The role of medication beliefs in side effects

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Declaration

I, Monika Katharina Heller, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. Study 1 involves the re-analysis of data from an existing clinical observational study. All other studies presented in this thesis are original investigations.

London, July 11, 2017

Monika Heller
Acknowledgements

I would like to take this opportunity to thank my family and friends for all their support. Thank you to all the people who listened, helped to babysit, had a kind word, encouraged me and gently pushed me over the finishing line. A particular thank you goes to my partner Ben and my two children, Ronan and Lili, who have been wonderful during this often difficult period. I hope I will be “doctor mummy” in the end. I am also immensely grateful to my friend Maggie, who took my children on holiday with her to give me more time to push ahead with the final write up of this thesis. I am indebted to all the participants who agreed to participate in my studies for very little financial return. My experimental nocebo study would not have been possible without the help of the Pharmacology Department at the UCL School of Pharmacy, who kindly let me use one of their labs to run the study. A big thank you also goes to my two supervisors, Dr Sarah Chapman and Professor Rob Horne, for guiding and supporting me through this exciting journey. I would also like to thank Dr Li Wei, a medical statistician, for checking the statistical methods used in my thesis. I was very fortunate to have Andy, my fellow PhD student, as a “partner in crime” during these four years. I could not have coped without having him by my side! Finally, I think this is also a good opportunity to apologize to all the people I have neglected over the past few months. You will hopefully see more of me in the future.
Dedication

There are many people I would like to dedicate this thesis to, but I have chosen my dear friend Joan, who died while I was working on this PhD. I got there in the end as you always said I would.
Abstract

The experience (or mere anticipation) of side effects influences patients’ beliefs about specific treatment and pharmaceuticals in general. In this thesis I postulate that beliefs about medication may also contribute to side effect reporting. Five studies were conducted to test this hypothesis and to explore putative underlying mechanisms.

The majority of studies examining the relationship between medication beliefs and side effect reporting are cross-sectional, precluding inferences about the direction of the relationship. I present evidence from a prospective study showing that baseline medication beliefs predict side effect reporting in a large multinational sample of women initiating bone-loss treatment.

The claim that non-pharmacological factors like medication beliefs can influence side effect reporting is supported by research on the nocebo effect (side effects to placebo). A sham trial was conducted showing that medication beliefs predict symptom reporting and attribution of symptoms as side effects in healthy volunteers taking Modafinil placebo.

Many symptoms that are frequently listed as side effects are also common in patients randomized to placebo and un-medicated healthy volunteers. Using an analogue scenario I demonstrate that people with more negative beliefs about medication are more likely to misattribute a common symptom as a side effect.

A related analogue study explored whether pre-existing beliefs about medication act as schemas that bias the way people process information about side effects. I show that individuals with more negative beliefs about pharmaceuticals recall and recognize fewer side effects from a patient leaflet, spend less time reading side effect information and are consequently more likely to attribute an unlisted symptom as a side effect.

Finally, I present findings from a feasibility study of interventions to modify unhelpful medication beliefs in order to reduce side effect attribution.

Together these findings confirm the importance of medication beliefs in side effect reporting and point to possible intervention strategies.
Dissemination plan

Published Manuscripts


Manuscripts in preparation

Heller, M. K., Chapman, S. C., & Horne, R. Beliefs about medicines predict side effect experiences among students receiving placebo-'Modafinil' to enhance cognition. (for Psychosomatic Medicine)

Analysis of Longitudinal Data to Identify Psychological Predictors of Side Effect Reporting in Postmenopausal Women Receiving Bone Loss Medication in Primary Care Settings Using the POSSIBLE EU® Study Database (for Osteoporosis International)

Exploring the feasibility of using a randomized controlled online trial to pre-test intervention components to change medication beliefs (for Journal of Medical Internet Research)
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List of Abbreviations

ADHD=Attention Deficit Hyperactivity Disorder
ADR=Adverse Drug Reaction
BMQ=Beliefs about Medicines Questionnaire
CFI=Comparative Fit Index
CI=Confidence Interval
CPT-AX=Continuous Performance Test - AX Version
CSM=Common Sense Model
DXA=Dual Energy X-ray Absorptiometry
ED=Eating Disorder
ELM=Elaboration Likelihood Model
EQ-5D=EuroQol health state index
FIML=Full Information Maximum Likelihood
HLT=Hosmer Lemeshow Test
IAT=Implicit Association Test
IBS=Irritable Bowel Syndrome
IPQ=Illness Perception Questionnaire
IRR=Incidence Rate Ratio
MAR=Missing at Random
MARS=Medication Adherence Report Scale
MI=Multiple Imputation
MOST=Multiphase Optimization Strategy
MRC=Medical Research Council
MUS=Medically Unexplained Symptoms
NA=Negative Affect
NCD=Necessity Concerns Differential
OR=Odds Ratio
PANAS=Positive Negative Affect Schedule
PHQ-15= Patient Health Questionnaire Somatization Scale
PIL=Patient Information Leaflet
POSSIBLE EU®= Prospective Observational Study Investigating Bone Loss Experience in Europe
PRO=Patient Reported Outcome
PSM=Perceived Sensitivity to Medicines Scale
RCT=Randomized Controlled Trial
RT=Reaction Time
SBA=Scale of Body Awareness
SDT=Signal Detection Theory
SEM=Structural Equation Model
SIT=Social Identity Theory
SRM=Self-Regulatory Model
STAI=State Trait Anxiety Inventory
TLI=Tucker Lewis Index
VAS=Visual Analogue Scale
WDST=Wechsler Digit Span Test
WHO=World Health Organization
Chapter 1: Introduction

1.1 Overview

The principal aim of this thesis is to get a better understanding of the relationship between medication beliefs and side effects. The introduction starts with an overview of the problems linked to side effects, in particular their negative impact on adherence. The next section introduces the construct of medication beliefs and briefly outlines their well-established role in explaining adherence. I then review more recent evidence linking medication beliefs to side effect reporting and discuss gaps in the literature. Existing prospective studies suggest that medication beliefs may contribute to the emergence of medication side effects. Yet to date little is known about potential mechanisms underlying this association. In the next section I review findings from research on the nocebo phenomenon, as it provides a useful model for understanding how psychological factors like patients’ beliefs may contribute to side effects. Common nocebo mechanisms and their putative relationship with medication beliefs will be discussed. The chapter concludes with a summary of the research questions addressed in this thesis. A “thesis roadmap” outlining the content of the remaining chapters will be provided.

1.2 The burden of side effects

Pharmaceutical medicines are the mainstay intervention for the effective management of most chronic conditions. Advances in pharmaceutical treatment have contributed to reduced morbidity and mortality rates in patients with cancer (Jemal et al., 2004), AIDS (Murphy et al., 2001), coronary heart disease (Hunink et al., 1997) and many other chronic conditions. Pharmaceuticals continue to play an important role in increasing life expectancy (Crémieux et al., 2005) and improving the quality of life of many patients (Strand & Singh, 2007). But, optimal therapeutic outcomes are compromised by side effects (Johnson & Bootman, 1995) and non-adherence (Sabaté, 2003): Patients do not benefit fully from even the most effective drugs when these are not taken as prescribed (i.e. if patients are non-adherent (Cramer et al., 2008)).

Side effects are typically defined as an action of a drug other than the one for which it is being used (Barsky, Saintfort, Rogers, & Borus, 2002). In clinical practice (and most clinical trials) side effects are primarily assessed via self-report and not through objective biochemical methods (e.g. by demonstrating drug induced tissue damage). But self-report measures are subject to psychological influences
(e.g. beliefs and expectations), biases (e.g. acquiescence bias (“yes”-saying tendency), investigator bias) and ascertainment strategies (Rief et al., 2011; Rief et al., 2009). This implies that not all symptoms that patients report as side effects are necessarily causally related to any pharmacological action of the drug (i.e. would not be classified as adverse drug reactions (ADRs) (Edwards & Aronson, 2000)). At the same time it is often patients’ subjective experience of symptoms and the attribution of these symptoms side effects, that will influence subsequent coping behaviour (e.g. non-adherence, self-medication to reduce side effects (De Smedt et al., 2012)).

Patient-reported side effects have been shown to reduce adherence to treatment for diabetes mellitus (Chao, Nau, & Aikens, 2007), HIV (Ammassari et al., 2001), cancer (Atkins & Fallowfield, 2006), schizophrenia (DiBonaventura, Gabriel, Dupclay, Gupta, & Kim, 2012) and many other long term conditions. Non-adherence to appropriately prescribed effective treatments may result in inadequate therapeutic effects (Dimatteo, Giordani, Lepper, & Croghan, 2002; Dunbar-Jacob & Mortimer-Stephens, 2001), reduced quality of life (Loon, Jin, & Goh, 2015), increased morbidity and mortality (Chisholm-Burns & Spivey, 2011) and higher health-care costs (Iuga & McGuire, 2014).

Patients typically take medication with the goal of relieving symptoms (Leventhal, Leventhal, & Contrada, 1998). The experience of additional symptoms (i.e. side effects) is therefore incongruent with patients’ treatment goals (Siegel, Schrimshaw, & Dean, 1999) and adds to the burden of treatment and disease. Side effects have been shown to increase patients’ anxiety (Coates et al., 1983) and reduce quality of life (Johnson, Stallworth, & Neilands, 2003). Non-adherence could be seen as a way to control these frightening and burdensome symptoms.

Side effects also put considerable strain on the healthcare system. Problems linked to side effects in ambulatory (e.g. treatment changes, increased healthcare utilization) and non-ambulatory settings (e.g. longer hospitalizations) were estimated at over $170 billion per year in the US alone (Rodriguez-Monguio, Otero, & Rovira, 2003). Given these important challenges it is essential to get a better understanding of what influences patients’ experience of side effects and to identify strategies to reduce the burden of side effects for patients.
1.3 Medication beliefs and side effect reporting

1.3.1 Theoretical foundations of medication beliefs

Probably owing to the prominent place of pharmaceutical treatment in modern health care, most people have well-formed preconceptions (or schemas) about pharmaceutical medicines in general, which may in turn influence how they perceive prescribed medications and evaluate whether prescribed treatment is appropriate for their illness (Horne, 1997). This section starts with an overview of patients’ beliefs about specific medications and their role in adherence. I then summarize current evidence on pharmaceutical schemas and show how pharmaceutical schemas and specific beliefs about medication are interlinked.

1.3.1.1 Beliefs about specific medications

Necessity and Concern Beliefs

Although patients’ ideas about medications are diverse and complex, many of the beliefs that patients express about specific prescribed medications can be grouped under two broad categories: perceptions of personal need for treatment to control the illness (necessity beliefs) and concerns about potential negative effects (Horne, 1997; Horne, Weinman, & Hankins, 1999).

Necessity beliefs are not restricted to perceptions of medication efficacy, but also encompass views about personal need for treatment. Patients’ perceptions of treatment necessity are thought to be influenced by their common sense (or lay) representations of their illness (Horne, 2003). According to the Common Sense Model (CSM) (Leventhal, Diefenbach, & Leventhal, 1992; Leventhal, Meyer, & Nerenz, 1980), cognitive representations of illness have five core domains: illness identity (illness label and characteristic symptoms), beliefs about the cause, timeline (e.g. likely duration, acute versus chronic), personal consequences and ability to control or cure the illness. For example, asthma patients who view their asthma as acute (versus chronic) with only minor personal consequences (e.g. only limited impact on daily life) may perceive preventative asthma treatment as less necessary (Horne, 1999; Horne & Weinman, 2002).

Medication concerns can be seen an evaluative representation of the threat posed by the medication (Horne, 2003). Potential side effects undoubtedly play an important part in patients’ representations of threat, but beliefs about other potential harms such as dependence, stigma (e.g. HIV treatment), disruption of daily life, and
concerns about unknown long term consequences equally play a role (Horne, 2003).

Treatment representations are thought to include both cognitive and emotional aspects (Horne, 2003). This is particularly plausible with regards to concerns about medication. Patients' beliefs that a medication may cause side effects (at times significant side effects, e.g. chemotherapy side effects, life-threatening allergic reactions, etc.) may lead to anxiety or worry. It is important to note here that patients' concerns about side effects are often disproportionate to the actual threat posed by the medication (Horne, 1997).

Symptom experiences, relative to patients' expectations of symptoms, are likely to influence both concerns and necessity beliefs. On the one hand, the experience of symptoms may serve as a reminder to patients that they need to take their medication (i.e. increase necessity beliefs). For example, if a Parkinson's patient's hands start shaking uncontrollably, s/he may be more inclined to take her anti-Parkinson medications. On the other hand, symptoms may be seen as evidence that the medication is not working (Cooper, Gellaitry, Hankins, Fisher, & Horne, 2009; Leventhal, Easterling, Coons, Luchterhand, & Love, 1986) or may be interpreted as side effects to the medication, thereby increasing patients' concerns. It is important to note here that in some instances the same symptom can be either a symptom of the disease or a side effect of the medication to treat the disease. Going back to the Parkinson' example, involuntary muscle movements (dyskinesia) are in fact a common side effect of many anti-Parkinson medications like L-dopa (Fabbrini, Brothie, Grandas, Nomoto, & Goetz, 2007). A central tenet of this thesis is that the interpretation and attribution of symptoms is likely to be influenced by their beliefs and expectations (see section 1.5). An empirical investigation of role of treatment beliefs in the attribution of symptoms as side effects will be presented in this thesis.

The role of necessity and concern beliefs in explaining adherence

A large body of research, spanning over two decades, shows that patients' beliefs about necessity for treatment and concerns about adverse effects influence treatment uptake (Horne, Cooper, Gellaitry, Date, & Fisher, 2007) and adherence to treatment across a range of chronic illness groups. A recent meta-analysis summarizing evidence from 94 studies across 24 long-term conditions and involving over 25 000 patients in 18 countries (Horne et al., 2013a), showed that higher
adherence was associated with stronger perceptions of necessity (pooled OR=1.74, \(p<.0001\)) and fewer concerns about treatment (pooled OR=0.504, \(p<.0001\)).

According to the Necessity Concern Framework (Clifford, Barber, & Horne, 2008; Horne, 1997; Horne & Weinman, 1999) patients (explicitly or implicitly) weigh up perceived necessity for a medication against any concerns they have about potential negative consequences. Medication uptake and adherence is thought to be greater, the more patients’ necessity beliefs exceed their concerns. This has often been operationalized through the Necessity Concerns Differential, which is computed by subtracting Concern from Necessity scores.

Figure 1: Attitudinal clusters of medication beliefs

![Diagram showing attitudinal clusters of medication beliefs: Sceptical, Ambivalent, Indifferent, Accepting]

Note. Illustration based on Aikens et al. (Aikens, Nease, Nau, Klinkman, & Schwenk, 2005)

In addition, an attitudinal analysis with four subgroups (Aikens et al., 2005; Clatworthy et al., 2009), representing four different attitudes to medication, has been proposed (see Figure 1): Sceptical (low Necessity, high Concerns), Ambivalent (high Necessity, high Concerns), Indifferent (low Necessity, low Concerns) and Accepting (high Necessity, low Concerns). Many patients are indeed faced with a necessity-concerns dilemma when deciding whether to take their medication: They are convinced that they need the treatment (high necessity), but are equally frightened by possible negative effects (high concerns), i.e. have ambivalent attitudes toward their medication (Aikens et al., 2005; Horne, Parham, Driscoll, & Robinson, 2009). Beliefs about personal necessity may however at times override concerns. If patients are convinced that the treatment is necessary to manage their condition patients are willing to overcome sometimes severe concerns about side
effects (Horne, 2011). Other patients have very little perceived personal need for treatment, but hold strong concerns, i.e. are “sceptical” about their treatment. These patients are least likely to adhere to treatment (Aikens et al., 2005; Clatworthy et al., 2009; Horne et al., 2009).

### 1.3.1.2 Pharmaceutical schemas

In addition to views about specific medicines, patients are thought to have more generalized schematic mental representations of pharmaceutical medicines as a class of treatment and their own self in relation to medicines.

#### Beliefs about Medicines in General

When talking about medications, people appear to access schemas relating to medicines as a class of treatment, which share certain general properties (Britten, 1994; Horne, 2003). These schemas have been linked to prior experience with medicines, media messages, education and training, and perceptions of technology in general (Horne, 2003). In particular views that pharmaceutical substances are potentially harmful (Horne et al., 1999) and that doctors overprescribe and rely too much on pharmaceutical medicines (Horne, Frost, Hankins, & Wright, 2001) seem to be widespread. Often these negative views about pharmaceuticals are linked to perceptions of pharmaceuticals as chemicals with unnatural origins and beliefs that complementary therapies (e.g. homeopathy) are safer and more natural (Gupta & Horne, 2001; Horne, 2003). Of course people also have positive views about pharmaceuticals and the benefits they can bring (Horne, 1997). The extent to which people view pharmaceuticals as helpful in improving health outcomes varies however substantially (Horne & Weinman, 1999). These general representations of pharmaceutical medicines are thought to be relatively stable over time (Porteous, Francis, Bond, & Hannaford, 2010).

#### Perceived Sensitivity to Medicines

In addition to these views about pharmaceuticals, people hold beliefs about themselves in relation to pharmaceuticals. Perceived sensitivity to medicines is the belief that one is sensitive to both positive and negative actions (i.e. side effects) of medication (Faasse, Grey, Horne, & Petrie, 2015a; Horne et al., 2013b). It is likely that beliefs about personal sensitivity are influenced by patients’ past experiences of adverse physiological reactions to treatment (i.e. ADRs). But it is extremely rare for patients to be sensitive to all types of medicines (Faasse et al., 2015a). High perceived sensitivity beliefs may thus be the result of an overgeneralization of
sensitivity (e.g. a patient who is allergic to penicillin may infer that s/he is sensitive to other types of antibiotics or pharmaceutical drugs in general). In addition, as outlined before, not all the symptoms that patients report as side effects are indeed related to any pharmacological reaction. Beliefs about perceived sensitivity to medicines may therefore be both a cause and a consequence of the misattribution of unrelated symptoms as side effects.

1.3.1.3 Interrelations between medication belief constructs

Patients’ beliefs about specific treatments are likely to be influenced by their beliefs about pharmaceutical medicines in general. If a patient believes pharmaceuticals to be essentially harmful, it is likely that s/he will express heightened concerns about a specific treatment. Patients who view pharmaceuticals as generally beneficial may be more convinced that a specific pharmaceutical treatment is necessary to effectively manage their condition. (Horne, 2003). Similarly, patients who perceive themselves as highly sensitive to medicines are likely to be sceptical about pharmaceuticals in general and specific prescribed treatment. Empirical evidence is largely supportive of the postulated interrelations between beliefs (Horne et al., 2013b; Horne et al., 2009; Horne et al., 1999).

1.3.2 Measuring medication beliefs

1.3.2.1 The Beliefs about Medicines Questionnaire (BMQ)

Several instruments have been developed to measure beliefs and attitudes towards specific types of medicines (Figueiras et al., 2009; Hogan, Awad, & Eastwood, 1983; Kampman et al., 2000). The most commonly used measure, which has been used to assess beliefs about treatments for a large number of long term conditions (e.g. HIV/AIDS (Horne et al., 2007), depression (Hunot, Horne, Leese, & Churchill, 2007), asthma (Horne, 2006) and irritable bowel disease (Horne et al., 2009)), is the Beliefs about Medicines Questionnaire or BMQ (Horne et al., 2013a; Horne et al., 1999).

The BMQ contains two sections (see Figure 2): The BMQ-Specific and the BMQ-General. The BMQ-Specific comprises two scales assessing beliefs about the necessity of a specific treatment for controlling an illness (5 items e.g. “My health, at present depends on Medication X”) and concerns about potential adverse consequences of taking it (6 items e.g. “Having to take Medication X worries me”). The BMQ-General comprises three 4-item scales assessing views about pharmaceutical medicines as a class of treatment. The General Harm scale
assesses beliefs about the degree to which medicines are essentially harmful (e.g. “Medicines do more harm than good.”). The General Overuse scale assesses beliefs about whether doctors place too much emphasis and trust on medicines (e.g. “If doctors had more time with patients they would prescribe fewer medicines.”).

Figure 2: Overview of the medication belief construct and its operationalization

Note. BMQ=Beliefs about Medicines Questionnaire, PSM=Perceived Sensitivity to Medicines Scale

The BMQ does not come without its problems. Some are inherent to all self-reported attitudinal/belief measures, others more related to its specific dimensional structure. With regards to the former, it is for example possible that the mere act of asking patients about illness and treatment constructs influences the way they think about their illness and treatment (Ogden, 2012, p. 47). In addition, self-report measures are not always accurate and can be subject to reporting bias. Patients may for example be reluctant to voice concerns when they believe that the researcher administering the questionnaire is hoping for more positive evaluations of the treatment.

More specific criticism of the BMQ concerns the question of whether it is an accurate reflection of all potential facets of treatment representations (Wouters et
al., 2013). In addition, researchers have at times struggled to replicate the proposed dimensional structure of the BMQ. Beck and colleagues (Beck et al., 2012) found for example that the General Harm and General Overuse scales were loading heavily on one factor, which they termed ‘General Distrust of Pharmacotherapy’. A similar finding was reported by other researchers (Gonzalez et al., 2007), who also combined these scales following a confirmatory factor analysis.

Despite these issues, the BMQ seems the best current measure to assess individuals' beliefs about medication. In contrast to many other instruments, it allows assessing beliefs about specific medication as well as schematic representations of treatment. In addition, it has been carefully validated and generally shown good internal consistency (Horne & Weinman, 1999; Horne et al., 1999). Most importantly, it has proved to reliably predict medication taking behaviour across very diverse patient populations and a broad range of chronic conditions (Horne et al., 2013a).

1.3.2.2 The Perceived Sensitivity to Medicines Scale (PSM)

The PSM is a validated scale (Horne et al., 2013b), which assesses beliefs about the self in relation to medicines, specifically about personal sensitivity to medicines. According to Horne and colleagues, the scale items are slight modifications of comments made by patients about their prescribed medications during physician visits (Horne et al., 2013b). Higher scores indicate greater perceived sensitivity to potential adverse effects of medication. The PSM has demonstrated high internal consistency and good re-test reliability. Probably owing to its brevity (5 items), it is well accepted by patients with 98-100% scale completion rates (Faasse et al., 2015a; Horne et al., 2013b).

