effects

(90% of people will not be affected)

- Cough
- Dizziness
- Pain in limb
- Runny nose
- Sore throat
- Stomach ache
- Tiredness
- Bloating

Rare side effects

(99% of people will not be affected)

- Itchy skin

Very rare side effects

(99.9% of people will not be affected)

- Confusion
- Agitation
- Anxiety

Reporting of side effects

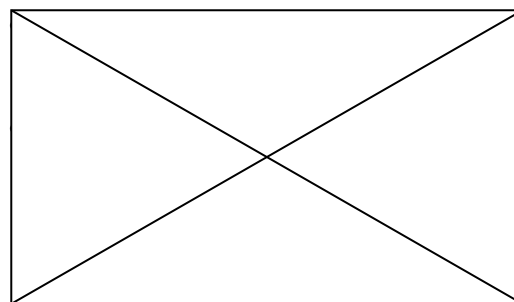
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

5. How to store XXXXXXXX

Keep out of the sight and reach of children. Do not use this tablet after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25 ° C.

Do not throw away any tablets via wastewater or household waste. Ask your pharmacist how to throw away tablets you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information**What XXXXXXXX contains****What XXXXXXXX looks like**

The tablets have a round white opaque body with a breakline.

This leaflet was last revised in 08/2015

Appendix J. Randomised controlled trial participant information sheet

INFORMATION SHEET FOR PARTICIPANTS

REC Reference Number: PNM 14/15-62

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET



Assessing the severity of short-term side effects to a well-known tablet

Invitation Paragraph

I would like to invite you to participate in this research project which forms part of my PhD research. You should only participate if you want to; choosing not to take part will not disadvantage you in anyway. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask me if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

The aim of this study is to assess the severity of short-term side effects to a well-known tablet. It is very likely that you will have heard about this tablet before. We will not tell you what the tablet is or what it is used for as we do not want to bias your views about it. In the study we will refer to the tablet as XXXXXXXX. The tablet has been tested in many previous clinical studies and shown to have beneficial effects for people. It is available without a prescription. It is also known that this tablet can cause short-term side effects. In this study, we will assess how severe these side effects are.

As part of the same study we will also give you one of two patient information leaflets that have been developed for this tablet. Which version you are given will be determined by random. We would like to test if a proposed change in the wording of the leaflet has any effect on what people think about the leaflet or the tablet. The only difference between the two patient information leaflets will be small changes to the wording in certain parts of the leaflet. Again, because we do not want to bias you, we will not tell you which parts have been changed.

What are the possible risks of taking part?

Due to the nature of this study, just like there is with any medication there is a risk for developing side effects. Any side effects from XXXXXXXX are known to be short lasting and no different from those experienced in everyday life (e.g. headache, feeling tired). If you do experience any side effects, they will not last longer than two hours after taking the tablet. In the unlikely event of an unexpected adverse reaction the Clinical Research Facility has protocols in place to ensure your safety.

What are the possible benefits of taking part?

There are no direct benefits to taking part. However, the information I get from the study will help to confirm the severity of short-term side effects related to XXXXXXXX. It will also help us to develop better information sheets about drugs in the future. I will provide you with a summary of a final report describing the main findings.

Why have I been invited to take part?

I am inviting healthy people, who are English speakers and writers, and over 18 years of age. You cannot take part if you have a serious medical disorder, an acute health problem, are taking pain killers, have been drinking alcohol or if you are pregnant, think you might be pregnant, or are breast-feeding.

Do I have to take part?

Participation is voluntary. You do not have to take part. You should read this information sheet and if you have any questions you should ask the research team. You should not agree to take part in this research until you have had all your questions answered satisfactorily.

What will happen to me if I take part?

If you are interested in taking part you will be emailed a set of questions to check your eligibility. If you meet the inclusion criteria we will arrange a time for you to come to the testing room to take part. Here the researcher will go through the information sheet with you again. If you are happy to proceed you will be asked to sign the consent form. At the start of the study you will be asked some background questions about you and any symptoms you have recently experienced. After completing these questionnaires, you will then receive an information leaflet about XXXXXXXX which you should read carefully. We will then ask you some questions about the patient information leaflet. You will then be asked to take one tablet of XXXXXXXX with water. Once you have taken XXXXXXXX you will remain in the study room for 1 hour and complete some cognitive tests so that we can monitor if you develop any short-term side effects. After this you are free to leave.

Average participation time is expected to be 1 hour 30 minutes to 2 hours.

You will find out the identity of the tablet you took at the end of data collection for the study.

Please note even if you have decided to take part, you are still free to cease your participation at any time and to have research data/information relating to you withdrawn without giving any reason up to 01/02/2017.

Location

The study will take part at the Clinical Research Facility at King's College Hospital.