1.3.3 Review of existing studies examining associations between medication beliefs and side effect reporting

Most of the empirical studies using the BMQ and PSM have examined associations with adherence (self-report and objectively measured, e.g. via prescription refill), but there is a growing number of studies exploring associations with side effect reporting. It is indeed plausible that medication beliefs do not only influence treatment preference, uptake and adherence, but have a more direct effect on health outcomes (Horne, 1999) for example via the nocebo effect (see section 1.4 below). Table 1 summarizes the studies identified by a literature search on Pubmed, Cochrane Library, PsychInfo and through cross-referencing.
Table 1: Associations between medication beliefs and self-reported side effects

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient group</th>
<th>Study n</th>
<th>Study design</th>
<th>Findings</th>
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<tr>
<td>Aikens and Klinkman (2012)</td>
<td>Depression</td>
<td>163</td>
<td>Prospective</td>
<td>BMQ-Specific Concerns at baseline predicted side effect reporting; Ratings of side effect burden and intensity were associated with Specific Concerns at trial exit</td>
</tr>
<tr>
<td>Bautista, Gonzales &amp; Jain (2011)</td>
<td>Epilepsy</td>
<td>121</td>
<td>Cross-sectional</td>
<td>BMQ-General (no differentiation between subscales reported) scores were associated with increased side effects when switching from branded to generic antiepileptic drug. BMQ-Specific not significant.</td>
</tr>
<tr>
<td>Shiyanbola and Farris (2010)</td>
<td>Geriatric patients</td>
<td>874</td>
<td>Cross-sectional</td>
<td>BMQ-Specific Concerns were associated with increased side effect reporting. Receiving inappropriate medication or the number of different medications taken was not related to side effect reports.</td>
</tr>
<tr>
<td>De Smedt et al. (2011)</td>
<td>Heart Failure</td>
<td>495</td>
<td>Cross-sectional</td>
<td>Illness identity (or having &gt; 5 symptoms) and BMQ-General Overuse were associated with increased side effect reporting. BMQ-General Harm and BMQ-Specific Concerns were significant predictors in univariate models.</td>
</tr>
<tr>
<td>De Smedt et al. (2012)</td>
<td>Heart Failure</td>
<td>250</td>
<td>Cross-sectional</td>
<td>BMQ-Specific Concerns and BMQ-General Harm were associated with the Identity and Consequences &amp; Emotions dimension of side effect representations.</td>
</tr>
<tr>
<td>Nestoriuc et al. (2010)</td>
<td>Arthritis</td>
<td>100</td>
<td>Prospective</td>
<td>BMQ-Specific Concerns at baseline predicted side effects at baseline and at 6 month.</td>
</tr>
<tr>
<td>Oladimeji et al. (2008)</td>
<td>&gt;65 old Medicare enrollees</td>
<td>1220</td>
<td>Cross-sectional</td>
<td>BMQ-Specific Concerns but not Specific Necessity were associated with self-reported side effects.</td>
</tr>
<tr>
<td>Oladimeji et al. (2009)</td>
<td>&gt;65 old Medicare enrollees Cardio-vascular disease</td>
<td>436</td>
<td>Partly prospective</td>
<td>Changes in BMQ-Specific Concerns predicted self-reported side effects</td>
</tr>
<tr>
<td>Berglund, Lytsy &amp; Westerling (2013)</td>
<td>Chronic Pain</td>
<td>239</td>
<td>Cross-sectional</td>
<td>BMQ-Specific Concerns correlated significantly with perceptions of unpleasant side effect experience.</td>
</tr>
<tr>
<td>Rosser et al. (2011)</td>
<td>Asthma</td>
<td>1542</td>
<td>Cross-sectional</td>
<td>Concerns about medication (measured with the Pain Medication Attitudes Questionnaire) were significantly positively correlated with the frequency of side effect reporting.</td>
</tr>
<tr>
<td>Cooper et al. (2014)</td>
<td>Asthma</td>
<td>1542</td>
<td>Cross-sectional</td>
<td>Patients who reported side effects had stronger concerns (BMQ-Specific Concerns) about their asthma medications (both inhaled and oral corticosteroids).</td>
</tr>
<tr>
<td>Petrie et al. (2004b)</td>
<td>Travel vaccine</td>
<td>121</td>
<td>Prospective</td>
<td>PSM scores predicted overall number of symptom complaints and the number of symptoms attributed to the medication immediately after the vaccination (but not at follow-up).</td>
</tr>
<tr>
<td>Faasse et al. (2015a)</td>
<td>General population</td>
<td>1000</td>
<td>Cross-sectional</td>
<td>Participants with higher PSM scores reported significantly more symptoms than patients with low or moderate PSM scores.</td>
</tr>
</tbody>
</table>

Note. BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale
1.3.3.1 Specific Concerns and side effect reporting

In a large cross-sectional study with 1220 elderly US residents (>65 years old) enrolled in Medicare (Oladimeji et al., 2008) around 18% of participants reported having experienced a severe side effect that led to physician visit. The odds of reporting such a side effect were significantly higher for participants who had stronger concerns about their medications as assessed with the BMQ-Specific. Beliefs about the necessity for treatment and the number of medications used were not associated with a higher risk of side effects. Several other cross-sectional studies have documented increased side effect reporting in patients with stronger concerns about treatment prescribed for specific conditions, e.g. asthma (Cooper et al., 2014), chronic pain (Rosser et al., 2011), heart failure (De Smedt et al., 2011) or cardiovascular disease (Berglund et al., 2013).

There is however a dearth of prospective studies examining this relationship. A follow-up survey with US Medicare enrollees identified 436 participants who had participated in both the original survey in 2005 (Oladimeji et al., 2008) and the follow-up survey in 2007 (Shiyanbola, Farris, Urmie, & Doucette, 2009). Among these respondents an increase in self-reported side effects between the two measurement points was predicted by specific concerns and the number of symptoms reported. In a study with patients with unipolar major depression, participants completed measures of treatment beliefs (BMQ-Specific) and depression before starting treatment with citalopram (Aikens & Klinkman, 2012). Side effects were assessed every two weeks for a 14 week follow up period. As in the cross-sectional studies, specific concerns, but not specific necessity beliefs were associated with increased side effect reporting.

Another study in patients undergoing treatment for rheumatic arthritis, showed that patients’ concerns about their arthritis medication at baseline predicted side effects at baseline and at 6 month follow-up, when controlling for relevant disease and treatment related variables (Nestoriuc et al., 2010). The authors also used a structural equation modelling technique (cross lagged panel model, see Figure 3) to test for a causal relationship between medication beliefs and side effects. The beliefs (Specific Concern) to side effect path was significant ($\beta=0.21$), while the side effects to belief path was non-significant ($\beta=0.06$) at $p=.05$ level. This finding supports a causal involvement of medication beliefs in the emergence of side effects. While certainly important, it is necessary to replicate this finding in a larger sample with more measurement points.
1.3.3.2 Beliefs about medicines in general and side effect reporting

There is also some evidence that patients’ beliefs about pharmaceutical medicines in general and about certain classes of pharmaceuticals are associated with side effect reporting. Research shows for example that many patients do not trust generic medicines (Iosifescu, Halm, McGinn, Siu, & Federman, 2008). Consequently, patients who were switched from a branded drug (actually a placebo) to a generic drug (also a placebo) were significantly more likely to report side effects than patients who did not make the switch, i.e. were given branded placebo in both sessions (Faasse, Cundy, Gamble, & Petrie, 2013). Unfortunately beliefs about medication were not explicitly assessed in this study. Similar findings were reported in a study with patients who changed from branded to generic treatment for epilepsy. About a fifth of the patients who switched from branded to generic anti-epilepsy medication reported increased side effects (Bautista et al., 2011). The increase in side effects was predicted by general medication beliefs (summed General Overuse, General Harm scales) but not Specific Concerns about the medication.

A cross-sectional study in patients with heart failure (De Smedt et al., 2011) also showed associations between general medication beliefs and side effect reporting. Patients who reported having experienced side effects from their heart failure medication believed pharmaceutical medicines to be generally overused by doctors. A follow up study in patients with heart failure (De Smedt et al., 2012) used structural equation modelling to examine the role of medication beliefs in side effect perception. A side effect perception questionnaire, modelled on the illness perception questionnaire (IPQ) (Moss-Morris et al., 2002) was developed for the
purpose of the study. Specific Concerns and General Harm explained 13% of the variance in number of symptoms that patients endorsed as side effects (“identity scale” of the IPQ) and 40% of variance in the negative emotions and consequences experienced because of side effects.

1.3.3.3 PSM and side effect reporting

There is also growing evidence for an association between patients’ perceptions of sensitivity to medicines and side effect reporting. A study with patients receiving travel vaccination showed that those with greater perceived sensitivity to medicines reported significantly more symptoms and attributed more symptoms as vaccination side effects 20 minutes after receiving the vaccination (Petrie et al., 2004b). In this study perceived sensitivity to medicines was also associated with increased symptom reporting one week after the vaccination, but not with the attribution of these symptoms to the medication at this later time point.

Another study with a nationally representative sample of New Zealand residents (Faassee et al., 2015a) showed that participants who reported high levels of perceived sensitivity to medicines were significantly more likely to report symptoms than participants with medium or low perceived sensitivity to medicines. Unfortunately the study assessed only general symptoms and not side effects to medication. However, participants who were currently taking prescription medications reported significantly more symptoms than participants not receiving prescription medication and there was a significant interaction effect: the impact of perceived sensitivity to medicines on the number of reported symptoms was greater for those who were currently receiving prescription medication.

1.3.3.4 Conclusion

At first sight there seems to be consistent evidence for an association between medication beliefs and side effect reporting. In line with theoretical considerations (Horne, 1999; Horne, 2003), concerns about specific medications and negative pharmaceutical schemas are associated with increased side effect reporting, suggesting that treatment beliefs play a role in the emergence of side effects. But it may yet be premature to make this inference. The majority of the reviewed studies failed to measure medication beliefs prospectively and evidence from cross-sectional data is likely to overestimate the extent of a possible relationship (Weinstein, 2007). In addition, the actual experience of side effects may have negatively influenced medication beliefs and not vice versa. It is indeed highly probable that patients who experience side effects from their medication develop
more negative views about the specific medication in question, generalize this to other pharmaceuticals and as a consequence perceive themselves as more sensitive to the negative effects of medication. In addition, two of the prospective studies had relatively small samples (Nestoriuc et al. (N=100) and Petrie et al. (N=121)). It is also important to note here that there is a non-negligible risk of publication bias, with studies that did not find associations between medication beliefs and side effect reporting less likely to be published and thus identified in the literature search. Taken together, this clearly shows a need for more large scale prospective studies.

1.4 The nocebo effect

The literature review suggests that patients’ beliefs about medicines may influence whether patients experience and report side effects. The fact that factors beyond the pharmacological action of the medication can influence side effect experience has received growing attention over the last few years. In particular, the ever growing body of research on the nocebo effect has shown that patients may report side effects even in response to pharmacologically inactive placebo treatment.

1.4.1 Specific and non-specific factors contributing to side effects

Side effects are often a by-product of the pharmacological action of the medication. The pharmacological effect on one tissue or organ system produces benefit, whereas a similar effect in another tissue or organ system produces harm. For example, aspirin inhibits prostaglandin pathways in an inflamed joint producing a beneficial anti-inflammatory and analgesic effect. Inhibiting similar pathways in the stomach can cause gastric erosion (Vane & Botting, 2003).

But just as any improvement following treatment stems both from the specific pharmacological effect of the medication and non-specific factors (e.g. placebo effects, natural course of the disease), symptom worsening and side effects may be influenced by factors unrelated to the pharmacological action of the drug (Barsky et al., 2002). Figure 4 provides an overview of some non-specific factors that have been linked to side effects (Mora, Nestoriuc, & Rief, 2011).

The relative contribution of specific (i.e. pharmacological) versus non-specific factors to side effects will not only vary between drugs, but also between individuals (e.g. the objective nociceptive input is not perceived as equally painful by different people (Tracey, 2010)) and even within individuals, depending on the
context (Horing, Weimer, Muth, & Enck, 2013). The specific and non-specific components of treatment interact (Edwards, Graedon, & Graedon, 2010) and are often undistinguishable in clinical practice (Caspi & Bootzin, 2002). Only side effects in response to pharmacologically inactive placebo treatment are certainly non-specific. It has therefore been suggested to consider specific and non-specific treatment effects not as distinct categories, but as theoretical endpoints of a continuum of specificity (Rief, Hofmann, & Nestoriuc, 2008).

Figure 4: Factors influencing side effects

![Diagram showing factors influencing side effects]

Note. Figure taken from Mora et al. (Mora et al., 2011)

1.4.2 Defining the nocebo effect

The term nocebo (“I shall harm”) was introduced to distinguish between the positive (e.g. symptom improvement) and negative effects (e.g. symptom worsening, emergence of new symptoms) of the placebo (“I shall please”) (Colloca & Miller, 2011). In their seminal paper on nocebo and non-specific side effects, Barsky and colleagues define the nocebo phenomenon as referring to “symptoms and/or physiological changes that follow the administration of an inert, chemically inactive substance that the patients believes to be an active drug” (Barsky et al., 2002, p. 622).

Several recent meta-analytic studies have examined the frequency of side effect reports in the placebo arms of randomized controlled trials (RCTs) across treatments for a range of conditions (see Table 2 for an overview). In many of the reviewed studies more than half of placebo treated patients reported at least one
side effect, but frequencies vary widely between studies (Symon, Williams, Adelasoye, & Cheyne, 2015). Side effects to placebo have also been examined in phase I drug trials with healthy volunteers. A systematic review of 109 of these trials found that overall 19% of healthy participants reported one or more side effects when taking placebo (Rosenzweig, Brohier, & Zipfel, 1995). In some instances placebos side effects are so severe that patients subsequently discontinue treatment (see Table 2), but discontinuation rates are again highly variable between studies.

Table 2: Overview systematic reviews of side effect frequency in placebo groups of randomized controlled trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Indication</th>
<th>Number of studies</th>
<th>Placebo side effect rate (^1) in % [95% CI]</th>
<th>Discontinuation rate (^2) in % [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papadopoulous and Mitsikostas (2012)</td>
<td>Neuropathic Pain</td>
<td>12</td>
<td>52.0 [35.7; 67.9]</td>
<td>6.0 [4.5; 8.0]</td>
</tr>
<tr>
<td>Papadopoulous and Mitsikostas (2011)</td>
<td>disease modifying Multiple Sclerosis treatment</td>
<td>56</td>
<td>74.4 [69.92; 88.30]</td>
<td>2.1 [1.6; 2.7]</td>
</tr>
<tr>
<td>Häuser, Bartram, Bartram-Wunn &amp; Tölle (2012)</td>
<td>symptomatic Multiple Sclerosis treatment Fibromyalgia Syndrome</td>
<td>44 58</td>
<td>25.3 [15.24; 36.90] 59.9 [53.8; 65.8]</td>
<td>2.4 [1.5; 3.3] 9.5 [8.6; 10.7]</td>
</tr>
<tr>
<td>Stathis, Smpiliris, Konitsiotis &amp; Mitsikostas (2012)</td>
<td>Diabetic Peripheral Neuropathy</td>
<td>62</td>
<td>46.2 [36.5; 56.1]</td>
<td>5.8 [5.1; 6.6]</td>
</tr>
<tr>
<td>Rief, Avorn &amp; Barsky (2006)</td>
<td>Cardiovascular Disease</td>
<td>20</td>
<td>NA(^2)</td>
<td>4-26(^3)</td>
</tr>
<tr>
<td>Amanzio, Corazzini, Vase &amp; Benedetti (2009)</td>
<td>Symptomatic migraine treatment</td>
<td>59</td>
<td>NA(^2)</td>
<td>0.3 [0.2; 0.5]</td>
</tr>
<tr>
<td></td>
<td>Alzheimer's Disease</td>
<td>16</td>
<td>66.7 [20.41; 25.93]</td>
<td>0-27(^5)</td>
</tr>
</tbody>
</table>

Note: 1 Rate of patients reporting at least 1 side effect, 2 only reported for individual side effects; 3 pooled discontinuation rate not reported; CI=Confidence Interval

According to the nocebo definition presented above all side effects reported in the placebo arm of RCTs would constitute nocebo effects: Patients take pharmacologically inactive treatment, which they probably believe to be active (most
studies do not assess patients’ allocation beliefs (Bang, Ni, & Davis, 2004)) and subsequently report symptoms. But the story is more complex. To get a better understanding of the problem it is helpful to consider placebo effects first. Imagine we treat a group of patients at the initial stages of a common cold with a placebo sugar pill. After a week of placebo treatment the common cold symptoms objectively improve (e.g. respiratory volume increases, amount of mucus is reduced). Does that show the power of the placebo, as has been suggested by authors presenting similar evidence (Beecher, 1955)? Not really. On average, common colds tend to get better after a week. It is now widely acknowledged that placebo effects need to be distinguished from other non-specific effects, like regression to the mean (McDonald, Mazzuca, & McCabe, 1983), spontaneous remission (Kienle & Kiene, 1997) or natural progression of the disease (Ernst & Resch, 1995). A true placebo effect can thus only be demonstrated by comparing outcomes in the placebo group to those in a no-treatment control group (Gøtzsche, 1994) or other appropriate control groups.

Likewise, any symptom worsening or the emergence of new symptoms in placebo treated patients could be caused by nonspecific factors unrelated to the placebo. This has not been sufficiently appreciated in the literature on nocebo effects (Colloca & Miller, 2011). Yet, imagine a placebo treated patient who is kept on a hospital ward for 2 weeks for the duration of an RCT. Just by changing her sleeping (Who sleeps well in an unfamiliar hospital bed?), eating (Is hospital food still as bad as I remember?) and activity pattern (12 hour daytime TV anyone?), a range of bodily changes and symptoms may occur (e.g. fatigue, insomnia, bloating, constipation, etc.). The same would have happened regardless of treatment (be it active or placebo). Gøtzsche makes a similar point: “If we treated patients with AIDS with loving care and noted that most of them had died after 3 years, we would hardly be willing to speak of loving care as a nocebo effect.” (Gøtzsche, 1994, p. 925).

Several researchers have thus recommended to distinguished between apparent nocebo effects (symptom reporting or symptom worsening observed in patients receiving placebo) and true nocebo effects (significantly greater symptom reporting or symptom worsening in patients randomized to placebo than to a natural history group) (Colloca & Finniss, 2012; Enck, Bingel, Schedlowski, & Rief, 2013). Most published research on the nocebo effect examines apparent nocebo effects (see also Table 2 here) and studies comparing symptom reporting in patients randomized to placebo or a natural history group are surprisingly rare (Colloca &
This thesis will make an important contribution to this literature by examining differences in symptom reporting in patients randomized to placebo or a natural history group (see Chapter 3). It is however not only symptom reporting, but also the attribution of these symptoms to the medication that matters. Patients may report symptoms while taking placebo (e.g. tiredness) which they do not attribute to the placebo pill but to other factors (e.g. disturbed sleep the previous night).

1.4.3 Explanatory mechanisms of nocebo effects

Conditioning and expectations are the two major explanatory accounts of nocebo effects (Benedetti, Lanotte, Lopiano, & Colloca, 2007; Enck, Benedetti, & Schedlowski, 2008), but a plethora of other explanations have been proposed (e.g. changes in emotion (Stewart-Williams, 2004), social modelling (Faasse, Grey, Jordan, Garland, & Petrie, 2015b; Lorber, Mazzoni, & Kirsch, 2007), or a negative doctor patient relationship (Greville-Harris & Dieppe, 2015)). Some authors have suggested that the misattribution of pre-existing or spontaneously occurring unrelated symptoms as medication side effects could be considered a nocebo mechanism (Barsky et al., 2002; Webster, Weinman, & Rubin, 2016). Others, applying the more stringent operational definition of nocebo effects, would not include misattributed symptoms (Colloca & Miller, 2011; Enck et al., 2013). It is now commonly accepted that there is not one single nocebo mechanism, but considerable overlap and interaction between mechanisms (Benedetti, 2008). In this thesis I will explore whether medications beliefs could be associated with nocebo mechanisms.

Classical conditioning

Classical conditioning accounts of the nocebo effect assume that a conditioned stimulus (CS), which could also be a complex combination of factors like the colour of the pill, hospital smell or the route of administration of the drug (Wickramasekera, 1980), becomes associated with an unconditioned stimulus (US), i.e. the pharmacologically active drug (e.g. emetic drug in red pill form) which induces the unconditional response (UR, e.g. nausea). After several US-CS pairings, the US (e.g. red placebo pill) can elicit the UR without the presence of the US.

The influence of classical conditioning on side effects can for example be seen in cancer patients undergoing chemotherapy. Around 20%-30% of patients who experienced nausea in earlier chemotherapy cycles, develop anticipatory nausea (i.e. experience nausea or vomiting before the treatment is administered) in
later cycles (Hickok, Roscoe, & Morrow, 2001; Roscoe, Morrow, Aapro, Molassiotis, & Olver, 2011). Simply being in the same environment (hospital waiting room with characteristic smell, etc.) is enough to trigger the side effect symptoms.

Medication beliefs and conditioning
It is plausible that beliefs about medication play a role in conditioned nocebo responses, although this will not be explicitly examined in this thesis. Conditioning is a learning process. In the case of nocebo effects, patients learn that there is an association between the drug and side effects/symptom worsening. It seems plausible that negative treatment beliefs predispose individuals to pay greater attention to any drug-symptom associations. Manipulations that are likely to increase concerns about other chemical substances, e.g. warnings about chemical pollution, have been found to increase conditioned learning of somatic symptoms (Winters et al., 2003). Patients with negative beliefs about treatment and high perceived sensitivity to medicines may thus be more likely to learn the association between medication cues and side effect responses.

Expectation
Expectation accounts of the nocebo effect postulate that the expectation of symptoms leads to the emergence of the expected symptoms (Hahn, 1997a). In experimental nocebo studies expectations are often explicitly induced (e.g. by stating that a sham treatment will lead to pain increase (Colloca & Benedetti, 2007; Kong et al., 2008)). Nocebo expectations in RCTs are however more indirect and related to patients’ construal of the situation and their underlying beliefs. Expectations have been shown to predict side effect reporting in patients undergoing chemotherapy (Colagiuri et al., 2013; Hofman et al., 2004; Roscoe, Hickok, & Morrow, 2000) and pharmacological treatment for other clinical conditions (Mondaini et al., 2007; Myers, Cairns, & Singer, 1987; Silvestri et al., 2003).

The evidence is however not unanimous. Some studies failed to show an association between expectations and side effects (Voudouris, Peck, & Coleman, 1990; Walach, Schmidt, Dirhold, & Nosch, 2002). In addition, many of the findings from experimental nocebo studies could be caused by demand effects (Roscoe et al., 2006) of the experimental situation. When an experimenter tells participants that they will experience more pain when taking a placebo, participants may report increased pain simply to please (and placebo="I shall please") the experimenter by going along with this suggestion (Weber & Cook, 1972). It is however important to note here that suggestibility (Angelucci & Pena, 1997; Bräscher, 2014) and social
desirability (Link, Haggard, Kelly, & Forrer, 2006; Put et al., 2004) do not seem to be associated with nocebo responding.

Although the general importance of expectations is undisputed, sometimes even making expectation a defining feature of nocebo effects (Hahn, 1997b), there is little consensus on how to best assess patients’ expectations and a lack of clarity about the mechanisms that link expectations to treatment outcomes (Geers, Helfer, Weiland, & Kosbab, 2006). It is in fact unlikely that there are many direct (i.e. non-mediated) effects from expectations on outcomes (Stewart-Williams, 2004). Several possible mechanisms linking beliefs and expectation to treatment outcomes will be explored in more detail in section 1.5.