Incentives

For taking part in this study you will receive a £40 gift voucher at completion.

Will my taking part be kept confidential?

All your data is strictly confidential and will be held securely until the research is finished. Your participation is entirely voluntary. If you change your mind, you are free to stop your participation and to have your data withdrawn without giving any reason up to 01/02/2017. All data for analysis will be anonymised. In reporting on the research findings, I will not reveal the names of any participants. At all times there will be no possibility of you as individuals being linked with the data.

The UK Data Protection Act 1998 will apply to all information gathered within the questionnaire booklet and held on password-locked computer files and locked cabinets within King's College London. No data will be accessed by anyone other than the research team; and anonymity of the material will be

protected by using anonymous participant ID numbers once data collection has finished. No data will be able to be linked back to any individual taking part in the study. You may withdraw your data from the project anytime up to 01/02/2017 at which point it will become anonymised. All questionnaire booklets will be shredded after answers have been uploaded to password-locked computer files. If you ask me to withdraw your data at any time before 01/02/2017 I will remove all traces of it from the records.

How is the project being funded?

The NIHR Health Protection Research Unit is funding this research. For further information visit: epr.hpru.nihr.ac.uk

The study has been approved by the King's College London Psychiatry, Midwifery and Nursing Research Ethics Subcommittee.

What will happen to the results of the study?

I will produce a final report summarising the main findings, which will be sent to you. I also plan to disseminate the research findings through publication and conferences.

Who should I contact for further information?

If you have any questions or require more information about this study, please contact me using the following contact details:

Rebecca Webster
Department of Psychological Medicine
Institute of Psychiatry, Psychology and Neuroscience
King's College London
Denmark Hill Campus
Weston Education Centre
10 Cutcombe Road
London
SE5 9RJ
Rebecca.webster@kcl.ac.uk
Tel: 020 7848 5686

What if I have further questions, or if something goes wrong?

If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact King's College London using the details below for further advice and information:

Dr James Rubin
Psychological Medicine Department
Weston Education Centre
10 Cutcombe Road
London
SE5 9RJ
gideon.rubin@kcl.ac.uk
Tel: 020 7848 5684

Thank you for reading this information sheet and for considering taking part in this research.

Appendix K. Randomised controlled trial participant consent form

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.



Title of Study: Assessing the severity of short-term side effects to a well-known tablet

King's College Research Ethics Committee Ref: PNM 14/15-62

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box I am consenting to this element of the study. I understand that it will be assumed that un-ticked/initialled boxes mean that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element I may be deemed ineligible for the study.

Please tick or initial

☐

Please tick or initial

1. I confirm that I have read and understood the information sheet dated, 12/03/15, version 2 for the above study. I have had the opportunity to consider the information and asked questions which have been answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. Furthermore, I understand that I will be able to withdraw my data up to February 2017.
3. I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998.
4. I understand that my information may be subject to review by responsible individuals from the College for monitoring and audit purposes.
5. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications.

☐☐☐☐☐

6. I agree that the research team may use my data for future research and understand that any such use of identifiable data would be reviewed and approved by a research ethics committee. (In such cases, as with this project, data would not be identifiable in any report).
7. I understand that the information I have submitted will be published as a report and I wish to receive a copy of it.
8. I understand that I must not take part if I fall under the exclusion criteria as detailed in the information sheet, screening questionnaire, and explained to me by the researcher.

☐☐☐

Name of Participant

Date

Signature

Name of Researcher

Date

Signature

Appendix L. Sensitivity analyses for randomised controlled trial results

The difference in symptom reporting between the two leaflets

Outcome	Standard worded PIL (n = 96)	Positively framed PIL (n = 98)	Test*	Effect size (95% CI)
Symptoms mentioned in PIL				
Experienced	46 (47.9%)	33 (33.7%)	z = -2.25	OR = 0.66
Did not experience	50 (52.1%)	65 (66.3%)	p = .024	(0.46-0.95)
Number of symptoms	0.75 (0.93)	0.69 (1.20)	z = 1.69 p = .091	RR = 1.20 (0.97-1.48)
Severity of symptoms	0.81 (1.06)	0.82 (1.45)	U = 4247.5 p = .187	r = - 0.09
Symptoms not mentioned in PIL				
Experienced	24 (25.0%)	21 (21.4%)	z = -0.82	OR = 0.85
Did not experience	72 (75.0%)	77 (78.6%)	p = .411	(0.57-1.26)
Number of symptoms	0.33 (0.66)	0.35 (0.79)	z = 0.76 p = .449	RR = 1.10 (0.86-1.39)
Severity of symptoms	0.40 (0.85)	0.41 (1.06)	U = 4565.5 p = .631	r = - 0.03
Any symptoms				
Experienced	54 (56.3%)	39 (39.8%)	z = -2.54	OR = 0.63
Did not experience	42 (43.8%)	59 (60.2%)	p = .011	(0.43-0.90)
Number of symptoms	1.08 (1.23)	1.04 (1.75)	z = 1.42 p = .155	RR = 1.19 (0.94-1.51)
Severity of symptoms	1.21 (1.48)	1.23 (2.17)	U = 4162.0 p = .1433	r = - 0.12

Note: Data are n (%) or mean (SD), OR = Odds ratio, RR = rate ratio, PIL = patient information leaflet, * = all adjusted for number of baseline symptoms apart from symptom severity tests, r = pearson's correlation which can be calculated from Mann-Whitney U output. 95% CI for r is not able to be calculated from Mann-Whitney U output.

The difference in satisfaction and credibility median scores between the two leaflets

Outcomes	Standard worded PIL (n = 96)	Positively framed PIL (n = 98)	Test	Effect size
Satisfaction				
Leaflet was clear	4.0 (1.0)	4.0 (1.0)	$U = 4571.0$ $p = .700$	$r = -0.03$
Leaflet was easy to understand	4.0 (1.0)	4.0 (1.0)	$U = 4467.5$ $p = .485$	$r = -0.05$
Leaflet contained words I did not understand	1.0 (1.0)	1.0 (1.0)	$U = 4553.5$ $p = .655$	$r = -0.03$
Leaflet was similar to other leaflets	4.0 (1.0)	4.0 (1.0)	$U = 4476.0$ $p = .509$	$r = -0.05$
There was enough information to make an informed choice	4.0 (2.0)	4.0 (0.0)	$U = 4568.0$ $p = .705$	$r = -0.03$
There was sufficient information about the risks and benefits	4.0 (1.0)	4.0 (1.0)	$U = 4485.5$ $p = .526$	$r = -0.05$
Overall I am satisfied with the leaflet	4.0 (1.0)	4.0 (1.0)	$U = 4344.5$ $p = .305$	$r = -0.07$
Anxiety after reading the leaflet	9.0 (3.0)	9.0 (4.0)	$U = 4555.0$ $p = .700$	$r = -0.03$
Credibility				
Trustworthy	4.0 (1.0)	4.0 (0.0)	$U = 4250.5$ $p = .177$	$r = -0.09$
Accurate	4.0 (1.0)	4.0 (0.0)	$U = 4546.0$ $p = .646$	$r = -0.03$
Fair	4.0 (0.0)	4.0 (0.0)	$U = 4615.0$ $p = .797$	$r = -0.02$
Tells the whole story	3.0 (1.0)	3.0 (1.0)	$U = 4685.5$ $p = .961$	$r = -0.004$
Unbiased	4.0 (1.0)	4.0 (1.0)	$U = 4156.0$ $p = .133$	$r = -0.12$

Note: Data are median (IQR), PIL = patient information leaflet, pearson's correlation r has been calculated as an effect size from Mann-Whitney U output. 95% CI for r is unable to be calculated from Mann-Whitney U output.

Post-hoc analysis

There was a significant interaction between the leaflet type and participants' baseline anxiety scores, controlling for number of baseline symptoms, OR = 1.06, $p = .037$, 95% CI [1.004 to 1.124]. For each one point increase in baseline anxiety score participants were 1.06 times more likely to experience symptoms if they received the standard worded PIL compared to the positively framed PIL.

Appendix M. Sensitivity analyses for predictor results

Predictors of attributing one or more symptoms to the sham medicine, and the number of symptoms which are subsequently attributed.