**Medication beliefs and expectations**

It is plausible that concerns about pharmaceuticals in general or about specific treatments may influence expectations of side effects and contribute to nocebo effects. In addition, individuals’ beliefs about perceived sensitivity to medicines are likely to play an important role in side effect expectations: Patients who believe that they are more sensitive to medicines will probably expect more (or more severe) side effects than patients who believe that they are not sensitive to the effect of medicines. Some authors have recommended using common measures of treatment beliefs (see section 1.3.2) to assess patients expectations of side effects (Faasse & Petrie, 2013).

**Review of existing studies linking medication beliefs to nocebo responding**

Although the theoretical relevance of treatment beliefs for understanding placebo and nocebo effects has been acknowledged in some review papers (Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001; Horne, 1999), there is a distinct lack of empirical studies examining whether medication beliefs predict side effect reporting in individuals taking placebo. A search of the PubMed and PsychInfo databases failed to identify any relevant studies.

**The role of other psychological factors in side effect reporting and nocebo responding**

Several other psychological factors have been linked to increased side effect reporting and nocebo responding. Converging evidence from clinical studies and experimental nocebo studies that anxiety and depression may increase side effect
reporting and nocebo responding. A study in patients with anxiety disorder demonstrated for example that patients were more likely to report side effects after the standard formulation of their medication (alprazolam) was switched to an extended release formulation if they had higher baseline scores on the anxiety, depression and phobia clusters of the Hopkins Symptom Checklist (Uhlenhuth et al., 1998). A study examining personality characteristics of healthy individuals in early stage (phase I) clinical trials also showed that trait anxiety was positively correlated with side effect reporting (Almeida et al., 2008). There is also good evidence for the role of anxiety in nocebo responding, which has been linked to increased pain perception in various experimental nocebo studies (Benedetti et al., 2007; Colloca & Benedetti, 2007).

Depression has also been frequently mentioned as a factor contributing to nocebo effects and non-specific side effects (Barsky et al., 2002), but this claim rests mainly on case reports and the sparse quantitative evidence is mixed. A study in patients with major depressive disorder found no effect of depression severity on the number of reported side effects to placebo. (Casper, Tollefson, & Nilsson, 2001), but it is possible that there was a ceiling effect (because depression levels were high in the whole sample). A study examining drug intolerance in patients taking anti-hypertensive medication (Davies, Jackson, Ramsay, & Ghahramani, 2003) found however that patients with co-morbid depression were more likely to report non-specific, but not drug-specific side effects as assessed by blinded clinicians judgement.

Various other psychological factors like Type A Personality (Drici, Raybaud, De Lunardo, Iacono, & Gustovic, 1995), somatosensory amplification (Withthöft & Rubin, 2013), neuroticism (Davis, Ralevski, Kennedy, & Neitzert, 1995; Mazzoni, Foan, Hyland, & Kirsch, 2010) and negative affectivity (Put et al., 2004) have also been identified as potential risk factors contributing to nocebo effects, but evidence is still relatively sparse and further complicated by a lack in consistency in the personality traits studied (see also recent review by Webster et al., 2016).

1.5 Putative cognitive processes linking medication beliefs to side effects

In this thesis I propose that treatment representations may influence various cognitive processes relevant for symptom perception and experience, which could contribute to nocebo effects.
1.5.1 Attention and symptom detection

Somatic focus

It is plausible that individuals with negative medication beliefs engage in increased monitoring of their body during pharmacological treatment. This may be particularly the case when starting a new type of treatment. In the prospective study by Nestoriuc and colleagues described earlier (Nestoriuc et al., 2010), the influence of concerns about arthritis medication on side effect reporting was stronger in patients who had just started using a new arthritis medication.

There is good evidence for the role of somatic focus in symptom perception in general. Research indicates that patients with medically unexplained symptoms (MUS) (Barsky & Wyshak, 1990; Cioffi, 1991; Rief & Broadbent, 2007; Rief, Hiller, & Margraf, 1998) tend to pay more attention to their bodily states, which increases the odds of detecting somatic changes. In addition, several experimental studies have shown that merely attending to bodily sensations may increase the perceived intensity (Pennebaker & Skelton, 1978) and frequency of symptoms (Schmidt, Wolfs-Takens, Oosterlaan, & van den Hout, 1994). Distraction and external attentional focus (e.g. counting the number of word occurrences versus focusing on heartbeat and breathing (Fillingim & Fine, 1986)) on the other hand can reduce the likelihood that symptoms are detected (Kolk, Hanewald, Schagen, & Gijsbers van Wijk, 2003; Pennebaker & Lightner, 1980).

Figure 5: Routes by which beliefs/expectations influence perceptual experience

Note. Adapted from Smith (2007)

Our bodies are constantly exposed to an enormous amount of sensations and not all of them reach conscious awareness thanks to a filtering mechanism
(often conceptualized as a gate control mechanism (Melzack & Wall, 1983), see Figure 5). Beliefs and expectations, as well as lack of distraction (Pennebaker & Lightner, 1980) and negative affect (Kolk et al., 2003), are thought to make this gate more permeable, allowing a greater number of sensations to reach awareness (Smith, 2007). These often ambiguous sensations may consequently be falsely interpreted as medication side effects. The association between treatment beliefs and self-reported somatic focus will be explored in Study 2 presented in Chapter 3.

The somatic focus hypothesis is in line with research showing increased symptom reporting following placebo administration in participants who were told to focus on their feelings and bodily reactions compared to participants for whom attention wasn’t manipulated (Geers et al., 2006). This attention augmentation effect could however only be found in the condition where participants were sure to receive the “drug” (which was in all cases placebo) and not in the condition were they were told that they had a 50:50 chance of receiving the drug or placebo.

**Selective (schema guided) attention**

There is also good evidence for the role of schema guided attention in symptom perception. Identical sensory stimulation can be perceived in different ways by the same person at different times (Pennebaker, 1982). Most internal sensations are vague and diffuse. Given their ambiguous nature, their perception and interpretation will depend on the schemata or the hypotheses a person holds. In a study by Anderson and Pennebaker (Anderson & Pennebaker, 1980), the same sensation induced by touching a vibrating emery board, was described as either painful or pleasurable. This interpretative schema was merely conveyed through the following statement in the consent form: “I understand I will come into contact with a stimulus that has been found to provide a degree of pleasure [or pain]”. The experimentally manipulated schema (pain or pleasure) influenced the perception of the identical sensation.

In a related experiment (Pennebaker & Skelton, 1981) participants were told that a bogus ultrasonic noise would increase [or decrease] skin temperature. Participants in the ‘increase condition’ reported attending more to sensations of skin temperature increase and less to sensations of decreasing skin temperature. The reverse pattern was found for participants in the ‘decrease condition’. Interestingly, whereas actual skin temperature did not differ in the increase and decrease conditions, the amount of fluctuations in skin temperature predicted skin temperature ratings: The more fluctuations a participant experienced, the warmer or...
colder (depending on the activated schema) their reported skin temperature. Participants selectively encoded change in a way that supported their hypothesis. While there is a fair amount of research on the role of schema directed attention in medically unexplained symptoms (Cioffi, 1991; Rief & Broadbent, 2007) and over-perception of illness symptoms (Janssens, Verleden, De Peuter, Van Diest, & Van den Bergh, 2009; Rietveld, 1998), there is a dearth of studies exploring this phenomenon in the medication context. The exception is a study by Geers and colleagues (Geers, Wellman, Fowler, Rasinski, & Helfer, 2011): One group of participants received a placebo pill, but were told that it was caffeine (‘deceptive condition’), a second group were told that there was a 50:50 chance that the pill contained caffeine or placebo (‘double-blind’) while a third group received no pill (‘no-expectation’). All participants were asked to monitor their bodily sensations during a seven minute period and to keep a tally of sensations related to stimulation (e.g. tension, anxiety) and non-stimulation sensations (e.g. hunger). Participants in the ‘double-blind condition’ identified an equal amount of stimulation and non-stimulation sensations. Participants in the ‘no-expectation condition’ detected more non-stimulation sensations. However participants in the ‘deceptive condition’ reported more stimulation sensations. Although experimental demand effects cannot be ruled out (e.g. participants reporting more caffeine congruent sensations to please the experimenter in the ‘deceptive condition’), this study provides support for the idea that individuals’ beliefs and schemas about the treatment influence the detection of somatic sensations.

The inclusion of side effects in the consent form has also been shown to increase the likelihood of side effect reports of the listed side effects in some studies (Colagiuri, McGuinness, Boakes, & Butow, 2012; Mondaini et al., 2007; Myers et al., 1987), but others failed to find an association (Howland, Baker, & Poe, 1990; Morris & Kanouse, 1982; Myers & Calvert, 1973). It is possible that individuals with unhelpful treatment beliefs engage more in side effect specific (as indicated on the patient information leaflet) monitoring of bodily sensations. Patients with low concerns and/or those who feel not vulnerable to side effect may be more likely to ignore the side effect information.

If patients with negative medication beliefs pay more selective attention to specific sensations, they are more likely to both detect these symptoms and attribute these symptoms to the medication. This may in turn confirm individuals’ initial negative beliefs about medication, leading to a vicious cycle of side effect
over-perception and belief confirmation. One of the studies in this thesis (see Chapter 3) aims to explore the selective attention hypothesis and the role of medication beliefs as attention guiding schemas. Both the role of specific schemas (e.g. side effects listed in the patient information leaflet (PIL)) and more general schemas (treatment representations in general) will be explored in this study.

1.5.2 Misattribution

Expectations and negative medication beliefs are likely to influence whether symptoms are attributed as side effects as individuals tend to interpret bodily sensations in line with their interpretative sets or schemata (Pennebaker, 1982). Treatment representations as well as illness representations can function as interpretative sets. Evidence suggests however that mental representations of illness symptoms and side effects overlap. DeWitt and Sorofman (1999) used the self-regulation model of illness representations (Leventhal et al., 1992) to study side effect representations. They found that individuals use the same dimensions (identity, timeline, cause, control and consequences) in their narratives of side effects as in those of illness symptoms. Identical somatic symptoms (e.g. rash) can in many instances be caused by either the illness (e.g. infection) or the treatment (medication to treat infection). In illness representation terms this means that rash forms part of the identity component of both the illness and side effect representation.

The direction of the attribution (illness, environmental factor, medication) will depend on the relative salience of the interpretative set, as salient information tends to be overrepresented in causal attribution (Hewstone, 1989; Taylor & Fiske, 1978). It is likely that strong negative medication beliefs increase the salience of the side effect concept. If symptoms are attributed to the medication, coping is likely to be different (non-adherence, dose reduction) than if they are attributed to internal causes (illness), where taking medication would be a potential coping strategy.

There has indeed been a long standing clinical impression that some patient-reported side effects are indeed symptoms of the disease to be treated, those of coexistent comorbid conditions, or common symptoms (Barsky et al., 2002) that are misattributed as side effects to the medication.

A study in patients with hypertension showed for example that those with comorbid depression frequently reported common symptoms of depression (e.g. low mood, lethargy, loss of libido, poor concentration) as side effects to their anti-
hypertensive medication (Davies et al., 2003). Similar findings have been reported with regards to side effects in the placebo arm of RCTs: Abdominal pain and bloating were more frequent in patients receiving placebos in trials of Irritable Bowel Syndrome (IBS) than those for other disorders (e.g. arthritis, hypertension, etc.) (Poitras, Gougeon, Binn, & Bouin, 2008). Both abdominal pain and bloating are characteristic digestive symptoms of IBS. In a placebo controlled trial for Attention Deficit Hyperactivity Disorder (ADHD) (Fine & Johnston, 1993), many of the side effects (both in the placebo and the active medication group) were again surprisingly similar to symptoms of ADHD.

Physical symptoms like headache, fatigue and nausea affect everyone from time to time. Even healthy individuals who are not taking medication frequently experience these common symptoms with an estimated three day prevalence rate between 70-90% (Khosla, Bajaj, Sharma, & Mishra, 1992; Meyer, Troger, & Rohl, 1996; Reidenberg & Lowenthal, 1968). It is interesting to note here that many of the side effects patients report in response to placebo treatment resemble common symptoms (Amanzio et al., 2012; Rief et al., 2009). Perhaps not surprisingly, many common symptoms appear frequently in the list of side effects of various patient information documents (Tan, Petrie, Faasse, Bolland, & Grey, 2014). In this thesis I hypothesize that patients who have more negative medication beliefs will be more likely to attribute these everyday symptoms as medication side effects. Several analogue studies (Studies 3-5) presented in this thesis will empirically test the role of misattribution of common symptoms as medication side effects.

Memory for side effect information and misattribution

We have seen that specific information about side effects (e.g. from the patient information leaflet) can be important in side effect perception. Side effect information is useful for patients when deciding whether a symptom is a side effect, but patients need to correctly remember this information. However, memory for treatment information (Barsky, 2002; Weinman, 1990), including side-effects (Tarn & Flocke, 2011), is known to be generally poor. To date little is known about potential systematic biases underpinning poor memory for side-effect information, but there is good evidence for the role of schemas in both recall and recognition memory (Alba & Hasher, 1983; Graesser & Nakamura, 1984) in general. In this thesis (see Study 4) I will explore whether pharmaceutical schemas influence how individuals process and remember side effect information and whether this is turn influences side effect attribution. I hypothesize that the attribution of a symptom as a
medication side effect will be more accurate when individuals have accurately remembered information they have been given about the specific side effects that are known to be associated with a particular medication.

1.6 General aim and research questions

General aim

The general aim of this thesis is to get a better understanding of the relationship between medication beliefs and side effects. Three broad research questions will be addressed in this thesis.

Research Question 1: Do medication beliefs prospectively predict side effect reporting to active medication and placebo?

In this thesis I postulate that there is a bi-directional relationship between treatment beliefs and side effects. Negative treatment beliefs increase the likelihood that individuals experience and report side effects (see path B Figure 6). The experience of side effects in turn strengthens negative treatment beliefs (see path A Figure 6).

Figure 6: Relationship between side effect experience and medication beliefs

I will test this in two ways:

1) I will examine the relationship between medication beliefs and side effect reporting over time in a large clinical sample of women taking bone loss prevention medication (see Chapter 2).

2) I will test whether medication beliefs prospectively predict side effect reporting in students receiving pharmacologically inactive Modafinil placebo (see Chapter 3).
Research Question 2: Why are medication beliefs associated with side effect reporting?

Several putative mechanisms underlying the relationship between medication beliefs and side effect reporting will be examined:

1) Expectation: The relationship between medication beliefs and side effect expectations will be examined in Studies 1-3.

2) Misattribution: The role of treatment beliefs in the misattribution of common symptoms (headache, nausea; Studies 3-5) and experimentally induced ambiguous sensations (itch, dizziness; Study 2) as medication side effects will be examined.

3) Biased memory: I will examine whether pharmaceutical schemas are associated with both the quantity and quality of memory for side effect information (Study 4). Better memory for factual side effect information is hypothesized to reduce symptom attribution errors.

4) Attention: There is good evidence that somatic focus and schema guided attention are important in symptom perception. It is plausible that these attentional processes also influence side effect perception, in particular in individuals with negative treatment beliefs. The role of treatment beliefs in these postulated attentional processes will be examined in the proposed Modafinil placebo study (Study 2).

Research Question 3: Can we change medication beliefs and thereby reduce non-specific side effects?

There is some evidence that treatment beliefs can be modified through cognitive-behavioural interventions (Petrie, Perry, Broadbent, & Weinman, 2012). In order to inform the development of future complex interventions, I will explore whether short online intervention components can be effective in changing individuals’ pharmaceutical schemas and test whether this in turn reduces the likelihood that a common symptom is attributed as a side effect (Study 5).
1.7 Thesis Roadmap

What will be presented in the following chapters?

The empirical section of this thesis starts with a chapter examining the role of treatment beliefs in prospectively predicting side effect reporting in women taking bone loss medication. This involves the re-analysis of data from a large clinical trial dataset from the POSSIBLE EU® study (Roux et al., 2011). The next chapter presents finding from a laboratory placebo experiment, showing a prospective association between treatment beliefs and symptom detection and attribution in healthy student volunteers who are led to believe they are taking “Modafinil” to enhance concentration and memory. The following two chapters summarize empirical evidence for the role of treatment beliefs in the misattribution of a common symptom as a side effects and memory for side effect information using an analogue scenario approach. The final empirical chapter shows findings from an exploratory online intervention study aimed at modifying negative pharmaceutical schemas.
Chapter 2: Medication beliefs and side effect reporting in women taking bone loss medication (Study 1)

2.1 General overview and study aims

We have seen from the literature review (see section 1.3.3) that a growing number of studies have documented associations between medication beliefs and side effect reporting in patients taking active medication. Findings suggest that patients with stronger concerns about their prescribed medications and more negative pharmaceutical schemas (e.g. beliefs that pharmaceutical medicines are harmful in general and high perceived personal sensitivity to medicines) report more side effects. As stated previously, there is however a dearth of large prospective studies examining the relationship between medication beliefs and side effects. In addition, very few studies have examined the role of medication beliefs in both side effect reporting and medication adherence within the same study.

The present study involves the secondary analysis of data from the Prospective Observational Study Investigating Bone Loss Experience in Europe (POSSIBLE EU® Study) (Roux et al., 2011). The primary aim of this study was to test whether patients’ specific medication beliefs and pharmaceutical schemas prospectively predict side effect reporting (see Research Question 1). In addition, I will also examine whether patients’ anxiety and depression ratings are associated with increased side effect reporting (see section 1.4.3 for a brief review of the existing literature).

The secondary aim was to examine associations between medication beliefs, side effect reporting and medication taking behaviours. Two different medication taking behaviours - adherence and persistence - will be investigated. Adherence refers to the extent patients take their medications as prescribed (Vrijens et al., 2012), while persistence refers to the act of continuing the treatment for the prescribed duration (Cramer et al., 2008). Patient reported side effects have been shown to reduce adherence to medications for many long term conditions (see also section 1.2) and patients often cite side effects as the primary reason to discontinue treatment (Garavalia, Garavalia, Spertus, & Decker, 2009; Monforte et al., 2000).

Previous studies exploring barriers to adherence to bone loss medications confirm the importance of medication beliefs and side effect experience (see section 2.2 below). Yet to date, few studies have examined how these factors are
interlinked. I have previously argued that negative medication beliefs could increase side effects through various cognitive-perceptual mechanisms (e.g. increased somatic focus, expectations; see also sections 1.4 -1.5). This implies that in addition to the well documented direct effect of medication beliefs on adherence, there may also be an indirect effect facilitated by increased side effect perception (see Figure 7).

Figure 7: Direct and indirect effects of medication beliefs on adherence

2.2 General study background

Osteoporosis is a chronic and progressive skeletal disease that is characterized by low bone mineral density and micro-architectural degeneration of bone tissue (Bone et al., 2004; Bouillon et al., 1991). The Word Health Organization has operationally defined osteoporosis as a bone mineral density score of 2.5 standard deviations below the mean peak density in young adults (WHO, 2008). In women hormonal changes that occur perimenopause and during the immediate post-menopausal years can accelerate bone loss (Watts et al., 2011). White and Asian women constitute the most at risk group (Barrett-Connor et al., 2005). If untreated, around 40% of White women will experience an osteoporotic fracture during their lifetime (Ross, 1996).

Postmenopausal osteoporosis significantly increases the risk of vertebral and non-vertebral fractures that occur in the absence of major external trauma (Riggs & Melton, 1995). Osteoporotic fractures can reduce quality of life (Guillemin
et al., 2013) and lead to continuing pain, impaired mobility and strong fear of further fractures (Meunier et al., 1999).

Bisphosphonates are the most widely used drugs to treat osteoporosis (Watts et al., 2011) and can significantly reduce the risk of osteoporotic fractures (Wells George et al., 2008). However uptake and adherence to these medications is sub-optimal, with 40-50% of patients failing to take their treatment as prescribed (Cummings et al., 2009; Siris et al., 2006).

Medication beliefs, such as doubts about the necessity for treatment and concerns about treatment risks (Freemantle et al., 2012; McHorney, Schousboe, Cline, & Weiss, 2007), have been shown to reduce adherence to bisphosphonates. Compared to the achieved reduction in osteoporotic fractures, the actual risk associated with bisphosphonates is relatively low (Abrahamsen, 2010). Upper gastrointestinal side effects and other non-serious side effects are however commonly reported by patients (Papapetrou, 2009). Patient reported side effects have been identified in several studies as important barriers to adherence to bisphosphonates (McHorney et al., 2007; Rossini et al., 2006; Tosteson et al., 2003).

2.3 Hypotheses

I hypothesized that patients who started out with more negative pharmaceutical schemas (i.e. beliefs that pharmaceuticals are more harmful and less beneficial and high perceived sensitivity to medicines), with stronger concerns about their bone loss medications and greater self-reported anxiety/depression would report more side effects at follow up and be less adherent and persistent with their bone loss medication. I also hypothesized that patient reported side effects would be associated with reduced adherence and persistence with treatment. Finally, I hypothesized that patient-reported side effects mediate the postulated relationship between medication beliefs and adherence.

2.4 Methods

2.4.1 Recruitment

This study uses data collected as part of the POSSIBLE EU® longitudinal cohort study. Baseline data and data collection methods have been described previously (Freemantle et al., 2010). The POSSIBLE EU® study recruited postmenopausal women in primary care settings across five European countries.
(UK, France, Germany, Italy and Spain). Patients were recruited at 196 different study sites during routine clinical visits to their GP.

2.4.2 Data collection

Investigators at the study sites reported data for each patient at study entry and at three month intervals (3 months, 6 months, 9 months, 12 months) during follow-up (see Figure 8). Patients completed a patient-reported outcome (PRO) questionnaire at baseline, either at the study site or at home. Subsequent PRO data at the 3 month follow-up intervals was collected at via mailed questionnaires.

2.4.3 Inclusion and exclusion criteria

Patients were included if they were over 18 years of age, ambulatory, postmenopausal (defined as no vaginal bleeding or spotting for at least 12 months) and initiating or continuing an eligible bone loss medication. Eligible treatments included bisphosphonates, selective oestrogen-receptor modulators, calcitonin, parathyroid hormone, strontium ranelate or any other therapy with a marketing authorization for osteoporosis. The sample was stratified into three groups of women: 1) initiating 2) switching or 3) continuing bone loss medication.

Women were excluded if they were receiving therapy with calcium and/or vitamin D, but no other eligible medication or were receiving only hormone replacement therapy. Women were also excluded if they were taking experimental treatments, had recently participated in another research study, had significant current disease (e.g. cancer) that impacted their ability to participate or were unable to give written informed consent.

In order to rule out previous experience with bone loss medication and side effects to bone loss medication, data for the current study was restricted to patients in the cohort initiating bone loss medication.

2.4.4 Measures

An overview of investigator and patient-reported measures is presented in Figure 8. Please note that these constitute only a subset of available measures from the original study.

2.4.4.1 Beliefs about Medicines Questionnaire (BMQ)

The BMQ-General (Horne et al., 1999) was used to assess patients’ beliefs about pharmaceutical medicines as a class of treatment (see section 1.3.2.1 for a detailed description of the measure). Patients completed the three BMQ-General
scales (General Harm, General Benefit, General Overuse) as part of the PRO-questionnaire booklet at baseline only.