		Symptom attribution		Number of attributed symptoms	
Variable	No (%) or Mean (SD)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
<u>Demographics</u>					
Gender					
Male	60 (30.9%)	1.46 (1.00-2.15)	1.62 (1.08-2.44)	0.91 (0.71-1.16)	0.85 (0.42-1.10)
Female	134 (69.1%)	†	†	†	†
Age					
	27.18 (8.66)	0.98 (0.96-1.00)	0.97 (0.94-0.99)	1.00 (0.99-1.02)	1.00 (0.99-1.02)
Ethnicity					
Other	79 (40.7%)	0.95 (0.67-1.37)	0.93 (0.64-1.35)	0.87 (0.68-1.11)	0.87 (0.68-1.11)
White	115 (59.3%)	†	†	†	†
Employment					
Working	74 (38.1%)	1.03 (0.72-1.48)	1.22 (0.80-1.88)	1.09 (0.85-1.39)	1.15 (0.88-1.50)
Not working	120 (61.9%)	†	†	†	†
Education					
School qualifications	67 (34.5%)	1.18 (0.81-1.71)	1.06 (0.71-1.57)	1.10 (0.85-1.41)	1.18 (0.91-1.54)
University degree	127 (65.5%)	†	†	†	†
<u>Experimental condition</u>					
Control leaflet	96 (49.5%)	1.52 (1.06-2.16)	1.52 (1.05-2.19)	0.81 (0.64-1.03)	0.76 (0.59-0.97)
Positively framed	98 (50.5%)	†	†	†	†
<u>Psychological factors</u>					
Anxiety before leaflet	9.64 (2.74)	1.00 (0.94-1.07)	1.01 (0.95-1.08)	1.03 (0.99-1.08)	1.03 (0.98-1.07)
Anxiety after leaflet	9.60 (2.53)	1.04 (0.97-1.11)	1.06 (0.98-1.14)	1.06 (1.02-1.11)	1.06 (1.01-1.11)
Anxiety 1 hour after taking tablet	9.14 (2.61)	1.03 (0.96-1.10)	1.04 (0.97-1.11)	1.04 (1.00-1.09)	1.04 (1.00-1.09)
Change in anxiety	-0.50 (2.31)	1.03 (0.95-1.11)	1.03 (0.95-1.12)	1.01 (0.97-1.06)	1.02 (0.97-1.06)
Optimism	14.78 (3.63)	1.03 (0.98-1.08)	1.03 (0.98-1.08)	0.99 (0.96-1.02)	0.99 (0.96-1.03)
Somatisation	4.18 (3.22)	1.03 (0.98-1.09)	1.05 (0.99-1.11)	1.04 (1.00-1.08)	1.03 (0.99-1.07)
Somatosensory amplification	23.6 (5.94)	1.01 (0.98-1.04)	1.02 (0.99-1.05)	1.00 (0.98-1.02)	0.99 (0.97-1.01)
<u>Symptoms</u>					
Number of symptoms in previous 24 hours	2.59 (2.68)	1.06 (0.99-1.13)	1.08 (1.01-1.17)	1.06 (1.01-1.10)	1.05 (1.00-1.09)
Severity of symptoms in previous 24 hours	2.94 (3.29)	1.04 (0.98-1.09)	1.06 (1.00-1.12)	1.05 (1.01-1.09)	1.04 (1.00-1.08)
Expected likelihood of symptoms	5.25 (5.82)	1.07 (1.04-1.11)	1.07 (1.03-1.11)	1.03 (1.02-1.05)	1.04 (1.02-1.05)
<u>Medicine-related beliefs</u>					
Modern health worries	25.88 (20.65)	1.01 (1.00-1.02)	1.02 (1.01-1.03)	1.01 (1.00-1.01)	1.01 (1.00-1.01)
BMQ overuse	10.92 (3.29)	1.01 (0.96-1.07)	1.03 (0.97-1.09)	1.02 (0.98-1.05)	1.01 (0.98-1.05)
BMQ harm	7.93 (2.70)	1.05 (0.99-1.13)	1.09 (1.02-1.18)	1.01 (0.97-1.06)	1.00 (0.96-1.05)
Perceived sensitivity to medicines	7.29 (2.82)	1.06 (0.99-1.13)	1.08 (1.01-1.16)	1.01 (0.97-1.05)	1.00 (0.96-1.04)
Trust in medicine development	11.74 (2.07)	0.93 (0.85-1.01)	0.91 (0.83-1.00)	0.95 (0.90-1.00)	0.96 (0.91-1.01)
Trust in pharmaceutical companies	5.42 (1.63)	0.87 (0.78-0.97)	0.87 (0.78-0.98)	0.92 (0.85-1.00)	0.93 (0.86-1.01)

Note: * Controlling for gender, age, ethnicity, employment, education and experimental condition using logistic regression, OR = Odds ratio, RR = Rate ratio, BMQ = belief about medicines questionnaire, † = Reference category, **bold** = significant at p<.05

Appendix N. Ethical approval for online survey

Research Ethics
Office

Franklin Wilkins Building
5.9 Waterloo Bridge Wing
Waterloo Road
London SE1 9NH
Telephone 020 7848 4020/4070/4077
reo@kcl.ac.uk



Mrs Rebecca Webster
Office 3.30, Weston Education Centre
10 Cutcombe Road
London
Greater London
SE5 9RJ

3 December 2015

Dear Rebecca

Reference Number: HR-15/16-2104

Study Title: Society's Understanding and Perception of Risk dDescriptors in MEDicine (SUPREME study)

Review Outcome: Approval with Provisos

Thank you for submitting your application for the above project. I am pleased to inform you that your application has now been approved with one very minor proviso which is specified below:

1. Information Sheet: The current College logo must be displayed.

All changes must be made before data collection commences. The Committee does not need to see evidence of these changes, however supervisors are responsible for ensuring that students implement any requested changes before data collection commences.

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (<http://www.kcl.ac.uk/college/policyzone/index.php?id=247>).