Figure 8: Overview of main measures

Note. Blue fields indicate patient reported measures, green fields indicate investigator reported measures; BMQ=Beliefs about Medicines Questionnaire, PSM=Perceived Sensitivity to Medicines Scale, EQ-5D=EuroQol generic health index, Medication=bone loss medications; Comorbidity=number of comorbid conditions, Concomitant=number of concomitant medications, Side effects=self-reported side effects, MARS=Medication Adherence Reporting Scale

Patients’ beliefs about the necessity for taking their bone loss medication and concerns about potential adverse consequences of taking it (Horne, 2003) were assessed with the BMQ-Specific (see 1.3.2.1). Medication beliefs were assessed across bone loss medications (and not per medication). Because women were initiating bone loss treatment in the selected subsample, BMQ-Specific measures are only available from the 3-month follow-up onwards. The Necessity-Concerns Differential (BMQ-Specific Necessity minus BMQ-Specific Concerns, see 1.3.1.1) was computed for all follow-up points. Internal consistency of all BMQ-scales was
acceptable at all measurement points, with BMQ-Specific scales showing better internal consistency than BMQ-General scales (see Table 3).

Table 3: Reliability of Patient Reported Outcome (PRO) Questionnaire Scales

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Number of items</th>
<th>Cronbach’s alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ-General Harm</td>
<td>4</td>
<td>.626</td>
</tr>
<tr>
<td>BMQ-General Overuse</td>
<td>4</td>
<td>.650</td>
</tr>
<tr>
<td>BMQ-General Benefit</td>
<td>4</td>
<td>.570</td>
</tr>
<tr>
<td>PSM</td>
<td>5</td>
<td>.841</td>
</tr>
<tr>
<td>BMQ-Specific Necessity</td>
<td>5</td>
<td>.823</td>
</tr>
<tr>
<td>BMQ-Specific Concern</td>
<td>6</td>
<td>.776</td>
</tr>
<tr>
<td>MARS</td>
<td>5</td>
<td>.626</td>
</tr>
<tr>
<td>BMQ-Specific Necessity</td>
<td>5</td>
<td>.828</td>
</tr>
<tr>
<td>BMQ-Specific Concern</td>
<td>6</td>
<td>.773</td>
</tr>
<tr>
<td>MARS</td>
<td>5</td>
<td>.694</td>
</tr>
<tr>
<td>BMQ-Specific Necessity</td>
<td>5</td>
<td>.853</td>
</tr>
<tr>
<td>BMQ-Specific Concern</td>
<td>6</td>
<td>.794</td>
</tr>
<tr>
<td>MARS</td>
<td>5</td>
<td>.711</td>
</tr>
<tr>
<td>BMQ-Specific Necessity</td>
<td>5</td>
<td>.831</td>
</tr>
<tr>
<td>BMQ-Specific Concern</td>
<td>6</td>
<td>.783</td>
</tr>
<tr>
<td>MARS</td>
<td>5</td>
<td>.626</td>
</tr>
</tbody>
</table>

*Note. BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale, MARS=Medication Adherence Report Scale*

2.4.4.2 Perceived Sensitivity to Medicines Scale (PSM)

The Perceived Sensitivity to Medicines Scale (see 1.3.2.2) (Horne et al., 2013b), was administered at baseline only to assess patients’ perceptions of their personal sensitivity to the positive and negative effects of medicines. Internal consistency was good (see Table 3).

2.4.4.3 EuroQol generic health index (EQ-5D)

The EQ-5D (Rabin & Charro, 2001) is a widely used measure of health status (Brooks, Rabin, & De Charro, 2013). The anxiety/depression item of this scale was used as a proxy measure of patients’ level of anxiety/depression. Individuals’ rate their anxiety/depression on three response options (1=I am not anxious or depressed, 2=moderately anxious or depressed and 3=I am extremely anxious or depressed). General health status was assessed with the EQ-5D visual analogue scale (VAS) item. Patients were invited to rate their general health on the 100-point VAS (from 0=worst imaginable health state to 100=best imaginable health state). The EQ-5D was administered at all five study time-points.
2.4.4.4 Comorbid conditions

At baseline clinicians recorded whether patients had experienced any of 28 pre-specified comorbid conditions (e.g. angina, asthma, hypertension, ulcers, seizure disorders) during adulthood and whether the condition was ongoing (see Appendix A). The total number of comorbid conditions and ongoing comorbid conditions at baseline was computed.

2.4.4.5 Concomitant medications

At baseline clinicians recorded the number of concomitant medications patients were taking, including non-eligible osteoporosis medications (vitamin D, calcium and hormone replacement therapy).

2.4.4.6 Osteoporosis diagnosis

Osteoporosis diagnosis at baseline was established using dual X-ray absorptiometry (DXA), normal X-rays, ultrasound or clinical history (see Roux et al., 2011). For patients with DXA results, WHO classification guidelines (WHO 2008) for defining osteopenia (bone density score ≤ -1 ≥ -2.5) and osteoporosis (bone density score ≤ -2.5) were applied. Clinicians also recorded the date of the first bone loss diagnosis, from which the duration since first diagnosis was derived.

2.4.4.7 Number and type of bone loss medications

Participants recorded side effects for up to two eligible bone loss medications at each follow-up. Medications were categorized according to drug type. A dichotomous classification was selected (1=at least one bisphosphonate, 2=other eligible medication or unknown). At each follow-up the majority of patients were taking at least one bisphosphonate (69.9%, 70.4%, 70.9%, 74.4% respectively).

2.4.4.8 Demographics and other variables

Patients’ age, ethnicity, country of residence, employment status, marital status, education level, country of residence, smoking status, body mass index,
number of previous osteoporotic and non-osteoporotic fractures were assessed at baseline.

### 2.4.4.9 Self-reported side effects

Side effects were assessed per bone loss medication at each follow-up time point. Patients indicated whether they had experienced any side effects from each medication (yes/no). Patients who had experienced side effects were then prompted to mark which of 27 pre-specified side effects (e.g. fluid retention, nausea, skin irritation) they had had experienced\(^1\) and to rate the severity (1=mild, 2=moderate, 3=severe) and bothersomeness (5=not bothered at all, 4=slightly bothered, 3= somewhat bothered, 2=very bothered, 1=extremely bothered) of each side effect (see Appendix B). The number of unique side effects across both medications (e.g. headache listed as a side effect for both medications at one time point was not counted twice) was computed per time-point. Severity and bothersomeness were highly correlated (all correlations between .45 and .90, \(ps<.01\)), but many patients only completed the initial severity rating. A total side effect severity score was computed by summing the maximum severity of all unique side effects across both medications (e.g. if headache was rate as moderate for medication 1 and mild for medication 2, the moderate severity rating was selected).

### 2.4.4.10 Adherence

Adherence to bone loss medications was assessed using the Medication Adherence Report Scale (MARS) (Horne & Hankins, 2004) at all follow-up points. Patients' self-reported frequency of five non-adherent behaviours (i.e. "I forget to take them."); "I alter the dose."); "I stop taking them for a while."); "I decide to miss out a dose."); "I take less than instructed.") was rated on a 5 point scale ranging from 5=never to 1=always. If at least three out of five questions had been completed, a mean MARS score was computed. Internal consistency of the MARS was relatively

\[\text{Exploratory factor analysis was performed to identify potential groupings of side effects, but at all time-points side effect loaded heavily on a single factor only (as examined with a scree plot of Eigenvalues).}\]
low (see Table 3), but this is to be expected as the scale aims to assess different facets of adherence related behaviours.

2.4.4.11. Persistence

Persistence was assessed based on a single item in which the patient indicated whether they had stopped taking their osteoporosis medication (yes/no) during the previous three months. Persistence was assessed at all follow-up time points.

2.4.5 Statistical considerations

2.4.5.1 Sample size

This study involves the secondary analysis of existing data (N=1787). A sample size calculation for a hierarchical regression model (Soper, 2015a) with 6 predictors (e.g. demographics and clinical variables) entered in the first step and 4 predictors (baseline medication beliefs) entered in the second step was performed. It showed that 130 participants were needed to achieve 80% power at an alpha level of .05, assuming that baseline beliefs have only a small effect on patient reported side effects (d=.01).

An additional sample size calculation (Soper, 2015b; Westland, 2010) was performed to calculate the minimum required sample size for a structural equation model with 4 latent variables and 8 observed variables. The calculation showed that a sample size of 1465 was needed to achieve 80% power at an alpha level of .05, assuming again a small effect size of d=.01.

2.4.5.2 Statistical modelling

Common descriptive statistics (mean, frequencies, etc.) were used to summarize and examine the distribution of demographic characteristics, predictor, and outcome measures. The number of unique reported side effects (and not the side effect severity score) was chosen as the main side effect measure (predictor and outcome) in order to reduce the number of statistical models presented in this thesis. This was deemed acceptable as the majority of side effects were relatively mild. In addition, exploratory analyses repeating analyses using the side effect severity score resulted in comparable findings. Correlational analyses were used to
explore associations between medication belief scales, side effects and adherence measures across the different time points.

Multivariate regression models were constructed to examine the strength of the associations when controlling for potential confounders. Linear regression was chosen to model continuous outcomes, logistic regression was used to model persistence (dichotomous outcome).

Structural equation modelling was used to examine associations between repeated measures over time. Three different linear growth curve models were constructed to examine the relationships: 1) between patients’ concerns about their bone loss treatment (BMQ-Specific Concerns) and the number of reported side effects 2) between BMQ-Specific Concerns and self-reported adherence (MARS) 3) between the number of reported side effects and MARS. BMQ-Specific Concerns (and not BMQ-Specific Necessity or the NCD) were selected for these and the subsequent analyses as Concerns had the strongest relationship with side effects (see also literature review in section 1.3.3).

In addition, a cross-lagged autoregressive path model (Kenny, 2005) (extending the 2 wave panel design (see Figure 3) used by Nestoriuc and colleagues (2010) to a four wave design), was used to examine time-lagged associations between BMQ-Specific Concerns and the number of patient reported side effects. Finally, an autoregressive mediation model with longitudinal and contemporaneous mediation (MacKinnon, 2008), was used to examine whether the effect of patients’ concerns on self-reported adherence was mediated by side effects.

Please note that exact model specifications for all SEM based models are described in the results section. Model fit of all SEM based models was examined using the Comparative Fit Index (CFI) and the Tucker Lewis Index (TLI) and by examining the size of the residuals (coefficient of determination).

2.4.5.3 Missing data

2.4.5.3.1 Exploration of missing data

Missing data is a ubiquitous problem in studies with patient reported outcome measures, and especially prevalent in longitudinal studies (Biering, Hjollund, & Frydenberg, 2015). Missing data can introduce bias and poses serious
challenges for the reliability, validity and efficiency of estimates (Little & Rubin, 2014). It was therefore crucial to examine the frequency of missing values, explore the underlying missing data mechanism and implement adequate solutions to handle the missing data (see 2.4.5.3.2). The amount of missing data in the main measures was high and increased across follow-up points (see Table 4). Data on several clinical and demographic variables (i.e. diagnosis, age, country of residence, concomitant medications at baseline) was available for all patients, data for several other variables (e.g. co-morbid conditions, BMI, osteoporosis duration) was missing for less than 5-7% of the sample.

The missing data mechanism was examined using correlational analyses (using the SPSS version 19 ‘Analyze Pattern’ and the STATA 13 ‘Misstable Patterns’ command) to see whether missingness could be predicted by any of the existing variables in the dataset. The data was not completely missing at random (MCAR), meaning list-wise deletion may lead to biased parameter estimates. As per guidance (Little & Rubin, 2014) we made the assumption that it was missing at random (MAR), i.e. we assumed that the probability that an observation was missing was unrelated to the observed value itself, after controlling for other variables in the analysis.

Table 4: Overview of missing values in main measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n available (%) missing</td>
<td>Baseline</td>
<td>3 months</td>
<td>6 months</td>
<td>9 months</td>
</tr>
<tr>
<td>BMQ-General</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harm</td>
<td>1567 (12.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overuse</td>
<td>1587 (12.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefit</td>
<td>1580 (11.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSM</td>
<td>1568 (12.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ-Specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necessity</td>
<td>1136 (36.4)</td>
<td>1082 (39.5)</td>
<td>1042 (41.7)</td>
<td>1005 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Concern</td>
<td>1140 (36.2)</td>
<td>1093 (38.8)</td>
<td>1036 (42.0)</td>
<td>1003 (43.9)</td>
<td></td>
</tr>
<tr>
<td>EQ-5D</td>
<td>1590 (11.0)</td>
<td>1137 (25.2)</td>
<td>1281 (28.3)</td>
<td>1211 (32.2)</td>
<td>1135 (36.5)</td>
</tr>
<tr>
<td>N Side effects</td>
<td>1288 (27.9)</td>
<td>1238 (30.7)</td>
<td>1156 (35.3)</td>
<td>1095 (38.7)</td>
<td></td>
</tr>
<tr>
<td>MARS</td>
<td>1096 (38.7)</td>
<td>1055 (41.0)</td>
<td>1000 (44.0)</td>
<td>946 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Persistence</td>
<td>946 (47.1)</td>
<td>888 (50.3)</td>
<td>847 (52.6)</td>
<td>841 (54.0)</td>
<td></td>
</tr>
</tbody>
</table>

Note. BMQ=Beliefs about Medicines Questionnaire, PSM=Perceived Sensitivity to Medicines Scale, EQ-5D= EuroQol generic health index Anxiety/Depression Item, MARS=Medication Adherence Report Scale
2.4.5.3.2 Dealing with missing data

Two different strategies - Multiple imputation (MI) and Full Information Maximum Likelihood (FIML) - were used to deal with missing values: MI, which is generally considered one of the best possible statistical methods to handle missing data (under the assumption that data is MAR) (Donders, van der Heijden, Stijnen, & Moons, 2006), was used for correlational and regression-based analyses. Missing data was imputed with SPSS version 19, using fully conditional specification (also called multiple imputation by chained equations), whereby each incomplete variable is imputed one at time, using the filled-in variable from one step as a predictor in all subsequent steps. Linear regression is used for continuous variables, logistic regression for categorical variables. In order to reduce bias in the analysis models, not only predictor and outcome measures, but a range of auxiliary variables (e.g. BMI, education level, smoking status) were included in the imputation model (White, Royston, & Wood, 2011). Five MI datasets were created. Results from regression based analyses are reported pooled across MI data sets. For SEM based models, the Full Information Maximum Likelihood (FIML) estimation method in STATA 13 was used. FIML uses information from all individual cases, including those that contain missing data, for the computation of maximum likelihood estimates (Acock, 2013). SEM using FIML produces unbiased and efficient parameter estimates (Enders & Bandalos, 2001; Schminkey, von Oertzen, & Bullock, 2016) under the condition that the data is at least MAR.

2.5. Results

2.5.1. Descriptive Statistics

2.5.1.1 Socio-demographic characteristics

Study participants were predominantly White Caucasian (n=1747, 97.8%), economically inactive (retired or homemakers), married (or living as married), with an average age of 67 years (see Table 5).

2.5.1.2 Clinical characteristics

The majority of patients for whom a bone loss diagnosis was established through DXA analysis were classified as osteoporotic. For almost half of the sample (n=862; 48.2%) diagnosis was established through normal X-rays, ultrasound or clinical history only (see Table 5). As to be expected from a cohort of patients initiating bone loss treatment, diagnosis was fairly recent (<2 years). Around a fourth of patients had experienced an osteoporotic fracture prior to enrolment in the
study. The vast majority of participants reported at least one continuing comorbid condition at baseline (n=1636; 91%) and took at least one concomitant medication (n=1601; 89.6%).

Table 5: Overview socio-demographic and clinical sample characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years^1</td>
<td>67.39 (10.12)</td>
<td>DXA-Diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteopenia</td>
<td>312 (17.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteoporosis</td>
<td>613 (34.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown</td>
<td>862 (48.2)</td>
</tr>
<tr>
<td>Country of residence</td>
<td></td>
<td>Osteoporosis duration in years^1</td>
<td>1.87 (3.47)</td>
</tr>
<tr>
<td>France</td>
<td>526 (29.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>404 (22.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>322 (18.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>282 (15.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>253 (14.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td>General Health Status at BL (EQ5D VAS)^1</td>
<td>63.66 (19.61)</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>1747 (97.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>32 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment Status</td>
<td></td>
<td>N osteoporotic fractures pre enrollment</td>
<td></td>
</tr>
<tr>
<td>Working full time</td>
<td>112 (6.3)</td>
<td>0</td>
<td>1360 (76.1)</td>
</tr>
<tr>
<td>Working part time</td>
<td>72 (4.0)</td>
<td>1</td>
<td>331 (18.5)</td>
</tr>
<tr>
<td>Economically inactive</td>
<td>1378 (77.1)</td>
<td>2</td>
<td>67 (3.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (0.3)</td>
<td>3</td>
<td>24 (1.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>219 (12.3)</td>
<td>4 and more</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Level of Education</td>
<td></td>
<td>N concomitant medications at BL</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>76 (4.3)</td>
<td>0</td>
<td>186 (10.4)</td>
</tr>
<tr>
<td>Primary School</td>
<td>607 (34.0)</td>
<td>1</td>
<td>248 (13.9)</td>
</tr>
<tr>
<td>Middle School</td>
<td>227 (12.7)</td>
<td>2</td>
<td>272 (15.2)</td>
</tr>
<tr>
<td>Secondary School</td>
<td>246 (13.8)</td>
<td>3</td>
<td>263 (14.7)</td>
</tr>
<tr>
<td>High School</td>
<td>184 (10.3)</td>
<td>4</td>
<td>218 (12.2)</td>
</tr>
<tr>
<td>Trade School</td>
<td>101 (5.7)</td>
<td>5 and more</td>
<td>598 (33.4)</td>
</tr>
<tr>
<td>University graduate</td>
<td>98 (5.5)</td>
<td>Missing</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>24 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>224 (12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marriage status</td>
<td></td>
<td>Continuing comorbid conditions at BL</td>
<td></td>
</tr>
<tr>
<td>Married (living as)</td>
<td>962 (53.8)</td>
<td>0</td>
<td>151 (8.4)</td>
</tr>
<tr>
<td>Single never married</td>
<td>87 (4.9)</td>
<td>1</td>
<td>366 (20.5)</td>
</tr>
<tr>
<td>Separated</td>
<td>26 (1.5)</td>
<td>2</td>
<td>343 (19.2)</td>
</tr>
<tr>
<td>Divorced</td>
<td>109 (6.1)</td>
<td>3</td>
<td>337 (18.9)</td>
</tr>
<tr>
<td>Widowed</td>
<td>412 (23.1)</td>
<td>4</td>
<td>214 (12.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>191 (10.7)</td>
<td>5 and more</td>
<td>267 (14.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missing</td>
<td>109 (6.1)</td>
</tr>
</tbody>
</table>

Note: PRO=Patient Reported Outcomes, EQ-5D VAS= EuroQol generic health index-Visual Analogue Scale; BL=baseline; ^1 mean (SD) reported

2.5.1.3 Medication beliefs

On average patients believed pharmaceutical medicines to be generally beneficial (i.e. scored on average well above the 2.5 scale mid-point on the BMQ-
General Benefit scale), but did express concerns that pharmaceuticals were overused and overprescribed by doctors (BMQ-General Overuse, see Table 6 for means). Beliefs that pharmaceuticals are generally harmful (BMQ-General Harm) and perceived sensitivity to medicines (PSM) were rated around the scale midpoint. Women’s perceived necessity for bone loss treatment (BMQ-Specific Necessity) was rated greater than their concerns about potential adverse effects (BMQ-Specific Concern) at all follow-up points as indicated by a positive necessity-concerns differential (NCD, see Table 6).

Table 6: Overview medication belief measures

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ-General Harm</td>
<td>2.67 (0.68)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMQ-General Overuse</td>
<td>3.08 (0.71)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMQ-General Benefit</td>
<td>3.97 (0.52)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PSM</td>
<td>2.64 (0.85)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMQ-Specific Concerns</td>
<td>-</td>
<td>2.56 (0.78)</td>
<td>2.59 (0.76)</td>
<td>2.55 (0.76)</td>
<td>2.56 (0.76)</td>
</tr>
<tr>
<td>BMQ-Specific Necessity</td>
<td>-</td>
<td>3.04 (0.82)</td>
<td>3.08 (0.80)</td>
<td>3.07 (0.82)</td>
<td>3.07 (0.79)</td>
</tr>
<tr>
<td>NCD</td>
<td>-</td>
<td>0.50 (1.01)</td>
<td>0.50 (1.00)</td>
<td>0.52 (1.02)</td>
<td>0.51 (0.99)</td>
</tr>
</tbody>
</table>

Note. BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale; based on complete case analysis; NCD=Necessity Concerns Differential

Patients’ schematic beliefs about pharmaceuticals (as measured with the BMQ-General and PSM, see also section 1.3.2) were associated with their specific evaluations of bone loss treatment (see Figure 9): Women who started out with more negative pharmaceutical schemas at baseline (i.e. perceptions that pharmaceuticals are generally harmful and overused and less beneficial, high perceived personal sensitivity to pharmaceuticals) had stronger concerns about their prescribed bone loss treatment at the first follow-up. Women who perceived pharmaceuticals as more beneficial in general expressed greater perceived personal necessity for bone loss treatment.
Figure 9: Pearson correlations between baseline pharmaceutical schemas and specific beliefs about bone loss treatment at 3 months

<table>
<thead>
<tr>
<th>Concerns about bone loss treatment</th>
<th>BMQ:Specific Concern</th>
<th>BMQ:General Harm</th>
<th>BMQ:General Benefit</th>
<th>BMQ:General Overuse</th>
<th>PSM</th>
<th>Perceptions of personal necessity for bone loss treatment</th>
<th>BMQ:Specific Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-2.62**</td>
<td>-0.057*</td>
<td>0.212**</td>
<td>0.313**</td>
<td>.023</td>
<td>.127**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.031</td>
<td>.034</td>
</tr>
</tbody>
</table>

Note. *p<.05; **p<.01; BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale

2.5.1.4 Side effect reporting

At each follow-up point patients reported on average between 1 and 2 side effects (see Table 7). The majority of side effects were rated as mild or moderate in severity, with only between 7.5% (at 12 months) and 9% (at 3 months) of participants reporting a severe side effect at any follow-up point. Fatigue was the most commonly reported side effect across the whole study period, followed by leg cramps and bloating (reported by >10% of study participants; see
Figure 10). Several women reported experiencing menstrual bleeding as a side effect to their bone loss medications. Hot flushes were reported as side effects by around 8% of study participants. Several other side effects (e.g. headaches, dizziness, skin irritation), that are common across a large number of medications (see also 1.5.2 and 4.2) were also prevalent at all follow-up points.

Table 7: Number of unique side effects/side effect severity index

<table>
<thead>
<tr>
<th></th>
<th>Mean/Median (SD/IQR)</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of side effects</td>
<td>1.62 (3.39)</td>
<td>1.70 (3.62)</td>
<td>1.71 (3.64)</td>
<td>1.63 (3.69)</td>
<td></td>
</tr>
<tr>
<td>Median number of side effects</td>
<td>0 (2)</td>
<td>0 (2)</td>
<td>0 (2)</td>
<td>0 (1)</td>
<td></td>
</tr>
<tr>
<td>Mean Severity Index</td>
<td>3.07 (6.60)</td>
<td>3.04 (6.72)</td>
<td>2.89 (6.64)</td>
<td>2.65 (2.65)</td>
<td></td>
</tr>
</tbody>
</table>

Note. IQR=Inter Quartile Range
Figure 10: Frequencies specific side effects

Note. M3-12=3-12 months follow up; n at M3=1228; n at M6=1238; n at M9=1156; n at M12=1095
2.5.1.5 Medication taking behaviour

Self-reported adherence, which was assessed with the MARS was relatively high (see Table 8), as indicated by MARS scores of 4.5 and above (Cohen et al., 2009). Around a fifth of participants failed to persist with their bone loss treatment at all follow-up points (see Table 8).

Table 8: Self-reported adherence and persistence

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MARS; Mean (SD)</td>
<td>4.85 (0.31)</td>
<td>4.84 (0.34)</td>
<td>4.82 (0.37)</td>
<td>4.82 (0.33)</td>
</tr>
<tr>
<td>Persisted with medication; n</td>
<td>738 (78.0)</td>
<td>706 (79.5)</td>
<td>671 (79.2)</td>
<td>640 (78.6)</td>
</tr>
<tr>
<td>(%)</td>
<td>208 (22.0)</td>
<td>182 (20.5)</td>
<td>176 (20.8)</td>
<td>174 (21.4)</td>
</tr>
</tbody>
</table>

Note. Percentages computed on non-missing values; missing values 1=899; 2=899; 3=940; 4=814

2.5.1.6 Anxiety/depression rating

At all study time points over 2/5th of women reported being at least moderately anxious/depressed (see Table 9). There were small, but statistically significant correlations between patients’ anxiety/depression ratings and medication beliefs. Women with higher baseline anxiety/depression ratings at baseline had higher perceived sensitivity to medicines ($r=.174$), believed pharmaceuticals as more harmful in general ($r=.174$, $p<.01$) and overused ($r=.065$, $p<.05$).

Anxiety/depression ratings at each time point also correlated significantly with patients concerns about their bone loss treatment at the respective time point, with correlations ranging between $r=.168$ and $r=.207$ (all $p<.01$).

Table 9: Self-reported anxiety depression (EQ-5D A/D)

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Baseline$^*$</th>
<th>3 months$^*$</th>
<th>6 months$^*$</th>
<th>9 months$^*$</th>
<th>12 months$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not anxious or depressed</td>
<td>718 (45.2)</td>
<td>679 (50.8)</td>
<td>659 (51.4)</td>
<td>640 (52.8)</td>
<td>582 (51.3)</td>
</tr>
<tr>
<td>Moderately anxious or depressed</td>
<td>737 (46.4)</td>
<td>580 (43.4)</td>
<td>545 (42.5)</td>
<td>506 (41.8)</td>
<td>486 (42.8)</td>
</tr>
<tr>
<td>Extremely anxious or depressed</td>
<td>135 (8.5)</td>
<td>78 (5.8)</td>
<td>77 (6.0)</td>
<td>65 (5.4)</td>
<td>67 (5.9)</td>
</tr>
</tbody>
</table>

Note. Percentages computed on non-missing values; missing values $^1=197; ^2=450; ^3=506; ^4=576; ^5=652$

2.5.2 Assessment of the stability of repeated measures

Specific medications beliefs (BMQ-Specific Necessity and Concerns), depression/anxiety ratings (EQ-5D), self-reported adherence (MARS) and the
number of reported side effects at each time point correlated strongly with respective scores from the subsequent time point (see Table 10).

Table 10: Time lagged correlations repeated measures

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>r(3, 6 months)</th>
<th>r(6, 9 months)</th>
<th>r(9,12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ-Specific Necessity</td>
<td>.673**</td>
<td>.704**</td>
<td>.750**</td>
</tr>
<tr>
<td>BMQ-Specific Concerns</td>
<td>.663**</td>
<td>.682**</td>
<td>.719**</td>
</tr>
<tr>
<td>EQ-5D A/D</td>
<td>.682**</td>
<td>.687**</td>
<td>.711***</td>
</tr>
<tr>
<td>MARS</td>
<td>.610**</td>
<td>.666**</td>
<td>.809**</td>
</tr>
<tr>
<td>N side effects</td>
<td>.587**</td>
<td>.702**</td>
<td>.662**</td>
</tr>
</tbody>
</table>

Note. **p<.01; BMQ=Beliefs about Medicines Questionnaire; MARS= Medication Adherence Report Scale; EQ-5D= EuroQol generic health index; A/D=anxious/depressed

2.5.3 Hypothesis testing

2.5.3.1 Medication beliefs predict side effects

2.5.3.1.1 Exploratory analyses

Correlational analyses were used to explore associations between baseline pharmaceutical schemas as well as baseline anxiety/depression ratings and the number of reported side effects at all follow-up points. Several medication beliefs scales correlated significantly with side effect reporting during the follow up period, although the size of the correlations was relatively small (see Table 11).

Table 11: Correlations between medication beliefs and anxiety/depression ratings and number of reported side effects

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>Number of side effects reported at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>BMQ-General Harm</td>
<td>.136**</td>
<td>.138**</td>
</tr>
<tr>
<td>BMQ-General Benefit</td>
<td>-.061**</td>
<td>-.075**</td>
</tr>
<tr>
<td>BMQ-General Overuse</td>
<td>.091**</td>
<td>.097**</td>
</tr>
<tr>
<td>PSM</td>
<td>.194**</td>
<td>.177**</td>
</tr>
<tr>
<td>BMQ-Specific Concerns²</td>
<td>.350**</td>
<td>.267**</td>
</tr>
<tr>
<td>BMQ-Specific Necessity²</td>
<td>.048</td>
<td>.030</td>
</tr>
<tr>
<td>NCD²</td>
<td>-.232**</td>
<td>-.182**</td>
</tr>
<tr>
<td>EQ-5D A/D¹</td>
<td>.140*</td>
<td>.137**</td>
</tr>
</tbody>
</table>

Note. **p<.01; *p<.05; BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale; NCD=Necessity-Concerns Differential; EQ-5D= EuroQol generic health index; A/D=anxious/depressed;² Spearman’s rho correlation, all other correlations Pearson correlations;¹ first available measure at 3 months, all other measures taken at baseline

Higher perceived personal sensitivity to medicines (PSM) and beliefs that pharmaceuticals are generally harmful (BMQ-General Harm) and overprescribed by
doctors (BMQ-General Overuse) and higher self-reported anxiety/depression ratings were associated with a significantly greater number of self-reported side effects at all follow-up points (see Table 11). Women who started out with more positive beliefs about the benefits of pharmaceuticals (BMQ-General Benefit) reported fewer side effects at the first two follow-up points (see Table 11).

Correlational analyses also showed that women’s concerns about their bone loss medications (BMQ-Specific Concerns), and the trade-off between perceived necessity and concerns (NCD) at the first available measurement point (3 months follow-up) were significantly associated with the number of reported side effects at all follow-up points. Beliefs about the necessity of bone loss treatment showed no association with the number of reported side effects (see Table 11).

2.5.3.1.2 Baseline pharmaceutical schemas predict side effect reporting

Hierarchical linear regression models were constructed to test whether baseline pharmaceutical schemas (BMQ-General scales, PSM) and anxiety/depression ratings (EQ-5D A/D) prospectively predicted the number of reported side effects at the different follow-up points, when controlling for sociodemographic and disease factors (see Table 12). Socio-demographic factors (age, country) and disease factors (osteoporosis diagnosis, duration of osteoporosis, number of osteoporotic fractures, number of comorbid conditions, number of concomitant medications, number and type of bone loss medications) were entered into the model in the first step. Baseline measures of pharmaceutical schemas and anxiety/depression ratings were entered jointly in the second step.

Socio-demographic and disease factors explained between 5% and 9% of variance in side effect reporting across the follow-up period (all ps<.001). In general, women who were younger, who were taking more concomitant and bone loss medications and who were classified as osteoporotic tended to report more side effects (see Step 1 Table 12). Adding psychological factors to the models significantly improved prediction at all time points (all ps<.001), explaining between 3% and 4% of additional variance in side effect reporting (see Step 2, Table 12). Women who perceived themselves as more sensitive to the effects of medicines (PSM) at baseline reported more side effects at all follow-up points. Higher perceived harmfulness of medicines was associated with increased side effect reporting at both the 6 and 9 month follow-up. Women who perceived pharmaceuticals as more beneficial in general and who indicated being less
anxious/depressed reported fewer side effects at the first two follow-ups (see Table 12).

Table 12: Baseline medication belief predict side effect reporting across follow-up

<table>
<thead>
<tr>
<th></th>
<th>N side effects 3 months</th>
<th>N side effects 6 months</th>
<th>N side effects 9 months</th>
<th>N side effects 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (SE)</td>
<td>B (SE)</td>
<td>B (SE)</td>
<td>B (SE)</td>
</tr>
<tr>
<td>Step 1 Control variables</td>
<td>$R^2 = .069^{***}$</td>
<td>$R^2 = .072^{***}$</td>
<td>$R^2 = .087^{***}$</td>
<td>$R^2 = .047^{***}$</td>
</tr>
<tr>
<td>Age</td>
<td>-.03 (.01)$^*$</td>
<td>-.03 (.01)$^{**}$</td>
<td>-.03 (.01)$^*$</td>
<td>-.03 (.01)$^{**}$</td>
</tr>
<tr>
<td>Country</td>
<td>-.23 (.08)$^{**}$</td>
<td>-.34 (.07)$^{**}$</td>
<td>-.25 (.08)$^{**}$</td>
<td>-.23 (.08)$^{**}$</td>
</tr>
<tr>
<td>Osteoporosis diagnosis</td>
<td>.51 (.25)$^T$</td>
<td>.54 (.24)$^T$</td>
<td>.51 (.24)$^T$</td>
<td>.77 (.25)$^T$</td>
</tr>
<tr>
<td>Duration of osteoporosis</td>
<td>-.07 (.03)$^{**}$</td>
<td>-.03 (.03)</td>
<td>-.03 (.03)</td>
<td>-.04 (.03)</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td>.15 (.05)$^{**}$</td>
<td>.02 (.05)</td>
<td>.01 (.06)</td>
<td>.00 (.06)</td>
</tr>
<tr>
<td>Osteoporotic fractures</td>
<td>.17 (.14)</td>
<td>.26 (.15)$^T$</td>
<td>.41 (.15)$^T$</td>
<td>.29 (.13)</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>.06 (.05)</td>
<td>.16 (.05)$^T$</td>
<td>.10 (.05)$^*$</td>
<td>.08 (.05)$^T$</td>
</tr>
<tr>
<td>N bone loss medications</td>
<td>2.2 (.30)$^{***}$</td>
<td>2.3 (.30)$^{***}$</td>
<td>2.7 (.30)$^{***}$</td>
<td>1.6 (.29)$^{***}$</td>
</tr>
<tr>
<td>Medication type</td>
<td>-.34 (.25)</td>
<td>-.20 (.20)</td>
<td>-.28 (.21)</td>
<td>.12 (.24)</td>
</tr>
<tr>
<td>Step 2 Baseline measures</td>
<td>$R^2 = .045^{***}$</td>
<td>$R^2 = .043^{***}$</td>
<td>$R^2 = .031^{***}$</td>
<td>$R^2 = .028^{***}$</td>
</tr>
<tr>
<td>PSM</td>
<td>.61 (.12)$^{***}$</td>
<td>.48 (.15)$^{***}$</td>
<td>.58 (.12)$^{***}$</td>
<td>.58 (.11)$^{***}$</td>
</tr>
<tr>
<td>BMQ-General Benefit</td>
<td>-.38 (.22)$^*$</td>
<td>-.51 (.23)$^*$</td>
<td>-.30 (.19)</td>
<td>-.26 (.19)</td>
</tr>
<tr>
<td>BMQ-General Overuse</td>
<td>-.06 (.16)</td>
<td>-.01 (.17)</td>
<td>-.21 (.16)</td>
<td>-.26 (.17)</td>
</tr>
<tr>
<td>BMQ-General Harm</td>
<td>.33 (.19)$^T$</td>
<td>.48 (.19)</td>
<td>.38 (.19)</td>
<td>.28 (.17)</td>
</tr>
<tr>
<td>EQSD Depression/Anxiety</td>
<td>.56 (.15)$^{***}$</td>
<td>.58 (.15)$^{***}$</td>
<td>.27 (.15)$^T$</td>
<td>.27 (.15)$^T$</td>
</tr>
<tr>
<td>Total $R^2$</td>
<td>$R^2 = .114^{***}$</td>
<td>$R^2 = .115^{***}$</td>
<td>$R^2 = .118^{***}$</td>
<td>$R^2 = .075^{***}$</td>
</tr>
</tbody>
</table>

Note. *p<.05; **p<.01; ***p<.001, $^T$p<.10; PSM=Perceived Sensitivity to Medicines Scale; BMQ=Beliefs about Medicines Questionnaire; NCD=Necessity Concerns Differential; EQ-5D= EuroQol generic health index Depression/Anxiety rating

2.5.3.1.3 The relationship between specific medication concerns and side effect reporting

A latent growth curve model was constructed to examine the relationship between patients’ specific concerns about their bone loss treatment and the number of reported side effects over time. Please note that the first available measure of either construct is at the 3 month follow-up point.

Model Specification

In latent growth curve models the observed repeated measures (here BMQ-Specific Concerns and reported side effects) are incorporated as latent factors (Intercept, Slope; see ellipses in Figure 11) to characterize the unobserved growth trajectories. Each observed variable (see rectangles in Figure 11) constitutes a scale score (here X for BMQ-Specific Concerns, Y for number of side effects) at one of the 4 time-points. The values of 0,1,2,3 assigned to the slope parameters...
represent the 3 month, 6 month, 9 month and 12 month time-point respectively. This is needed for model identification and allows this factor to be interpreted as a slope. All paths from the Intercept factor are constrained to 1, indicating that the Intercept values remain constant across time for each individual. Please note that equivalent model specification was used for the other two growth curve models.

Figure 11: Latent Growth Curve Model Specifications

Note. $X_{it} = \text{first repeated measures variable; } Y_{it} = \text{second repeated measures variable; } t_i = \text{measurement point with } 1=3 \text{ month follow-up; } 2=6 \text{ month follow-up, } 3=9 \text{ month follow-up, } 4=12 \text{ month follow-up; } \epsilon_i = \text{error terms; numbers in blue represent constraints}$

**Results latent growth curve model 1**

The mean intercept for Specific Concerns was estimated at 3.92 (95% CI [3.71; 4.13]), the mean intercept for side effects at 0.64 (95% CI[0.57,0.71]), see Figure 12. On average, Concerns did not increase significantly over time as indicated by a non-significant slope parameter (slope Concerns=.07; 95% CI[-.07; .18], $p=.37$). The number of reported side effect also did not change significantly (slope Side Effects=-0.06; 95% CI[-0.18;0.06], $p=.30$).

Patients who started out with higher concerns about their bone loss medications at 3 months, showed a marginally lower increase in concerns than participants who started out with lower concerns as indicated by significant negative covariance (cov) between the Intercept and Slope for Concerns (cov Intercept Concerns, Slope Concerns=-.14; 95% CI [-0.28; .00], $p=.05$; see Figure 12). The number of reported side effects at 3 months was not associated with growth in side
effects over time (cov Intercept Side effects, Slope Side effects=-0.10; 95%CI [-0.24; 0.05]), p=.19).

There was a significant association between a growth in Concerns and side effects, as indicated by significant covariance between the slopes of Concerns and side effects (cov Slope Concerns, Slope Side Effects=0.70, 95% CI[0.42; 0.97], p<.001). Patients who had more Concerns on average, reported having significantly more side effects on average (cov Intercept Concerns, Intercept Side effects=.43; 95% CI[0.37; 0.49], p<.001).

Figure 12: Standardized parameter estimates growth curve model 1

Note. Concerns=Beliefs about Medicines Questionnaire Specific-Concerns scale, M3/6/9/12= 3/6/9/12 month follow-up; please note error terms not displayed to simplify presentation

Model fit

Model fit was good (Hu & Bentler, 1999), with an estimated CFI of 0.96 and a TLI of 0.97. The coefficient of determination was estimated at 0.99.

2.5.2.1.4 Inter-relations between concerns and side effects

Cross-lagged path model specification

A cross-lagged autoregressive path model was constructed to examine the time-lagged (3 months lag) relationships between patients' concerns about their bone loss medication (see X in Figure 13) and the number of reported side effects
(see $Y_i$ in Figure 13) across the different follow-up points, allowing the error terms ($\epsilon_i$) of the endogenous variables to be correlated at each follow-up point. Standard errors were determined based on the observed information matrix (OIM).

Figure 13: Specification of cross-lagged autoregressive path model

Note. $X_{ti}$=repeated measures independent variable, $Y_{ti}$ =repeated measures dependent variable; $t_i$=measurement point with 1=3 month follow-up, 2=6 month follow-up, 3=9 month follow-up, 4=12 month follow-up; $\epsilon_i$=error terms

**Cross-lagged path model – direct effects**

Standardized coefficients for the direct effects in the model are depicted in Figure 14. Replicating findings from the simple time-lagged correlational analyses (see Table 10), Specific Concerns at each time point were highly correlated with Specific Concerns at the subsequent follow-up point (all $p$s<.001). The same was true for the number of reported side effects, with coefficients ranging between .59 and .66 (all $p$s<.001).

There was support for a bi-directional relationship between medication beliefs and side effects: Patients’ concerns about their bone loss medication at the 3 month follow-up predicted the number of reported side effects at 6 months ($B=.06; 95\%CI [.01, .11]; p<.05$), Specific Concerns at 6 months predicted the number of side effects at 9 months ($B=.05; 95\%CI [.01, .09], p<.05$). Specific Concerns at 9 month were marginally significant predictors of the number of side effects at the 12 month study end-point ($B=.04; 95\%CI [-.00,.10], p=.06$). There was also a significant time-lagged association between side effect reporting and patients’ concerns about their bone loss medication at all measurement points (see Figure 14, all $p$s<.05).
In addition to the direct effects, I also tested for indirect effects (through mediating variables) in the model (see Table 13). There was a significant indirect effect of Concerns at 3 months on side effects at both the 9 month and 12 month follow-up (see Table 13). In addition, there was an indirect effect of Concerns at 6 months on the number of reported side effects at 12 month follow-up. All other paths examining the association between patients’ concerns and the number of side effects are direct (see Figure 14).

Table 13: Indirect effect of BMQ-Specific Concerns on the number of reported side effects

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (SE)</th>
<th>Standardized Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side effects at 9 months ←</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerns at 3 months</td>
<td>.368 (.121)</td>
<td>.080</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Side effects at 12 months ←</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerns at 6 months</td>
<td>.309 (.075)</td>
<td>.064</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Concerns at 3 months</td>
<td>.336 (.091)</td>
<td>.071</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note. Concerns=BMQ-Specific Medication Concerns

Cross-lagged path model - indirect effects

The Comparative Fit Index (CFI), which compares the fit of the target model to the fit of an independent model (i.e. a model in which the variables are assumed to be uncorrelated) was above .90 (CFI=.92), indicating that the model fit was
acceptable (Hu & Bentler, 1999). The Tucker Lewis Index was estimated at .83. This is acceptable given that the model was theoretically derived and not optimized using modification indices to improve model fit (e.g. by adding previously omitted paths). The model explained 64% of variance overall and equation level of fit was good for all observed measures, with R² estimates ranging between .38 and .56 (see Figure 14).

2.5.3.2 Medication beliefs predict medication taking behaviour

2.5.3.2.1 Exploratory analyses

At all measurement points adherence was significantly lower for participants who perceived medicines as more harmful and who indicated being more sensitive to their effects (see Table 14). Self-reported adherence across the whole study was also reduced for women who reported more concerns about their bone loss medication. Adherence was higher for women who reported a more positive necessity-concerns trade off (NCD).

Table 14: Correlations between medication beliefs and self-reported adherence

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ-General Harm</td>
<td>-.139**</td>
<td>-.198**</td>
<td>-.162**</td>
<td>-.173**</td>
</tr>
<tr>
<td>BMQ-General Benefit</td>
<td>.034</td>
<td>.011</td>
<td>.028</td>
<td>.019</td>
</tr>
<tr>
<td>BMQ-General Overuse</td>
<td>-.112**</td>
<td>-.125**</td>
<td>-.125**</td>
<td>-.119**</td>
</tr>
<tr>
<td>PSM</td>
<td>-.169**</td>
<td>-.194**</td>
<td>-.154**</td>
<td>-.146**</td>
</tr>
<tr>
<td>EQ-5D A/D¹</td>
<td>-.078**3</td>
<td>-.067**3</td>
<td>-.088**3</td>
<td>-.051</td>
</tr>
<tr>
<td>BMQ-Specific Concerns²</td>
<td>-.241**</td>
<td>-.227**</td>
<td>-.218**</td>
<td>-.207**</td>
</tr>
<tr>
<td>BMQ-Specific Necessity²</td>
<td>.075**3</td>
<td>.072</td>
<td>.045</td>
<td>.078**3</td>
</tr>
<tr>
<td>NCD²</td>
<td>.247**</td>
<td>.240**</td>
<td>.202**</td>
<td>.226*</td>
</tr>
</tbody>
</table>

Note. **p<.01; *p<.05; BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale; NCD=Necessity-Concerns Differential; ¹Spearman's rho correlation, all other Pearson correlations; ²first available measure at 3 months; ³correlation not significant when using complete case analysis

Logistic regression analyses were conducted to examine whether medication beliefs were associated with persistence. The odds of non-persisting with bone loss treatment at each follow-up point were significantly higher for participants who believed pharmaceuticals to be more harmful in general, with pooled odds ratios (ORs) ranging between 1.34 for persistence at 12 months and 1.60 for persistence at 3 months (all ps<.05). Odds of non-persistence were also significantly higher for patients who perceived themselves as more sensitive to medicines, with pooled ORs ranging between 1.33 for persistence at 12 months and 1.76 for persistence at 3 months (all ps<.05). In a similar vein, odds of non-
persistence were also significantly increased for patients who expressed greater concerns about their bone loss medications, with pooled ORs ranging from 1.53 at 12 months to 1.92 at 3 months using 3 month BMQ-Specific Concerns as predictor (all ps<.001).

### 2.5.3.2.2 Relationship between concerns and adherence

A latent growth curve model was constructed to examine the relationship between patients’ concerns about their bone loss medications and self-reported adherence. Model specifications are equivalent to those outlined for the first growth curve model (see Figure 11), whereby X=BMQ-Specific Concerns and Y= MARS scores.