For your information, ethical approval is granted until **3rd December 2018**. If you need approval beyond this point, you will need to apply for an extension at least two weeks before this. You will be required to explain the reasons for the extension. However, you will not need to submit a full re-application unless the protocol has changed. If you have been granted approval for only 12 months, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the data-collection phase of the study. This will be until the date specified in this letter. However, you do not need ethical approval to cover subsequent data analysis or publication of the results.

For secondary data-analysis, ethical approval is applicable to the data that is sensitive or identifies participants. Approval is applicable to period in which such data is accessed or evaluated.

Please note you are required to adhere to all research data/records management and storage procedures agreed to as part of your application. This will be expected even after the completion of the study.

If you do not start the project within three months of this letter please contact the Research Ethics Office.

Please note that you will be required to obtain approval to modify the study. This also encompasses extensions to periods of approval. Please refer to the URL below for further guidance about the process:

<http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx>

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact your panel/committee administrator in the first instance (<http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx>)

We wish you every success with this work.

Yours sincerely,

James Patterson - Senior Research Ethics Office

For and on behalf of
Professor Gareth Barker, Chair
Psychiatry, Nursing and Midwifery Research Ethics Subcommittee
Cc: James Rubin

14 March 2016

Dear Rebecca

Reference Number: RESCMR-15/16-2104

Study Title: Society's Understanding and Perception of Risk dEscriptors in MEDicine (SUPREME study)

Modification Review Outcome: Approval with provisos

Thank you for submitting a modifications request for the above study. I am writing to confirm that your request has been approved with the proviso specified below:

1. Please carefully consider your decision to impose an upper age limit.

You are not required to provide evidence that these provisos have been met. However, the approval of your modification is only valid if these changes are made. You must not implement this modification until these provisos have been met.

If you have any questions regarding this application please

contact the Research Ethics Office. Kind regards

Research Ethics Office

On behalf of

PNM Research Ethics Subcommittee

Appendix O. Online survey questionnaire

Measuring Perceptions of Side Effect Risk

Section 1

Q1. Please state your date of birth:

Date:

Month:

Year:

Q2. Please state the gender you identify yourself with:

- ☐ Male
- ☐ Female

Q3. In which of the following regions do you live? Please select one answer only.

1. North East
2. North West
3. Yorkshire and Humberside
4. West Midlands
5. East Midlands
6. East of England
7. South West
8. South East
9. London

Q4. Which of the following best describes your employment status? Please select one answer only.

1. Working – Full-time (30 or more hours a week)
2. Working – Part-time (less than 30 hours a week)
3. Self-employed
4. Unemployed but looking for a job
5. Unemployed and not looking for a job / Long-term sick or disabled / Housewife/husband / Full-time carer
6. Retired
7. Pupil / Student / In full time education

Section 2

SPLIT SAMPLE A:

RANDOMISE ORDER OF Q5A-Q23A

In this section, you will be asked about some of the possible side-effects of a new drug. Please read the questions carefully, as many of them may seem very similar. If you are unsure, please give your best estimate. We are not expecting you to be accurate.

Q5A. A new drug has been developed that has **nausea** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is a **fair chance** of nausea”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get nausea? Please type a number in the box below.

..... out of 10,000 people

Q6A. A new drug has been developed that has **nausea** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Nausea is **extremely unlikely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get nausea? Please type a number in the box below.

..... out of 10,000 people

Q7A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Headache is **uncommon**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q8A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Headache is **very common**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q9A. A new drug has been developed that has **nausea** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Nausea is **fairly unlikely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get nausea? Please type a number in the box below.

..... out of 10,000 people

Q10A. A new drug has been developed that has **nausea** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is a **very high chance** of nausea”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get nausea? Please type a number in the box below.

..... out of 10,000 people

Q11A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is a **low chance** of a headache”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q12A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Headache is **very unlikely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q13A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is a **high chance** of a headache”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q14A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Headache is **somewhat unlikely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q15A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Headache is **very likely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q16A. A new drug has been developed that has **nausea** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Nausea is **rare**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get nausea? Please type a number in the box below.

..... out of 10,000 people

Q17A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Headache is **extremely rare**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q18A. A new drug has been developed that has **nausea** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Nausea is **very rare**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get nausea? Please type a number in the box below.

..... out of 10,000 people

Q19A. A new drug has been developed that has **nausea** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Nausea is **common**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get nausea? Please type a number in the box below.

..... out of 10,000 people

Q20A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Headache is **very uncommon**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q21A. A new drug has been developed that has **nausea** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is a **very low chance** of nausea”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get nausea? Please type a number in the box below.

..... out of 10,000 people

Q22A. A new drug has been developed that has **headache** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is an **extremely low chance** of a headache”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get a headache? Please type a number in the box below.