#### Results latent growth curve model 2

Figure 15 summarizes standardized parameter estimated for the second growth curve model. The mean intercept for Concerns was estimated at 3.94 (95% CI [3.73; 4.17]), the mean intercept for self-reported adherence (MARS) at 17.92 (95% CI[16.77,19.08]). On average, concerns did not increase significantly over time as indicated by a non-significant slope parameter (slope=.08; 95% CI[-.04; .20], p=.19), but there was a significant decrease in self-reported adherence (slope=−.32; 95% CI[−.44; -.20], p<.001).

Figure 15: Standardized parameter estimates growth curve model 2

![Diagram of standardized parameter estimates growth curve model 2](image)

**Note.** Concerns=Beliefs about Medicines Questionnaire Specific-Concerns Scale, MARS=Medication Adherence Report Scale; M3/6/9/12= 3/6/9/12 month follow-up

Patients who started out with higher concerns about their bone loss medication at 3 months, showed a lower increase in concerns than participants who
started out with lower concerns as indicated by statistically significant covariance between the Intercept and Slope for Specific Concerns (cov=-.17; 95% CI [-.31; -.04], p<.05; see Figure 15). Patients who reported being more adherent at 3 months showed a higher decrease in self-reported in adherence over time (cov=.43; 95% CI [.20; .65], p<.001). There was no significant association between a growth in BMQ-Specific Concerns and a decline in self-reported adherence, as indicated by non-significant covariance between the slopes of Specific Concerns and self-reported adherence (cov=-.17, 95% CI[-.39; .05], p>.05). But patients who had more Concerns on average, reported being significantly less adherent on average as indicated by a significant negative covariance between the Intercepts for Concerns and MARS (cov=-.32; 95% CI[-.39, -.26], p<.001).

Model Fit
The model fitted the data well, as indicated by a CFI of 0.981 and a TLI of 0.983. The coefficient of determination was estimated at 0.995.

2.5.3.3 Side effects predict medication taking behaviour

2.5.3.3.1 Exploratory data analysis
The number of side effects reported at each follow-up time point significantly increased the odds of patients failing to persist with their bone loss medication (see Table 15). The more side effects participants reported at each follow-up point, the lower their self-reported adherence. Reported parameter estimates are pooled across the MI datasets. Findings from full-case analysis are similar (except for MARS at the 9 month follow-up, see Table 15).

Table 15: Side effects and self-reported persistence and adherence

<table>
<thead>
<tr>
<th></th>
<th>Non-persistence at respective time point</th>
<th>Adherence (MARS) at respective time point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR [95 % CI] p-value</td>
<td>B [95 % CI] p-value</td>
</tr>
<tr>
<td>N side effects at M3</td>
<td>1.19 [1.14,1.26] .001</td>
<td>-.014 [-.019,.009] &lt;.001</td>
</tr>
<tr>
<td>N side effects at M6</td>
<td>1.17 [1.12,1.21] .001</td>
<td>-.018 [-.023,.013] &lt;.001</td>
</tr>
<tr>
<td>N side effects at M9</td>
<td>1.15 [1.09,1.21] .001</td>
<td>-.014 [-.020,.008] &lt;.001</td>
</tr>
<tr>
<td>N side effects at M12</td>
<td>1.16 [1.16,1.23] .001</td>
<td>-.023 [-.029,.017] &lt;.001</td>
</tr>
</tbody>
</table>

Note. Parameter estimates pooled across MI data; ¹ not significant in complete-case analysis, M3/6/9/12= 3/6/9/12 month follow-up point
2.5.3.2 Relationship between side effects and adherence

Another growth curve model was constructed to examine the relationship between the number of self-reported side effects and adherence over time (see Figure 11 for model specifications with X=number of reported side effects, Y=MARS scores).

Results latent growth curve model 3

The mean intercept for side effects was estimated at 0.62 (95% CI [0.56; 0.70]), the mean intercept for self-reported adherence (MARS) at 18.00 (95% CI[16.84,19.17]), see Figure 16. Self-reported adherence decreased significantly over time as indicated by a significant negative slope parameter (slope=-.32; 95% CI[-.45; -.20], p<.001), side effects did not change significantly over time (slope=-0.73; 95%CI[-.019;.045], p=.23).

Figure 16: Standardized parameter estimates growth curve model 3

Patients who reported a greater number of side effects at 3 months, showed a lower increase in the number of reported side effects than patients who reported fewer side effects at the first measurement point (cov=-.18; 95% CI [-.32; -.04], p<.05; see Figure 16). Patients who reported being more adherent at 3 months showed a higher decrease in self-reported in adherence over time (cov=.44; 95%CI [.21;.67]), p<.001).

There was no significant association between a growth in the number of reported side effects and a decline in self-reported adherence, as indicated by non-significant covariance between the slopes of side effects and self-reported adherence (cov=-.09, 95% CI[-.30; .12], p=.41). But patients who had more side effects on average, reported being significantly less adherent on average as
indicated by a significant negative covariance between the Intercepts for side effects and MARS (cov=-.15; 95% CI[-.22, -.08], p<.001).

**Model fit**

Model fit was good as indicated by a CFI of .952 and TLI if .955. The coefficient of determination was estimated at .994.

### 2.5.3.4 Side effects mediate the relationship between Specific Concerns and adherence

An autoregressive mediation model was constructed to test whether self-reported side effects mediated the relationship between patients’ concerns about their bone loss treatment and adherence. Longitudinal data with repeated measures of both the predictor (see Figure 17, $X_i=$BMQ-Specific Concerns, whereby $i=1$ indicates 3 months follow-up, $i=2$ indicates 6 months follow-up, etc.), mediator ($M_i$, i.e. number of reported side effects) and outcome ($Y_i=$ MARS scores) provides more information with regards to the temporal ordering of the predictor, mediator and outcome variables and is therefore preferable to single mediator models where all three constructs are measured at the same occasion (MacKinnon, 2008).

Figure 17: Autoregressive mediation model with longitudinal and contemporaneous mediation

Note. Error terms omitted to simplify representation; $X_i=$Predictor, $M_i=$Mediator, $Y_i=$Outcome
Model Specification

Model specifications were based on the autoregressive mediation model with longitudinal and contemporaneous mediation proposed by MacKinnon (2008), which was extended to a four wave design (see Figure 17). The model is constructed as follows: First relations one lag apart are specified (see a and b paths in Figure 17, e.g. a1 = association between Concerns at 3 months and side effects at 6 months). The stability of each individual measure (X, M and Y) is assessed with the relation of the individual measure over time (e.g. see s paths for stability of the BMQ-General Concerns Scale). Covariances among the variables (e.g. between Concerns at 3 months and Side effects at 3 months) in the first wave are included. Coefficients c'1, c'2 and c'3 represent direct longitudinal effects from the predictor X to the outcome Y between adjacent waves. In this model the relations between the X1 and M2 (i.e. coefficient a1), X2 and M3 (i.e. coefficient a2) and X3 and M4 (i.e. coefficient a3) represent the relations between the predictor X and the mediator M. In a similar vein, the lagged associations between M and Y (see coefficients b1, b2 and b3), represent the relation between the mediator and the outcome. In addition, this model allows for contemporaneous mediation at each time point (e.g. X2 -> M2 -> Y2), by including relations between X, M and Y at each time point (see light blue shaded areas in Figure 17).

The contemporaneous mediated effect can be estimated by examining the indirect effect of X2 on Y2 (i.e. product of standardized coefficients a4 and b4) at 6 months, at 9 month by examining the indirect effect of X3 on Y3 (i.e. a5*b5) and at 12 month by examining the indirect effect of X4 on Y5 (i.e. a6*b6). Longitudinal autoregressive mediated effects can for example be estimated by looking at the products of the standardized coefficients a1*b1; a2*b2; a3*b3. The products of a1*b2 and a2*b3 allow to examine longitudinal mediated effects (MacKinnon, 2008). In addition, it is possible examine the total indirect effect of the predictor at the first measurement instance (X1) on the outcome at trial exist (Y4), by summing all indirect effects of X1 on Y4. Statistical significance of the mediated effects was examined using the multivariate delta method (or Sobel Test) (MacKinnon, 2008), whereby tindirect = a*b/SEa*b.

Mediation Results

Figure 18 summarizes standardized model parameter estimates. Stability of all three constructs was relatively high (see green paths in Figure 18, all paths
significant at \(p<.001\), indicating only small changes in individual differences (i.e. only minor changes in rank order of individuals) (Selig & Preacher, 2009).

Figure 18: Standardized parameter estimates autoregressive mediation model

<table>
<thead>
<tr>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerns</td>
<td>Concerns</td>
<td>Concerns</td>
<td>Concerns</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Side Effects</td>
<td>Side Effects</td>
<td>Side Effects</td>
</tr>
<tr>
<td>MARS</td>
<td>MARS</td>
<td>MARS</td>
<td>MARS</td>
</tr>
</tbody>
</table>

Note. Concerns=BMQ Specific Concerns; MARS=Medication Adherence Report Scale

There was a significant longitudinal direct effect of patients’ concerns on adherence at the adjacent time point at both 3 months (\(c_1'=-.063; 95\% \text{ CI}[-.12, -.01], p<.05\)) and 6 months (\(c_2'=-.066; 95\% \text{ CI}[-.12, -.03], p<.05\)), but not at 9 months (\(c_3'=-.019; 95\% \text{ CI}[-.063, .024], p=.395\)). Lagged associations between Concerns and reported side effects were statistically significant at alpha level of .01 at all time points. There was evidence for contemporaneous mediation at all time points, with the indirect effect of Concerns at 6 months on MARS at 6 months \(a_4*b_4=-.014, z=6.90, \ p<.001\), the indirect effect of Concerns at 9 months on MARS at 9 months \(a_5*b_5=-.012, z=-6.57, \ p<.001\) and the indirect effect of Concerns at 12 months on MARS at 12 months \(a_6*b_6=-.004, z=-8.19, \ p<.001\).

The total indirect effect of Concerns at 3 months on adherence at 12 months was significant and in the predicted direction (indirect effect=-.0828; \(z=-3.55, \ p<.001\)). However, individual longitudinal mediation effects were not significant (e.g. \(a_1*b_1=.0033; z=.97, \ p=.332\); \(a_2*b_2=.0086; z=-.188, \ p=.060\); \(a_3*b_3=-.02663; z=-.58 \ p=.565\); \(a_4*b_2:.0089; z=-1.83, \ p=.068\) and \(a_2*b_3:.0015, z=-.057, \ p=.570\)).
Model fit

Model fit was acceptable with a CFI of 0.911 and a TLI of 0.856. The coefficient of determination was estimated at 0.795.

2.6. Discussion

2.6.1 Summary of findings

The study provided strong empirical support for the postulated prospective association between medication beliefs and side effect reporting (Research Question 1) in a large sample of post-menopausal women initiating bone loss treatment. As hypothesized, patients who had more negative pharmaceutical schemas at baseline and stronger concerns about their newly prescribed bone loss medications reported more side effects across the 12 months follow-up period. Findings from the cross-lagged structural equation model suggest that there is in fact a bi-directional relationship between patients’ concerns about their treatment and side effect reporting; Patients who have stronger concerns about their prescribed treatment report more side effects, the experience/reporting of side effects in turn leads to increased concerns. I also found support for the postulated role of anxiety/depression in side effect reporting, whereby higher baseline anxiety/depression ratings increased the number of reported side effects at all four follow-up points. Even when controlling for socio-demographic and disease factors, psychological factors (i.e. medication beliefs and anxiety/depression ratings) explained a significant amount of variance in side effect reporting.

The study further replicated the well documented association between medication beliefs and medication taking behaviour: Patients who had more concerns about their bone loss medications and more negative pharmaceutical schemas (high perceived sensitivity to medicines, perceptions that pharmaceuticals are generally harmful) were less adherent and less likely to persist with their bone loss medication. The experience of side effects also affected medication taking behaviour: Adherence and persistence were reduced for women who reported more side effects. The autoregressive mediation model further showed, that at each time-point, the effect of patients’ concerns on self-reported adherence was mediated by side effect reporting.

2.6.2 Integration with previous literature

The results are consistent with findings from existing cross-sectional studies showing that patients who have more negative beliefs about pharmaceuticals in
general and stronger concerns about a specific prescribed treatment report more side effects (Bautista et al., 2011; De Smedt et al., 2011; De Smedt et al., 2012; Oladimeji et al., 2008; Shiyanbola & Farris, 2010) (see also literature review section 1.3.3). Yet, the present study adds to the limited existing evidence concerning the nature of the relationship between medication beliefs and side effect reporting. A previous study in patients with arthritis (Nestoriuc et al., 2010) showed that patients’ concerns about their arthritis medication at baseline predicted side effect reports at 6 month follow up, while the experience of side effects at baseline was not associated with concerns about treatment at 6 month follow up (see Figure 3). Yet in this study I found evidence for a time-lagged association between side effects and concerns at all follow-up points. I would argue that this is indeed what the theoretical model of treatment representations would predict, which acknowledges dynamic role of symptom experiences (Horne, 2003) in shaping treatment beliefs and patients’ engagement with treatment (see also 1.3.1): The experience of side effects can be worrying for patients (Larsen & Gerlach, 1996). It is thus understandable that patients who experience negative side effects during treatment develop more negative beliefs about the specific treatment.

The study also added to the existing literature on the role of anxiety and depression in side effects reporting (see section 1.4.3). Despite being assessed with a very crude one item scale, there was a clear tendency for patients with stronger self-reported anxiety/depression to report more side effects across the whole follow-up period. This is in line with meta-analytic evidence showing that individuals with increased depression and anxiety scores report more medically unexplained symptoms: Depression and anxiety were more severe or more prevalent in patients with four different functional somatic syndromes (fibromyalgia, non-ulcer dyspepsia, chronic fatigue syndrome and irritable bowel syndrome) compared to healthy controls or control patients with known organic pathology (Henningsen, Zimmermann, & Sattel, 2003). It has been suggested that anxiety and depression lower the threshold for the detection and reporting of symptoms (Pennebaker & Watson, 1991), some of which could be subsequently attributed as side effects. This may be particularly likely in patients who have more negative medication beliefs.

Indeed a closer look at the types of side effects patients reported in the study suggests that attributional processes likely played a role. It is conceivable that some of the reported side effects were in fact caused by factors unrelated to the medication, but nevertheless attributed as caused by the medication. For example, hot flushes could either be caused by the medication or be symptoms of the
menopause. The same is true for menstrual bleeding, which is not listed a side effect to bisphosphonates in the British National Formulary BNF (BNF, 2012), but which could be due to irregularities in menses and skipped menses (Mitchell, Woods, & Mariella, 2000) in pre-menopausal women. The attribution of unrelated symptoms as side effects will be examined in more detail in Studies 3-5.

The study also replicated the well documented findings on the role of medication beliefs on medication taking behaviour. Patients who had stronger concerns about their prescribed medication relative to their perceived necessity for treatment were less adherent and less likely to persist with their bone loss medications. Yet, the study went beyond replicating this well established finding by showing that the effect of patients concerns on self-reported adherence was mediated by side effects.

### 2.6.3 Strengths and limitations

The present study has several strengths and limitations. The study involved the secondary analysis of a large data set, allowing me to conduct multivariate analyses without compromising statistical power. The longitudinal design of the original study enabled me to examine prospective associations between medication beliefs side effect reporting and medication taking behaviours and to examine how these factors change over time. As common in longitudinal datasets, drop-out rates were relatively high, a problem which was mitigated by using appropriate statistical techniques (i.e. multiple imputation (Little & Rubin, 2014) and Full Information Maximum Likelihood).

Although the majority of outcomes were patient reported and hence subject to reporting biases, other key outcomes and covariates (co-morbid conditions, concomitant medications, bone loss diagnosis) were ascertained by clinician report. Although data was collected across 5 different European countries, the sample was demographically homogenous. Due to the nature of the original investigation, the sample was restricted to older (menopausal) women and consisted of predominantly white women (most at risk of osteoporotic fractures). Several studies have demonstrated stronger nocebo effect for women than men (Ashraf & Saaiq, 2014; Klosterhalfen et al., 2009; Ströhle, 2000). It is therefore difficult to tell whether the findings from this study generalize to men and demographically more diverse patient populations.
The original data was not collected for the purpose of examining psychological influences on side effect reporting. Therefore several potentially important psychological variables were therefore not measured (e.g. negative affect (Foster, Sanderman, van der Molen, Mueller, & van Sonderen, 2008), somatosensory amplification (Davis et al., 1995), Type A personality (Drici et al., 1995), somatization (Uhlenhuth et al., 1998)) or in the case of depression/anxiety not measured using standard validated scales (i.e. use of EQ-5D item instead of Hospital Anxiety Depression Scale (Zigmond & Snaith, 1983)). In addition, adherence to bone loss medication was measured by self-report only. Although self-report adherence measures have been found to have good concurrent and predictive validity with more objective adherence measures (e.g. pharmacy refill, biomedical outcomes) (Garfield, Clifford, Eliasson, Barber, & Willson, 2011; Shi et al., 2010), they are susceptible to recall and social desirability biases (Ho, Bryson, & Rumsfeld, 2009).

The effect sizes observed in this study were relatively small. This could be related to the absence of other potentially relevant belief measures in the models (e.g. illness beliefs, which were not included in the original study). In addition, it is possible that the predictive power of the SEM models could be improved through the inclusion of clinical variables in the models.

2.6.4 Clinical implications

The study has several clinical implications. It demonstrates the need to consider patients pre-existing beliefs about medications and psychiatric co-morbidities when prescribing and evaluating treatment in clinical practice. The Beliefs about Medicines Questionnaire and Perceived Sensitivity to Medicines Scale may help guide practitioners assessment of negative medication beliefs. Interventions to change medication beliefs, which are currently being developed, may be useful in reducing perceived side effect burden and in improving adherence and thereby optimizing treatment outcomes. The findings from the study are also relevant for drug safety monitoring. Volunteers in phase I clinical trials have been shown to be less anxious, less neurotic and less depressed than the norm (Almeida et al., 2008) and may therefore underreport side effects compared to patients taking prescribed treatment. This may lead to differences in side effect prevalence rates between trial data and post-marketing patient-reported side effects.
2.6.5 Conclusion

Taken together the study highlights that not only clinical and pharmacological factors determine whether patients report side effects. Psychological factors like medication beliefs and comorbid anxiety/depression are also likely to contribute to side effect reporting. It is therefore essential for clinicians to consider these person specific factors when prescribing treatment and evaluating the tolerability of medication.
Chapter 3: Medication beliefs and side effect reporting in healthy students receiving Modafinil placebo (Study 2)

3.1. General study aims

I have reviewed existing studies examining the association between medication beliefs and side effect reporting in clinical samples (see 1.3.3) and provided additional empirical evidence in Chapter 2. But while there is growing support for the existence of a prospective relationship between medication beliefs and side effects, so far very little is known about possible underlying mechanisms. As outlined in the introduction, it is plausible (but hitherto unproven) that medication beliefs are associated with nocebo responding. The aim of this study is thus:

1) to test whether medication beliefs prospectively predict side effect reporting in patients receiving placebo (see Research Question 1)

2) and to shed more light on the underlying mechanisms and processes linking medication beliefs to side effects (see Research Question 2).

3.2 General study background

As outlined in section 1.4, it is plausible that the nocebo effect contributes to patient reported side effects in clinical trials and clinical practice. However while there is an abundance of studies documenting apparent nocebo side effects (i.e. symptom reporting following placebo administration) either through examination of data from patients in the placebo arm of RCTs (see Table 2) or from participants receiving pharmacologically inactive substances in experimental settings (Link et al., 2006; Schweiger & Parducci, 1981; Webster et al., 2016), there is a distinct lack of studies using appropriate control groups (e.g. natural history control group) (Neukirch & Colagiuri, 2014).

Yet without appropriate control groups it is impossible to tell whether patients receiving placebo treatment would have experienced symptoms regardless of any placebo administration. Examining differences in symptom reporting in a deceptive placebo versus a no-treatment natural history group thus helps to understand whether symptoms are actually generated through nocebo mechanisms (i.e. could be considered true nocebo effects, see Chapter 1). Using a natural history control group also helps to shed light on nocebo mechanisms: Symptoms in the natural history arm where no drug is given can logically not be linked to expectations about
side effects of the drug. But using a natural history control group doesn’t come without its problems. For one it is impossible to blind this condition and the certainty of not receiving anything is likely to lead to a different mind-set (Hróbjartsson, 2002). Secondly it is not possible to probe symptom attribution in this group as no drug is given to which symptoms could be attributed to.

Evidence from the few existing studies comparing symptom reports in individuals randomized to placebo or no treatment is mixed. Colagiuri and colleagues (Colagiuri et al., 2012) recruited university students with sleeping difficulty to participate in a trial for a novel “sleeping pill”. Participants were randomized to two placebo groups (the leaflet listed either 1 or 4 possible side effects) or no treatment. Participants in the placebo groups (43%) did indeed report side effects, but every symptom (with the exception of headache) was reported more frequently by participants in the no treatment group. In a related study participants who were warned about changes in appetite before taking placebo sleeping pills were more likely to report this symptom than participants who were warned but did not receive (placebo) treatment (Neukirch & Colagiuri, 2014). Another study compared symptom reports in patients randomized to daily placebo (described as treatment to reduce blood potassium levels) or no treatment for six days (Erbguth, Hamacher-Erbguth, Fuhr, & Sörgel, 2015). Participants in the placebo group reported significantly more symptoms than patients in the no treatment group. Several other studies that compared placebo and no treatment groups failed to measure and/or report adverse symptom reports in the no treatment group (Kaptchuk et al., 2010; Wechsler et al., 2011).

Other researchers (Enck, Klosterhalfen, & Zipfel, 2011; Horing et al., 2013) have suggested that an open-label placebo group (i.e. whereby individuals are correctly informed that the administered pill is pharmacologically inactive) could serve as another potential control group to study placebo and nocebo effects. For example in the half-balanced placebo design, all participants are given placebo but are explicitly told that it is either a placebo (Open Placebo) or the active drug (Deceptive Placebo). This could be seen as a manipulation of expectancy, maximizing expectations in the Deceptive Placebo group and minimizing expectations in the Open Placebo group. Differences in the positive and negative outcomes between these groups can be interpreted as evidence for placebo and nocebo effects. The problem is however that an instruction of inertness does not necessarily induce the expectation of inertness (Horing et al., 2013). Given the potential downfalls of both a natural history and open placebo group, I decided to
use a three arm design in the present study: Deceptive Placebo (given placebo – told drug), Open Placebo (given placebo – told placebo) and Natural History (no pill).

As an interesting aside, including an Open Placebo group allowed me to verify claims that placebos can be effective without deception (Kaptchuk et al., 2010; Sandler & Bodfish, 2008). Kaptchuk and colleagues (Kaptchuk et al., 2010) gave patients with irritable bowel syndrome (IBS) either a placebo pill (n=37) or no treatment (n=43). Patients were informed that the pill was a placebo, but told that placebos have powerful mind-body effects. Patients in the open-label placebo arm reported significantly greater improvement of their IBS symptoms than those in the control group. But patients were allowed to continue active IBS treatment during the trial and patients in the open-placebo group were more likely (54%) than those in the no treatment group (35%) to receive IBS treatment at baseline. In this study I used a more conventional description of placebo, based on typical descriptions of placebos in RCTs (Bishop, Adams, Kaptchuk, & Lewith, 2012). Apart from testing whether there can be a placebo effect without deception, the study design also allowed me to examine whether there was a “nocebo without deception”- effect, i.e. greater symptom reporting in an Open Placebo versus Natural History group.