..... out of 10,000 people

Q23A. A new drug has been developed that has **nausea** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Nausea is **likely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will get nausea? Please type a number in the box below.

..... out of 10,000 people

SPLIT SAMPLE GROUP A:

RANDOMISE ORDER OF Q24A – Q28A

Q24A. A new drug has been developed that has **dizziness** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Dizziness is **very common (may affect more than 1 in 10 people)**”

How likely do you think it is that you personally will experience dizziness if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

Q25A. A new drug has been developed that has **dizziness** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Dizziness is **common (may affect up to 1 in 10 people)**”

How likely do you think it is that you personally will experience dizziness if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

Q26A. A new drug has been developed that has **dizziness** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Dizziness is **uncommon (may affect up to 1 in 100 people)**”

How likely do you think it is that you personally will experience dizziness if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

Q27A. A new drug has been developed that has **dizziness** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Dizziness is **rare (may affect up to 1 in 1000 people)**”

How likely do you think it is that you personally will experience dizziness if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

Q28A. A new drug has been developed that has **dizziness** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

"Dizziness is **very rare (may affect up to 1 in 10,000 people)**"

How likely do you think it is that you personally will experience dizziness if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

SPLIT SAMPLE B:

RANDOMISE ORDER OF Q5B-Q23B

In this section, you will be asked about some of the possible side-effects of a new drug. Please read the questions carefully, as many of them may seem very similar. If you are unsure, please give your best estimate. We are not expecting you to be accurate.

Q5B. A new drug has been developed that has **seizures (fits)** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

"There is a **fair chance** of a seizure (fit)"

Imagine 10,000 people take the drug. Out of these people, how many do you think will have a seizure (fit)? Please type a number in the box below.

..... out of 10,000 people

Q6B. A new drug has been developed that has **seizures (fits)** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

"Seizures (fits) are **extremely unlikely**"

Imagine 10,000 people take the drug. Out of these people, how many do you think will have a seizure (fit)? Please type a number in the box below.

..... out of 10,000 people

Q7B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Difficulty breathing is **uncommon**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q8B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Difficulty breathing is **very common**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q9B. A new drug has been developed that has **seizures (fits)** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Seizures (fits) are **fairly unlikely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have a seizure (fit)? Please type a number in the box below.

..... out of 10,000 people

Q10B. A new drug has been developed that has **seizures (fits)** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is a **very high chance** of seizure (fit)”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have a seizure (fit)? Please type a number in the box below.

..... out of 10,000 people

Q11B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is a **low chance** of difficulty breathing”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q12B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Difficulty breathing is **very unlikely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q13B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is a **high chance** of difficulty breathing”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q14B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Difficulty breathing is **somewhat unlikely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q15B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Difficulty breathing is **very likely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q16B. A new drug has been developed that has **seizures (fits)** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Seizures (fits) are **rare**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have a seizure (fit)? Please type a number in the box below.

..... out of 10,000 people

Q17B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Difficulty breathing is **extremely rare**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q18B. A new drug has been developed that has **seizures (fits)** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Seizures (fits) are **very rare**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have a seizure (fit)? Please type a number in the box below.

..... out of 10,000 people

Q19B. A new drug has been developed that has **seizures (fits)** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Seizures (fits) are **common**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have a seizure (fit)? Please type a number in the box below.

..... out of 10,000 people

Q20B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Difficulty breathing is **very common**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q21B. A new drug has been developed that has **seizures (fits)** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is a **very low chance** of a seizure (fit)”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have a seizure (fit)? Please type a number in the box below.

..... out of 10,000 people

Q22B. A new drug has been developed that has **difficulty breathing** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“There is an **extremely low chance** of difficulty breathing”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have difficulty breathing? Please type a number in the box below.

..... out of 10,000 people

Q23B. A new drug has been developed that has **seizures (fits)** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Seizures (fits) are **likely**”

Imagine 10,000 people take the drug. Out of these people, how many do you think will have a seizure (fit)? Please type a number in the box below.

..... out of 10,000 people

SPLIT SAMPLE B:

RANDOMISE ORDER OF Q24B-Q28B

Q24B. A new drug has been developed that has **kidney failure** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Kidney failure is **very common (may affect more than 1 in 10 people)**”

How likely do you think it is that you personally will experience kidney failure if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

Q25B. A new drug has been developed that has **kidney failure** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Kidney failure is **common (may affect up to 1 in 10 people)**”

How likely do you think it is that you personally will experience kidney failure if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

Q26B. A new drug has been developed that has **kidney failure** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Kidney failure is **uncommon (may affect up to 1 in 100 people)**”

How likely do you think it is that you personally will experience kidney failure if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

Q27B. A new drug has been developed that has **kidney failure** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Kidney failure is **rare (may affect up to 1 in 1000 people)**”

How likely do you think it is that you personally will experience kidney failure if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

Q28B. A new drug has been developed that has **kidney failure** as one of its listed side effects. The patient information leaflet accompanying the drug states that:

“Kidney failure is **very rare (may affect up to 1 in 10,000 people)**”

How likely do you think it is that you personally will experience kidney failure if you took the drug? Please select one answer only.