Conducting nocebo research with patients, especially if it involves deception, raises ethical questions (Benedetti, 2010). I used a healthy student sample, but selected the drug "Modafinil", as it is relevant to a healthy student population. Students' off-label use of prescription stimulants (so-called "smart drugs") like Modafinil to boost cognitive performance has received growing attention in the media (Partridge, Bell, Lucke, Yeates, & Hall, 2011). Although many news sources state that off-label use of Modafinil is on the rise in UK student populations (one informal survey reporting that a fifth of UK students have used it), the prevalence of Modafinil use in Europe is uncertain (Ragan, Bard, & Singh, 2013). However reported lifetime usage rates in some US college samples ranged between 3-25% (Smith & Farah, 2011). Yet, the cognition enhancing effects (e.g. improved memory, sustained attention) of Modafinil in healthy samples are still unclear (Smith & Farah, 2011), providing an excellent cover story for conducting this study in a UK student population. In addition, side effects have been reported in the placebo arm of Modafinil RCTs (Bittencourt et al., 2008), with patients receiving Modafinil placebo as likely to report side effects (54.4%) as those receiving active Modafinil (55.8%) (Spathis et al., 2014).
3.3 Medication beliefs and nocebo responding

One of the main aims of the study was to examine whether psychological factors like medication beliefs and other psychological characteristics (see 3.4 below) can predict symptom and side effect reporting in participants randomized to placebo or no treatment. As stated in the Introduction (see section 1.4), this is to my knowledge the first empirical study to test whether medication beliefs are associated with nocebo responding. The following putative mechanisms that could explain a link between medication beliefs and nocebo responding will be examined in the present study:

Medication beliefs and expectations

I have previously argued (see section 1.5) that negative beliefs about specific medications, pharmaceutical medicines in general and perceptions of high sensitivity to medicines should lead to increased side effect expectations. To my knowledge this has not been empirically tested so far. The general role of expectations in side effect reporting (to both active medication and placebo) is however well documented (see also section 1.4.3).

Medication beliefs and somatic focus

It is plausible that individuals with more negative beliefs about medicines monitor their body more carefully for bodily changes when taking medication (see section 1.5.1). Only few previous studies have examined the role of somatic focus in nocebo effects (Geers et al., 2006), but there is good evidence for the role of somatic focus in symptom perception in general (Pennebaker, 1981, 2000).

Medication beliefs and symptom attribution

There is extensive evidence for the role of schemas in causal attributions (Fiske & Taylor, 1991; Kelley, 1972), but only few previous studies have examined the role of medication beliefs in the attribution of symptoms as side effects (Cooper et al., 2009; Cooper et al., 2014). In order to examine the role of medication beliefs in the appraisal of symptoms in more detail, I decided to experimentally induce two sensations (itch and dizziness) using visual stimuli (see section 3.6.7 for a detailed description). The idea behind this was to examine whether individuals with more negative medication beliefs are more likely to attribute these sensations as side effects when taking Modafinil-placebo.
3.4. Other psychological factors and nocebo responding

In addition to medication beliefs, the role of several other psychological factors in nocebo responding will be examined in the study. Although many reviews of the nocebo effect stress the importance of psychological and personality factors in the nocebo effect (Barsky et al., 2002; Mora et al., 2011; Rief et al., 2008), empirical evidence is still limited (Webster et al., 2016). The following constructs will be examined:

**Somatization**

Somatization, which could be described as a tendency to experience and communicate distress in a somatic rather than psychological mode (Lipowski, 1988) has been linked to increased nocebo responding (De La Cruz, Hui, Parsons, & Bruera, 2010; Szemerszky, Köteles, Lihi, & Bárdos, 2010). However, many of the existing studies have examined the role of somatization in response to sham electromagnetic fields and not pharmaceutical placebos (see Webster et al., 2016).

**Negative Affectivity**

Negative affectivity (NA) is defined as a mood-dispositional dimension, which reflects stable and pervasive differences in negative mood (Watson & Clark, 1984). It has been linked to over-perception of symptoms in asthma (Janssens et al., 2009; Peuter et al., 2007), medically unexplained symptoms (Rief & Broadbent, 2007) and common symptoms (Pennebaker, 1982). However, there is only limited evidence for the role of NA in nocebo effects from studies using pharmacological placebos (Webster et al., 2016).

**General Body Awareness**

Body awareness could be described as an attentional focus on and awareness of bodily sensations, which can be maladaptive at times and lead to increased symptom detection (Mehling et al., 2009). Several studies have shown that symptom reporting is higher for individuals with greater body awareness (Ferguson & Ahles, 1998; Martin, Ahles, & Jeffery, 1991; Mehling et al., 2009). Yet, to my knowledge there is no study examining the role of general body awareness on nocebo responding.

Although there is likely to be an overlap between the factors mentioned above and medication beliefs, there is one important difference in that medication beliefs are more specific to the context of medication taking. Increased negative
affect, somatization and general body awareness on the other hand should be associated with increased symptom reporting even when no “drug” is given.

3.5. Hypotheses

1) Participants randomized to Deceptive Modafinil Placebo will report more symptoms than those randomized to receive open-label placebo (Open Placebo group) or no pill (Natural History group) and will attribute more symptoms as side effects than those in the Open Placebo Group.

2) It was hypothesized that participants with more negative pharmaceutical schemas (beliefs that pharmaceuticals are generally harmful, high perceived sensitivity to medicines) and concerns about the study pill would report more symptoms and attribute them as side-effects when receiving deceptive Modafinil placebo. Higher negative affectivity, somatization and body will be associated with higher symptom reporting in all experimental groups.

3) More negative beliefs about medicines will be associated with increased side effect expectations and increased attention to bodily changes.

4) I also tested whether there was a placebo effect on cognitive enhancement. It was hypothesized that participants in the Deceptive Modafinil Placebo group would show greater cognitive enhancement than participants in the Open Placebo and Natural History groups.

5) Finally, I examined whether there was a placebo/nocebo effect without deception. Participants receiving open label placebo were expected to show greater cognitive enhancement and to report more symptoms than participants in the Natural History group.

3.6. Methods

3.6.1 Design

A randomized between group design with the following experimental conditions was used (see Figure 20):

1) Deceptive Modafinil Placebo: Told Modafinil – given placebo

2) Open Placebo: Told placebo – given placebo

3) Natural history: No placebo given
3.6.2 Participant recruitment and inclusion criteria

UCL students were invited via posters (displayed in student union cafes and university noticeboards), electronic student newsletters and the UCL research participation website to take part in a placebo controlled trial to evaluate the efficacy and safety of the “smart drug” Modafinil. Interested participants (N=276) contacted me by e-mail and were e-mailed a participant information sheet and a pre-screening questionnaire (see Appendix C) to determine eligibility. Participants were eligible to participate if they were over 18 years of age and not taking any medication (except hormonal contraceptives). Eligible participants were e-mailed a link to book an appointment for the trial via doodle (http://www.doodle.com). They received £10 for their participation in the 60 minute study.

3.6.3 Materials

Before randomization to experimental conditions participants were shown the following information about Modafinil and the placebo pill:

3.6.3.1 Modafinil patient information leaflet

A three page long Modafinil patient information leaflet (see Appendix F) was adapted from the leaflet of commercially available Modafinil. It contained information about the active ingredient in Modafinil, its indication for treating narcolepsy, off-label or life-style uses (e.g. age-related memory decline, attention deficit disorder, fatigue caused by high pressure jobs, jet lag), contraindications (e.g. uncontrolled moderate to high blood pressure, depression, kidney disease) and possible interactions with other medications (e.g. omeprazole, ciclosporin). A list of possible side effects (including the induced symptoms itch and dizziness) was presented. All side effects were Modafinil side effects as listed in the British National Formulary (BNF; 2012) and in online drug information sources (e.g. drugs.com).

3.6.3.2 Placebo information

Participants received the following information about the placebo pills: “A placebo is a “dummy treatment”, which looks like the genuine medicine but contains no active ingredient. It is used in clinical trials to assess the efficacy and safety of an active drug by comparing the outcomes in the placebo group to outcomes in the active treatment group. Please note that the placebo tablets used in this study contain sucrose (table sugar) and gelatine and no active medication. The placebo pills have been manufactured according to industry standards to ensure that they are not contaminated by any active ingredients in the manufacturing process.”
description was adapted from a review paper examining typical descriptions of placebo in randomized controlled trials (Bishop et al., 2012).

3.6.3.3 Placebo pills

The placebo pills used in the study were sucrose filled gelatine caps (see Figure 19). But not any sucrose was used! The sucrose pills that were inserted into the size 0 gelatine caps were in fact “untreated” sugar globuli for homeopathic dispensing (i.e. before homeopathic method is applied).

![Figure 19: Placebo pill preparation](image)

3.6.4 Randomization to experimental conditions and experimenter blinding

The Qualtrics block randomization function was used to randomize participants to the experimental conditions. Participants were informed about their allocation by the computer, but told to conceal the condition allocation in the two placebo conditions from the experimenter by revealing only their randomization code (see Figure 20). The randomization code (ZTR013) was identical in the Deceptive and Open Placebo condition and the experimenter always delivered the study pill from the same pill bottle (see Figure 21). Participants were correctly informed that the randomization code was necessary to keep the researcher blind to the condition allocation (“single blinded trial”), but led to believe that they themselves had to be informed about their allocation due to ethical considerations and safety issues.
Figure 20: Overview of study procedures and experimenter blinding

Note. Mode of Administration: * Qualtrics survey software, † experimenter, ‡ E-prime; PSM=Perceived Sensitivity to Medicines Scale, BMQ= Beliefs about Medicines Questionnaire, SBA=Scale of Body Awareness, PANAS=Positive and Negative Affect Schedule, PHQ-15=Somatization Scale of the Patient Health Questionnaire.
3.6.5 Predictor questionnaire measures

Perceived Sensitivity to Medicines (PSM)

The PSM (Horne et al., 2013b) (see section 1.3.2.2) was used to assess perceived sensitivity to medicines. The five scale items showed high internal consistency (Cronbach’s α=.85).

Beliefs about Medicines Questionnaire (BMQ)

The standard version of the BMQ-General (Horne et al., 1999) (see section 1.3.2.1) was used to assess participants’ beliefs about pharmaceutical medicines as a class of treatment.

Table 16: Internal consistency BMQ subscales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Number of items</th>
<th>Cronbach’s alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ General Overuse</td>
<td>4</td>
<td>.66</td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>4</td>
<td>.72</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>4</td>
<td>.64</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>4</td>
<td>.75</td>
</tr>
<tr>
<td>BMQ Specific Concern</td>
<td>4</td>
<td>.85</td>
</tr>
</tbody>
</table>

Note. BMQ=Beliefs about Medicines Questionnaire

Participants’ beliefs about the study pill were assessed after participants had learned about their allocation (Deceptive Modafinil Placebo and Open Placebo conditions only) with a modified version of BMQ-Specific (see Appendix D). Four items measured participants’ necessity beliefs (e.g. “My performance in the upcoming tasks, depends on taking this pill”), four items measured concerns (e.g. ...
“Having to take this pill worries me.”). All BMQ scales had adequate internal consistency (see Table 16).

**Baseline Symptoms**

Baseline symptoms were assessed using a symptom checklist proposed by Pennebaker (Pennebaker, 1982). Participants were asked to indicate on 7-point bipolar rating scales (e.g. 1=no headache to 7=headache) whether they were currently experiencing any of 12 listed symptoms (headache, itch, dizziness, upset stomach, shortness of breath, racing heart, sweaty hands, numbness, vertigo, watering eyes, cold hands, congested nose). A total baseline symptom score was computed by summing ratings (Cronbach’s α=.77).

**Positive and Negative Affect Schedule (PANAS)**

State Negative Affect was assessed with the short form of the PANAS (Mackinnon et al., 1999). Participants were asked to indicate to what extent (from 1=not at all to 5=extremely) they generally experienced ten negative (e.g. distressed, upset) and ten positive feelings (e.g. excited, relaxed). State Negative (NA) and Positive Affect (PA) scores were computed by averaging scores for all negative and positive adjectives respectively. Internal consistency was high (Cronbach’s αs >.83).

**Patient Health Questionnaire (PHQ-15)**

Somatization was assessed with the Patient Health Questionnaire (PHQ-15) (Kroenke, Spitzer, & Williams, 2002). The PHQ-15 contains a list of 15 symptoms and participants are asked to indicate whether they have been bothered by each symptom during the past 4 weeks on a 3-point Likert scale (0=not bothered at all, 1=bothered a little, 2=bothered a lot). For the purposes of the study the female only item (menstrual cramps) was replaced with “racing heart”. Individual item scores were summed to form a total score. Internal consistency was good (Cronbach’s α=.71).

**Scale of Body Awareness (SBA)**

Individuals’ cognitions about bodily sensations were assessed with the Scale of Body Awareness (SBA) (Hansell, Sherman, & Mechanic, 1991). The SBA contains 4 items (e.g. How much do you think about how your body feels?) which are rated on 5 Likert scales ranging from 1=very little to 5=very much. An average
SBA score was computed by summing item scores and dividing by the number of scale items (Cronbach’s α = .83).

3.6.6 Other measures

Demographics

Participants were asked to indicate their age, gender, ethnic background, first language and highest level of education.

Self-focused attention

Participants indicated on a 7-point Likert scale (from 1=not at all to 7=very much) how closely they had paid attention to changes in bodily sensations during the study. This measure of self-focused attention was taken from a previous study exploring the role of somatic focus in placebo effects (Geers et al., 2006)

Side effect expectations

Side effect expectations were measured with an indirect question about expected bodily wellbeing. Participants are asked to indicate on 100-point Visual Analogue Scales (VAS) how they expect their body to feel if they were taking placebo or Modafinil or no substance (from 0=not well at all to 100=extremely well).

Efficacy Expectations

Participants were asked to rate on 100-point VAS how well they expected to perform in the concentration and alertness tasks if they were taking placebo or Modafinil or no substance (from 0=not well at all to 100=extremely well).

Cognitive enhancement drug and caffeine use

Previous use of prescription only and non-prescription concentration enhancing drugs was assessed with a multiple choice question. Participants were also asked to indicate how frequently they consumed caffeine (1=never to 5=daily).

Suspicion probe/Unblinding questions

Participants were invited to describe in a couple of sentences what the study was about. The experimenter coded whether participants correctly guessed deceptive nature and aim of the study.
3.6.7 Symptom induction tasks

The two symptom induction tasks were programmed and administered with E-prime version 2.0.

Itch Induction

Itch sensations were induced using images of insects crawling on skin, that were embedded among other stimuli in an alleged reaction time task involving the categorization of images. FMRI studies have shown that this type of imagery can be effective in inducing itch (Lloyd, Hall, Hall, & McGlone, 2013) by activating neural regions linked to the physical perception of itch (Ward, Burckhardt, & Holle, 2013). Other images with potential itch associations (e.g. cat/dog fur, pollen, pictures of rash) were also included (see Appendix E for all stimuli).

Figure 22: Example screens of the itch induction IAT task

The task itself was modelled on the Implicit Association Test (IAT) (Greenwald, McGhee, & Schwartz, 1998). Participants were asked to press either the Q or the P button to categorize images from four different categories: insects, flowers, unpleasant, pleasant. There were eight images in each category (see Appendix E for all stimuli). Response keys and category labels were presented at the top left and top right corners of the screen (see Figure 22 for example screens).
As in the original IAT participants completed five different blocks, which were presented in a fixed order (see Table 17 for block sequence).

Table 17: Implicit Association Task (IAT) block sequence

<table>
<thead>
<tr>
<th>Block Sequence</th>
<th>Response Key on Keyboard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left (Q)</td>
</tr>
<tr>
<td>1 Initial Target-Concept Discrimination</td>
<td>Insects</td>
</tr>
<tr>
<td>2 Associated Attribute Discrimination</td>
<td>Pleasant</td>
</tr>
<tr>
<td>3 Initial combined Task</td>
<td>Insects</td>
</tr>
<tr>
<td>4 Reversed Target-Concept Discrimination</td>
<td>Flowers</td>
</tr>
<tr>
<td>5 Reversed Target-Concept Discrimination</td>
<td>Flowers</td>
</tr>
</tbody>
</table>

*Note.* Naming of blocks based on (Kim, 2003)

**Dizziness induction**

Dizziness was induced using black and white concentric circles as a background picture in a bogus visual attention task (see Figure 23). Similar black and white patterned stimuli (Adjamian et al., 2004; El Shakankiry & Kader, 2012) have been used to examine visually induced vertigo. Participants were instructed to press the spacebar as soon as a blue dot that moved across the patterned background changed to red. There were 64 trials with 15 targets which were presented in blocks of 16, with a user determined break after each block.

Figure 23: Overview dizziness induction ‘visual attention’ task
3.6.8 Symptom and side effect reporting measures

Scratching

The experimenter observed whether participants scratched themselves during or after the itch induction task.

Symptom Checklist

Participants were shown a checklist which was based on the Illness Perception Questionnaire Identity subscale (Moss-Morris et al., 2002). It contained 25 symptoms, 17 of which had been listed in the Modafinil patient information leaflet and 8 non-listed symptoms (nausea, swollen hands/feet, vertigo, upset stomach, slowing heart, weakness, fatigue) as well as two textboxes allowing participants to specify other symptoms (see Appendix G). The order of the symptoms was randomized. Participants were asked to indicate (yes/no) whether they had noticed each symptom. The following outcome variables were computed: number of total symptoms, symptoms from Modafinil leaflet and symptoms not from leaflet detected.

Side effect attribution

In the two placebo conditions participants were asked to indicate on a 5-point Likert scale whether each of the noticed symptoms was caused by the study pill (from 1=definitely caused by the study pill, 2=likely to be caused by the study pill, 3=uncertain, 4=unlikely to be caused by the study pill, 5=definitely not caused by the study pill). Responses were dichotomized (ratings of 4 and 5 were recoded as not attributed as side effect) to facilitate analysis.

3.6.9 Cognitive enhancement measures

Both subjective (perceived improvement) and objective (standardized cognitive tasks) outcome data was collected. Cognitive tasks were programmed and administered with E-prime version 2.0.

Perceived cognitive enhancement

Participants were asked to rate their alertness, ability to concentrate, and ability to remember on 100-point VAS ranging from 0=less than usual, 50=no change, 100=more than usual. A mean perceived cognitive enhancement score was computed by averaging the responses per participant over the three VAS (Cronbach’s α=.86).
Wechsler Auditory Digit Span Test (WDST)

A computerized version of the Wechsler Auditory Digit Span Test (Wechsler, 2008) was used to measure short term memory performance. Digit span tests have been used in other studies examining the effect of active Modafinil on cognitive performance (Pigeau et al., 1995; Wesensten, 2006). Both forward and backward auditory digit span were assessed:

In the forward digit span procedure participants heard a series of spoken digits and had to reproduce the digits in order by typing the numbers on a keypad. Each spoken digit was presented individually (approximately 1000 msec) with a 1000 msec interval between each digit. Digit sequences were chosen randomly, with the constraint of non-repetition of previously chosen digits. Digit sequences started with 3 digits and increased to 9 digits with two trials per digit length, resulting in 14 forward digit sequences.

In the backward digit span procedure, participants were instructed to type the digits in reverse order (e.g. 1-3-4 would be 4-3-1). Presentation and randomization of digits was identical to the forward procedure, but the sequence started with two digits, increasing to eight digits, resulting in 14 backward digit sequences. The total number correctly repeated forward (forward digit span) and backward sequences (backward digit span) were computed.

Continuous Performance Test (CPT-AX)

The continuous performance test (CPT) (Rosvold, Mirsky, Sarason, Bransome Jr, & Beck, 1956) is a well validated measure of vigilance and sustained attention (Riccio, Reynolds, Lowe, & Moore, 2002). The CPT-AX version of this test has been previously used to assess effects of Modafinil on sustained attention in sleep deprived emergency room physicians (Gill, Haerich, Westcott, Godenick, & Tucker, 2006) and healthy volunteers (Repantis, Schlattmann, Laisney, & Heuser, 2010). Participants saw sequences of letters, one letter per screen, and were instructed to make a target response (press 2) whenever the stimulus “X” immediately followed the presentation of the letter “A” and to make a non-target response (press 1) to all other stimuli (see Figure 24).
Stimuli were presented for 200 msec. Participants were given brief visual feedback (green tick for correct responses, red cross for incorrect responses presented for 100 msec) after each response (see Figure 25). The inter-trial interval length varied randomly between 1000, 1500 and 2000 msec.

After reading the task instructions participants completed 40 practice trials (with 20% targets). The 150 main trials contained 20% (n=30) target trials. There were 20% (n=30) X lure trials (non-A-X trials), 10% (n=15) A-lures (A-non X) trials and 50% (n=75) neutral trials.

Reaction times were measured from the end of the stimulus presentation until a response was detected. Responses over 1500 msec and under 200 msec were coded as incorrect (Whelan, 2010). Responses below the 200 msec threshold are considered guesses and not deliberate reactions. The number of correct target responses and average reaction times for correct target responses (in msec) were computed.
Note. RT=Reaction Time; ITI=Inter Trial Interval, msec=milliseconds

3.6.10 Procedures

The study was approved by the UCL Research Ethics Committee (ID: 4716/002). After giving informed consent, participants completed the predictor questionnaire measures, read the Modafinil and placebo information and completed the expectation (side effects and efficacy) VAS. The computer then randomized participants to the experimental conditions and participants received either a placebo pill (labelled as either Modafinil or placebo) or no pill. Participants were asked to wait for approximately 10 minutes for the drug to take effect (or simply told to wait in the Natural History group). Participants then completed the Wechsler Digit Span Test, Continuous Performance Test and the two symptom induction tasks (fixed order). They then rated self-perceived cognitive enhancement and were given the symptom checklist. In the two placebo conditions participants were also asked to make the symptom attribution rating. Finally, participants completed the demographic and control questions and were immediately debriefed about the
deception at the end of the experimental session. A 10-15 minute time-window was reserved for the debriefing session. Please refer to Figure 20 for a schematic overview of procedures.

3.6.11 Sample size and statistical considerations

Required sample size for predicting side effect attribution (yes/no) in the two placebo groups was calculated using the POWERLOG function in STATA13, using data from a previous analogue study (Heller, Chapman, & Horne, 2015). The power analysis showed that 132 participants were required to achieve 80% power at an alpha level.05 (two-sided). In order to achieve balanced distribution of participants in the three experimental groups an additional 66 participants were added for the no treatment control group, leading to total of 198 required participants.