1. Very likely
2. Likely
3. About as likely as not
4. Unlikely
5. Very unlikely
6. Don't know

Section 3

Q29. How often, if at all, do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy? Please select one answer only.

- ☐ Never
- ☐ Rarely
- ☐ About half the time
- ☐ Often
- ☐ Always
- ☐ Don't know

Q30. When you take new medications how often, if at all do you read the patient information leaflet accompanying them? Please select one answer only.

1. Never – *GO TO Q32*
2. Rarely
3. About half the time
4. Often
5. Always
6. Don't know – *GO TO Q32*

Q31. Which sections of the patient information leaflet do you read? Please tick all that apply.

- ☐ What the medicine is and what it is used for
- ☐ What you need to know before you take the medicine
- ☐ How to take the medicine
- ☐ Possible side effects
- ☐ How to store the medicine
- ☐ Contents of the pack and other information
- ☐ Don't know

Section 4

We would now like to ask you about your personal views about medicines in general.

Q32. The following are things that other people have said about medicines in general. Please indicate the extent to which you agree or disagree with each statement by ticking the appropriate box.

There are no right or wrong answers. We are interested in your personal views.

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
Doctors use too many medicines					
People who take medicines should stop their treatment for a while every now and again					
Most medicines are addictive					
Natural remedies are safer than medicines					
Medicines do more harm than good					
All medicines are poisons					
Doctors place too much trust on medicines					
If doctors had more time with patients they would prescribe fewer medicines					

Section 5

The following question asks about you and your general thoughts and feelings.

Q33. Please indicate how far you agree with each statement by ticking the appropriate box. Be as honest as you can throughout, and try not to let your responses to one question influence your response to other questions. There are no right or wrong answers.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
In uncertain times, I usually expect the best					
It's easy for me to relax					
If something can go wrong for me, it will					
I'm always optimistic about my future					
I enjoy my friends a lot					
It's important for me to keep busy					
I hardly ever expect things to go my way					
I don't get upset too easily					
I rarely count on good things happening to me					
Overall, I expect more good things to happen to me than bad					

Section 6

The following question is about your general thoughts and feelings about your own health.

Q34. Please read each of the statements carefully and then select the one which best describes your feelings, over the past six months. Identify the statement by selecting the box next to it.

1. I do not worry about my health.
2. I occasionally worry about my health.
3. I spend much of my time worrying about my health.
4. I spend most of my time worrying about my health.

Q35. These are some things other people have said when prescribed medication during regularly scheduled and patient-requested visits. Please indicate to what extent, if at all, you agree or disagree with each statement.

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
My body is very sensitive to medicines					
My body overreacts to medicines					
I usually have stronger reactions to medicines than most people					
I have had a bad reaction to medicines in the past					
Even very small amounts of medicines can upset my body					

Section 7

And finally, the following questions ask for some more information about you.

Q36. Which of the following ethnic groups would you describe yourself as belonging to? Please select one answer only.

A. White

- ☐ English/Welsh/Scottish/Northern Irish/British
- ☐ Irish
- ☐ Gypsy or Irish Traveller
- ☐ Any other white background (please specify).....

B. Mixed / Multiple ethnic groups

- ☐ White and Black Caribbean
- ☐ White and Black African
- ☐ White and Asian
- ☐ Any other Mixed/Multiple ethnic background (please specify).....

C. Asian / Asian British

- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Chinese
- ☐ Any other Asian background (please specify).....

D. Black / African / Caribbean / Black British

- ☐ African
- ☐ Caribbean
- ☐ Any other Black/African/Caribbean background (please specify).....

E. Other ethnic group

- ☐ Arab
- ☐ Any other ethnic group (please specify).....
- ☐ Prefer not to say

Q37. Please state the highest level of education you have achieved

- ☐ Left school without qualifications
- ☐ Secondary education (O-level/GCSE/A-level)
- ☐ Higher education (BSc,BA/higher qualification)
- ☐ Prefer not to say

Q38. Do you, or anyone else in your household have any long-standing illness, disability or infirmity?

1. Yes – myself
2. Yes – someone else in my household
3. No
4. Prefer not to say

Finish page

Thank you for taking part in this survey; that is all the questions we have for you.

Effectively communicating the risk of side effects is an important challenge in the UK.

The information we gave you about side effects was adapted from the current European guidelines and patient information leaflets for some of the most commonly dispensed medicines.

All the situations explained in this survey have been hypothetical. If you have any concerns about any medication you may be taking, please contact your GP.

If you would like to talk about any other issues raised by this survey, please contact Rebecca Webster by email (rebecca.webster@kcl.ac.uk) or on her direct telephone line (020 7848 5686).

Appendix P. Online survey participant information sheet and consent form

Brief Information Screen to be displayed to Potential Participants



Measuring Perceptions of Side Effect Risk

We would like to invite you to participate in this survey which is being conducted as part of a PhD study at King's College London [ref: HR-15/16-2104]. You should only participate if you want to; choosing not to take part will not disadvantage you in any way.

Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve.

The aim of this survey is to improve the explanation of side effects used in patient information leaflets that accompany all medications.

The survey will take about 15 minutes to complete and we would like you to complete it in one sitting. After you complete it we will credit your account with XXX points.

All the information that we collect will be kept strictly confidential and in accordance with the UK Data Protection Act 1998. We will not pass on any details that might identify you to the researchers at King's College London, or to anyone else.

Click [here](#) [[HYPERLINK TO FULL INFORMATION SHEET](#)] for the full information sheet about this study. If you would like more details about the survey, please contact the lead researcher at King's College London (Rebecca Webster; rebecca.webster@kcl.ac.uk).

To begin the survey, please tick both boxes below and then click on the link.

- ☐ I consent to the processing of my personal information for the purposes of this research study. I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- ☐ I agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read the notes above and understand what the research study involves.

CONTINUE TO SURVEY [[LINK TO SURVEY ONLY ACTIVE WHEN BOTH BOXES ARE TICKED](#)]

Full information sheet

Measuring Perceptions of Side Effect Risk

We would like to invite you to participate in this survey which is being conducted as part of a PhD study at King's College London. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve.

What is the purpose of this research?

All medicines in the UK come with patient information leaflets that explain the side effects associated with each medicine. Researchers from King's College London want to improve the explanation of side effects used in these patient information leaflets. In particular they want to assess how people think about the risks associated with medication side effects. This is so that they can develop new ways of explaining side effects that people will find easier to understand.

Who can take part?

You can take part in the survey if you are between 18 and 65 years of age and speak fluent English.

What will I be asked to do?

If you decide to take part, you will first be asked to read some information about the risk of side effects for a newly developed drug. This information will be based on the words and phrases currently used to explain side-effect risks, as well as new words and phrases that have been developed by the researchers'. We are using two different lists of side effects in this study and we will select one list at random to give to you. Once you have read this information, we will then ask you to complete a series of short questions about the side effect risks. For example we will ask you to judge how many people might be affected by a certain side effect. After this we will ask you to complete a small number of questions about your experience with patient information leaflets and your thoughts on medicines in general.

The survey will take about 15 minutes to complete and we would like you to complete it in one sitting. After you complete it we will credit your account with XXX points [to be decided].

Confidentiality – who will know I am taking part in the study?

All the information that we collect will be kept strictly confidential and in accordance with the UK Data Protection Act 1998. We will not pass on any details that might identify you to the researchers at King's College London, or to anyone else.

What will happen to the results of the study?

The team from King's College London hope to publish the results of this study in a Pharmaceutical journal. If you would like to receive a copy of their final report, you can contact the lead researcher (Rebecca.webster@kcl.ac.uk) for more information. Your anonymous data will also be archived to share with other researchers who may be interested in this work in the future.

Who has funded and approved the research?

This work is funded by the National Institute for Health Research, the part of the NHS that funds new research. It has been approved by King's College London's Psychiatry, Nursing and Midwifery Research Ethics Committee (Reference: HR-15/16-2104). The survey is being run in accordance with the Market Research Society Code of Conduct.

Do I have to take part?

No. It is up to you to decide whether to take part or not. If you decide to take part you are free to withdraw from the survey at any time by simply closing the browser window on your computer. By closing the survey before completion your data will be withdrawn and not used in the analysis.

What happens now?

If you would like to take part, please click on the link below to begin. Completing the survey implies that you give consent to participate. You can also return to this page later if you would like to take more time to think about whether you want to take part.

Who should I contact for further information?

If you would like more details about the survey, please contact the lead researcher at King's College London (Rebecca Webster). Her details are:

Rebecca Webster
King's College London
Department of Psychological Medicine
Weston Education Centre, Cutcombe Road
London SE5 9RJ
Phone: +44(0)20 7848 5686
e-mail: rebecca.webster@kcl.ac.uk

What if I have further questions, or if something goes wrong?

If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact King's College London using the details below for further advice and information:

Dr James Rubin
Psychological Medicine Department
Weston Education Centre, Cutcombe Road
London SE5 9RJ
Phone: +44(0)20 7848 5684
e-mail: gideon.rubin@kcl.ac.uk

If you do not want to take part in the study, you do not need to do anything.