The distribution of outcome data was examined graphically and numerically. Count outcomes (the number of reported and attributed symptoms) were not normally distributed, but showed a good fit with a Poisson distribution. Differences in these outcomes between experimental groups were examined with non-parametric tests (Kruskall-Wallis, Mann-Whitney U-Tests). Between-group differences in continuous outcomes were examined with One-Way ANOVAS and t-tests. Negative binomial regression modelling was used to test for associations between predictor measures and symptom and side effect count outcomes. Negative binomial regression was chosen instead of Poisson regression because the Poisson regression assumption of equidispersion (i.e. a distribution where the mean equals the variance) (Long & Freese, 2006) was violated. Results of the negative binomial regression models are reported using incidence rate ratios (IRR). An IRR of 1.5 indicates that the expected count is multiplied by a factor of 1.5 with every one unit increase in the predictor.

Sensitivity analysis was performed to test whether findings differed when excluding participants who guessed that the study involved deception. No substantial differences were observed and data from all participants (expect those excluded for other reasons (see 3.7.1) is presented below.

3.7 Results

3.7.1 Sample characteristics and exclusions

Of the 276 participants who expressed interest in the study, 11 were not eligible to participate because they were currently taking medication (although this was mentioned as an exclusion criterion in the recruitment materials). In total 201
participants took part in the trial (appointment booking was stopped once the sample size target was reached). The majority of the 201 study participants were white and relatively young (M=22.9 years) as to be expected from a student sample. The sample was 44.3% male and 55.7% female. Table 18 summarizes demographic characteristics in the experimental groups.

Two participants in the Open Placebo condition indicated that they had experienced all of the pre-specified 25 symptoms (including vomiting, which was not observed by the experimenter). They also failed to follow instructions for other tasks and their data was excluded from the analysis.

Table 18: Baseline sample characteristics by experimental group

<table>
<thead>
<tr>
<th></th>
<th>Deceptive Placebo (n=66)</th>
<th>Open Placebo (n=65)</th>
<th>Natural History (n=68)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female n (%)</td>
<td>38 (57.6)</td>
<td>32 (49.2)</td>
<td>41 (60.3)</td>
<td>.411</td>
</tr>
<tr>
<td>Age M (SD)</td>
<td>22.79 (5.57)</td>
<td>22.71 (5.32)</td>
<td>23.13 (3.91)</td>
<td>.871</td>
</tr>
<tr>
<td>Native English speaker n (%)</td>
<td>38 (57.6)</td>
<td>41 (63.1)</td>
<td>45 (66.2)</td>
<td>.583</td>
</tr>
<tr>
<td>Ethnicity n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White British/Irish</td>
<td>25 (37.9)</td>
<td>15 (23.1)</td>
<td>22 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Any other White background</td>
<td>18 (27.3)</td>
<td>21 (32.3)</td>
<td>20 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Black British</td>
<td>1 (1.5)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>.342</td>
</tr>
<tr>
<td>Any other Black background</td>
<td>1 (1.5)</td>
<td>3 (4.6)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Indian/Pakistani/Bangladesi</td>
<td>4 (6.1)</td>
<td>4 (6.2)</td>
<td>3 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Any other Asian background</td>
<td>1 (1.5)</td>
<td>6 (9.2)</td>
<td>3 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>14 (21.1)</td>
<td>8 (12.3)</td>
<td>10 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>2 (3.0)</td>
<td>5 (7.7)</td>
<td>6 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>3 (4.6)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Past smart drug use n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription-only</td>
<td>6 (9.1)</td>
<td>4 (6.2)</td>
<td>4 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Non-prescription</td>
<td>3 (4.1)</td>
<td>8 (12.3)</td>
<td>11 (16.2)</td>
<td>.174</td>
</tr>
<tr>
<td>Both types</td>
<td>2 (3.0)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>55 (83.3)</td>
<td>53 (81.5)</td>
<td>53 (77.9)</td>
<td></td>
</tr>
<tr>
<td>Coffee use M (SD)</td>
<td>3.95 (1.12)</td>
<td>3.75 (1.23)</td>
<td>3.76 (1.31)</td>
<td>.570</td>
</tr>
<tr>
<td>BMQ-General Harm M (SD)</td>
<td>2.19 (0.70)</td>
<td>2.24 (0.76)</td>
<td>2.18 (0.68)</td>
<td>.569</td>
</tr>
<tr>
<td>BMQ-General Overuse M (SD)</td>
<td>3.02 (0.70)</td>
<td>3.10 (0.76)</td>
<td>3.05 (0.71)</td>
<td>.805</td>
</tr>
<tr>
<td>BMQ-General Benefit M (SD)</td>
<td>4.13 (0.54)</td>
<td>4.12 (0.47)</td>
<td>4.08 (0.52)</td>
<td>.327</td>
</tr>
<tr>
<td>PSM M (SD)</td>
<td>1.91 (0.68)</td>
<td>2.16 (0.74)</td>
<td>1.98 (0.64)</td>
<td>.106</td>
</tr>
<tr>
<td>PANAS NA M (SD)</td>
<td>1.97 (0.56)</td>
<td>1.91 (0.66)</td>
<td>1.78 (0.60)</td>
<td>.162</td>
</tr>
<tr>
<td>PHQ-15 M (SD)</td>
<td>4.55 (3.33)</td>
<td>4.60 (3.22)</td>
<td>4.51 (3.21)</td>
<td>.988</td>
</tr>
<tr>
<td>SBA M (SD)</td>
<td>3.35 (0.79)</td>
<td>3.47 (0.73)</td>
<td>3.39 (0.84)</td>
<td>.665</td>
</tr>
<tr>
<td>Baseline Symptoms M (SD)</td>
<td>17.36 (6.86)</td>
<td>16.03 (5.14)</td>
<td>16.54 (5.19)</td>
<td>.413</td>
</tr>
</tbody>
</table>

Note. BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale; PANAS=Positive Negative Affect Schedule; NA=Negative Affect; PHQ=Patient Health Questionnaire, SBA=Scale of Body Awareness

3.7.2 Examination of baseline differences

Demographic characteristics did not differ significantly between experimental groups. One-way ANOVAS further confirmed that there were also no significant
differences in any of the baseline predictor measures (BMQ-General, PSM, PANAS, Baseline Symptoms, SBA, PHQ-15). There were also no significant differences in previous cognition enhancing drug or coffee use between conditions (all ps>.11, see Table 18), suggesting that the randomization was successful in creating homogenous experimental groups.

Please note that one would expect to find differences in specific beliefs about the medication, because these beliefs were assessed after the study pill allocation was disclosed to participants. Not surprisingly participants who believed they would receive active Modafinil (Deceptive Placebo) had stronger concerns about the study pill (M=2.83, SD=0.82) than participants who were told they would receive placebo (Open Placebo: M=1.70, SD=0.68; t(129)=8.51, p<.0001).

Participants also expressed greater perceived necessity for the study pill in the Deceptive Placebo (M=2.78, SD=0.51) than the Open Placebo group (M=1.68, SD=0.61; t(129)=5.10, p<.001), suggesting that the information manipulation was successful in creating different expectations in the two placebo conditions.

### 3.7.3 Inter-correlations of predictor measures

Correlations between the BMQ-General subscales were in line with theoretical predictions (see section 1.3): Participants who believed medicines to be generally harmful had significantly higher perceived sensitivity to medicines and believed pharmaceutical medicines to be overprescribed by doctors (see Table 19). Only perceived sensitivity to medicines showed strong associations with the other examined psychological predictors:

Higher perceived sensitivity to medicines was associated with increased negative affectivity, somatization, body awareness as well as stronger symptom burden at baseline (ps<.01). Specific Concerns and Necessity beliefs, which were assessed only in the two placebo arms (n=133; not presented in Table 19) were highly positively correlated (r=.575, p<.001). Surprisingly only Specific Necessity (r=.204, p<.05), but not Specific Concerns (r=.147, p=.09) were associated with increased perceived sensitivity to medicines. Neither Specific Necessity nor Specific Concern beliefs were associated with any of the non-belief predictor measures (ps>.05).

### 3.7.4 Unblinding

The experimenter coded whether participants had correctly guessed the deception used in the experiment. Six participants receiving Modafinil placebo, five
receiving open-label placebo and one participant in the natural history condition \( (\chi^2(2)=3.948, p=.14) \) correctly guessed that deception was used in the study.

Table 19: Inter-correlations predictor measures

<table>
<thead>
<tr>
<th></th>
<th>BMQ General Harm</th>
<th>BMQ General Overuse</th>
<th>BMQ General Benefit</th>
<th>PSM</th>
<th>PANAS-NA</th>
<th>PHQ-15</th>
<th>SBA</th>
<th>Baseline Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ General Harm</td>
<td>1</td>
<td>-.664**</td>
<td>-.463**</td>
<td>.225**</td>
<td>.101</td>
<td>.149*</td>
<td>.062</td>
<td>.049</td>
</tr>
<tr>
<td>BMQ General Overuse</td>
<td></td>
<td>1</td>
<td>-.363**</td>
<td>.173*</td>
<td>.021</td>
<td>.001</td>
<td>.117</td>
<td>-.029</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td></td>
<td></td>
<td>1</td>
<td>-.125</td>
<td>.029</td>
<td>-.110</td>
<td>.056</td>
<td>-.048</td>
</tr>
<tr>
<td>PSM</td>
<td>1</td>
<td></td>
<td></td>
<td>.226**</td>
<td>.339**</td>
<td>.236**</td>
<td>.225**</td>
<td></td>
</tr>
<tr>
<td>PANAS-NA</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>.436**</td>
<td>.161*</td>
<td>.287**</td>
<td></td>
</tr>
<tr>
<td>PHQ-15</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.214**</td>
<td>.453**</td>
<td></td>
</tr>
<tr>
<td>SBA</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.144**</td>
<td></td>
</tr>
</tbody>
</table>

Note. *p<.05; **p<.01; BMQ=Beliefs about Medicines Questionnaire, PSM=Perceived Sensitivity to Medicines Scale, PANAS=Positive Negative Affect Schedule, PHQ=Patient Health Questionnaire; SBA=Scale of Body Awareness

3.7.5 Overview reported symptoms

Across the whole sample extreme tiredness (24.5%), nervousness (22.6%) and drowsiness (16.1%) were the most frequently reported symptoms, with the induced symptoms of dizziness and itch reported by 9.5% and 6.0% of participants (see Table 20). Only a fourth (25.1%) of participants did not report any symptoms.

3.7.6 Differences in symptom reporting in the experimental groups

Participants reported on average 2.65 symptoms in the Modafinil Placebo Group, versus 1.92 and 1.68 in the Open Placebo and Natural History Group.
respectively (see Table 23). Mann-Whitey U-Tests were used to examine whether the number of reported symptoms differed significantly between the experimental groups. Participants in the Modafinil Placebo group reported significantly more symptoms than those in the Natural History (Mann Whitney U=1640, z=2.74, p<.01) and Open Placebo group (Mann Whitney U=1654, z=2.30, p<.05). When looking only at symptoms that had been listed as Modafinil side effects, differences between the Deceptive Placebo group and both the Natural History (Mann Whitney U=1683, z=2.58, p<.05) and Open Placebo Group (Mann Whitney U=1622, z=2.49, p<.05) remained significant. Non-listed symptoms were only more frequent compared to the Natural History (Mann Whitney U=1754, z=2.47, p<.05), but not the Open Placebo Group (Mann Whitney U=1893, z=1.28, p=.20).

<table>
<thead>
<tr>
<th>Listed as SE</th>
<th>All groups (N=199)</th>
<th>Deceptive Placebo (n=66)</th>
<th>Open Placebo (n=65)</th>
<th>Natural History (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty breathing n (%)</td>
<td>4 (2.0)</td>
<td>2 (3.0)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Rash n (%)</td>
<td>2 (1.0)</td>
<td>2 (3.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mood change n (%)</td>
<td>22 (11.1)</td>
<td>4 (6.1)</td>
<td>5 (7.7)</td>
<td>13 (19.1)</td>
</tr>
<tr>
<td>Confusion n (%)</td>
<td>28 (14.1)</td>
<td>10 (15.2)</td>
<td>7 (10.8)</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Anxiety n (%)</td>
<td>20 (10.1)</td>
<td>8 (12.1)</td>
<td>10 (14.9)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Nervousness n (%)</td>
<td>45 (22.6)</td>
<td>17 (25.8)</td>
<td>14 (21.5)</td>
<td>14 (20.6)</td>
</tr>
<tr>
<td>Headache n (%)</td>
<td>24 (12.1)</td>
<td>12 (18.2)</td>
<td>8 (12.3)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Itch n (%)* yes</td>
<td>12 (6.0)</td>
<td>5 (7.6)</td>
<td>3 (4.6)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Dizziness n (%)*</td>
<td>19 (9.5)</td>
<td>11 (16.7)</td>
<td>6 (9.2)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Dry mouth n (%)</td>
<td>26 (13.1)</td>
<td>13 (19.7)</td>
<td>4 (6.2)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Racing heart n (%)</td>
<td>28 (14.1)</td>
<td>11 (16.7)</td>
<td>8 (12.3)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Chest pain n (%)</td>
<td>3 (1.5)</td>
<td>3 (4.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Numbness/Tingling n (%)</td>
<td>6 (3.0)</td>
<td>4 (6.1)</td>
<td>2 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Blurred vision n (%)</td>
<td>27 (13.6)</td>
<td>10 (15.2)</td>
<td>9 (13.8)</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>Vomiting n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal urine n (%)</td>
<td>2 (1.0)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Sweating n (%)</td>
<td>18 (9.0)</td>
<td>8 (12.1)</td>
<td>8 (12.3)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Extreme tiredness n (%) no</td>
<td>49 (24.6)</td>
<td>15 (22.7)</td>
<td>21 (32.3)</td>
<td>13 (19.1)</td>
</tr>
<tr>
<td>Nausea n (%)</td>
<td>2 (1.0)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Swollen hands n (%)</td>
<td>3 (1.5)</td>
<td>2 (3.0)</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Vertigo n (%)</td>
<td>16 (8.0)</td>
<td>8 (12.1)</td>
<td>4 (6.2)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Upset stomach n (%)</td>
<td>4 (2.0)</td>
<td>3 (4.5)</td>
<td>0 (0.0)</td>
<td>0</td>
</tr>
<tr>
<td>Slowing heart n (%)</td>
<td>7 (3.5)</td>
<td>2 (3.0)</td>
<td>3 (4.6)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Weakness n (%)</td>
<td>10 (5.0)</td>
<td>4 (6.1)</td>
<td>2 (3.1)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Drowsiness n (%)</td>
<td>33 (16.6)</td>
<td>14 (21.2)</td>
<td>8 (12.3)</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Other n (%)</td>
<td>5 (2.5)</td>
<td>5 (7.6)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| Total number detected symptoms | 415 | 175 | 126 | 114 |

Note. SE= side effect; * induced symptoms

Chi-square tests showed that more participants reported at least one symptom in the Modafinil Placebo group (84.8%), than in the Natural History group (69.1%) (χ²(1)=4.66, p<.05) and marginally more than in the Open Placebo group.
(70.8%, $\chi^2(1)=3.77$, $p=.052$, see Figure 26). The experimenter witnessed scratching in 16 participants in the Modafinil Placebo, 13 in the Open Placebo and 12 participants in the Natural History group ($\chi^2(2)=0.91$, $p=.63$).

Figure 26: Percentages of participants reporting symptoms and side effects

3.7.7 Differences in side effect reporting the two placebo groups

Of the 175 symptoms that were reported in the Modafinil Placebo group 93 (53.14%) were attributed as side effects (see Figure 27 for an overview of individual symptoms), whereas only 18 of the 126 symptoms (14.29%) in the Open Placebo group were attributed as side effects. Both the number of reported side effects (Mann Whitney U=1189, $z=5.144$, $p<.001$; see Figure 27) and the number of participants reporting at least one side effect ($\chi^2(1)=31.32$, $p<.001$) was significantly higher in the Modafinil Placebo than the Open Placebo group.
Figure 27: Number of symptoms and side effects in the Modafinil Placebo Group

- nervousness
- extreme tiredness
- drowsiness
- dry mouth
- headache
- racing heart
- dizziness
- blurred vision
- confusion
- vertigo
- sweating
- anxiety
- other symptoms
- itch
- weakness
- numbness/tingling
- mood change
- upset stomach
- chest pain
- slowing heart
- swollen hands
- rash
- difficulty breathing
- nausea
- abnormal urine
- vomiting
3.7.8 Medication beliefs and other psychological characteristics predict symptom reporting

Participants who had stronger concerns (IRR=1.22, 95% CI [1.03, 1.45], \(p<.05\)) and higher necessity beliefs (IRR=1.46, 95% CI [1.13, 1.87], \(p<.01\)) about the study pill reported significantly more symptoms.

Perceived sensitivity to medicines was associated with increased symptom reporting only when participants were led to believe they were taking active Modafinil, whereas negative affect, somatization and self-reported attention increased side effect reporting across all three experimental groups (see Table 21). Body awareness (SBA) was associated with symptom reporting in the Open Placebo group only.

Table 21: Univariate negative binomial regression models predicting symptom reporting by experimental group

<table>
<thead>
<tr>
<th>IRR [95% CI]</th>
<th>Modafinil Placebo (n=66)</th>
<th>Open Placebo (n=65)</th>
<th>Natural History (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSM</td>
<td>1.44 [1.11, 1.89]**</td>
<td>1.33 [0.90, 1.96]</td>
<td>1.17 [0.77, 1.77]</td>
</tr>
<tr>
<td>General Harm</td>
<td>1.31 [0.99, 1.73]†</td>
<td>0.87 [0.61, 1.24]</td>
<td>1.37 [0.87, 2.15]</td>
</tr>
<tr>
<td>General Overuse</td>
<td>1.16 [0.88, 1.54]</td>
<td>1.11 [0.77, 1.58]</td>
<td>1.39 [0.94, 2.04]</td>
</tr>
<tr>
<td>General Benefit</td>
<td>0.92 [0.64, 1.34]</td>
<td>1.36 [0.78, 2.35]</td>
<td>0.68 [0.43, 1.11]</td>
</tr>
<tr>
<td>NA</td>
<td>1.77 [1.28, 2.44]**</td>
<td>1.58 [1.08, 2.30]*</td>
<td>1.66 [1.15, 2.38]**</td>
</tr>
<tr>
<td>PHQ-15</td>
<td>1.08 [1.02, 1.13]**</td>
<td>1.13 [1.04, 1.23]**</td>
<td>1.12 [1.05, 1.92]**</td>
</tr>
<tr>
<td>SBA</td>
<td>0.96 [0.75, 1.24]</td>
<td>1.89 [1.30, 2.75]**</td>
<td>1.01 [0.74, 1.34]</td>
</tr>
<tr>
<td>Self-attention</td>
<td>1.19 [1.05, 1.36]***</td>
<td>1.31 [1.10, 1.56]**</td>
<td>1.22 [1.06, 1.41]**</td>
</tr>
</tbody>
</table>

*Note:* † \(p<.10\), *\(p<.05\), **\(p<.01\); IRR=Incidence Rate Ratio, PSM=Perceived Sensitivity to Medicines Scale, NA=Negative Affect, PHQ=Patient Health Questionnaire, SBA=Scale of Body Awareness, self-attention=self-reported attention to bodily sensations during study

**Induced symptoms**

Participants who reported experiencing itch in the Deceptive Placebo condition had significantly higher PSM scores (M=2.52) than those who didn’t notice this sensation (M=1.85, \(t(64)=2.16, p<.05\)), all other predictors \(p>.05\). No significant differences were detected between participants who did or did not report dizziness.

3.7.9 Medication beliefs and other psychological characteristics predict side effect reporting

Participants who had stronger concerns (IRR=2.10, 95% CI [1.43, 3.06]) and necessity beliefs (IRR=2.64, 95%CI [1.49, 4.65], \(p<.001\)) about the study pill reported significantly more side effects.
Participant who believed they were taking active Modafinil reported more side effects if they had greater perceived sensitivity to medicines (IRR=1.68, 95% CI[1.13,2.52], p=.011) and believed pharmaceutical medicines to be generally harmful (IRR=1.70, 95% CI[1.09, 2.67], p=.019), all other pharmaceutical schemas ps>.13). The number of reported side effects in the Modafinil Placebo group was also higher for participants with greater negative affectivity (IRR=2.37, p<.001) and those who reported having paid closer attention to their bodily sensations during the study (IRR=1.37, 95% CI[1.11, 1.69], p<.01), but not those with higher somatization (IRR=1.08, 95% CI[0.99, 1.67], p=.07).

Only self-reported attention to bodily sensations (IRR=2.12, 95% CI[1.23, 3.64], p<.01) was associated with side effect reporting in the Open Placebo group (all other predictors ps>.05).

3.7.10 The role of self-reported attention

Participants who expected that they were taking an active drug (Deceptive Placebo group) reported paying significantly more attention to changes in bodily sensations during the study, than participants who did not expect to take an active drug either because it was correctly labelled as placebo (Mean difference =-1.08; 95%CI[-.173; -.42]) or because they were given no pill (Mean difference=-1.22; 95%CI[-.187, -.057], both ps<.05), see also Figure 28.

Figure 28: Self-reported attention by experimental group

Pearson correlations were used to explore whether individuals with more negative beliefs about medication paid closer attention to changes in bodily sensations. As predicted participants who had stronger concerns about the study pill
reported paying closer attention to bodily changes ($r = .211, p < .05$). Interestingly, participants with higher perceived necessity for the study pill also paid greater attention to bodily changes ($r = .263, p < .01$).

Participants with more negative pharmaceutical schemas (beliefs that medicines are generally harmful, high perceived sensitivity to medicines) did not pay significantly more attention to changes in bodily sensations in the Deceptive Placebo group (nor the other experimental groups, all $rs < .15, ps > .05$). In line with theoretical predictions, participants with higher general body awareness ($r = .262, p < .05$) as measured with the SBA, reported paying more attention to bodily changes in the Deceptive Placebo Group ($r = .262, p < .05$) and across the whole sample ($r = .204, p < .01$).

### 3.7.11 The role of expectations

Pearson correlations were used to examine whether participants with more negative beliefs about medicines expect their body to feel worse when taking Modafinil. As expected participants who believed pharmaceutical medicines to be more harmful ($r = -.194$) and less beneficial ($r = -.232$) and who perceived themselves as more sensitive to the effects of medicines ($r = -.337, ps < .01$) expected their bodies to feel worse when taking Modafinil (see Table 22).

<table>
<thead>
<tr>
<th></th>
<th>Expectations of bodily wellbeing VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Modafinil Placebo Group (n=66)</td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-.204</td>
</tr>
<tr>
<td>BMQ General Overuse</td>
<td>.003</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>.150</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>-.384**</td>
</tr>
<tr>
<td>BMQ Specific Concern</td>
<td>-.384**</td>
</tr>
<tr>
<td>PSM</td>
<td>-.414**</td>
</tr>
</tbody>
</table>

**Note.** **p < .01; BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale; VAS=Visual Analogue Scale

### 3.7.12 Differences in cognitive enhancement between experimental groups

Participants rated their cognitive performance as better than usual (50 scale midpoint equalling no change, see Table 23) in all experimental groups, but perceived cognitive enhancement was not significantly higher in the Modafinil Placebo compared to the Open Placebo ($t(129)=1.76, p=.08$) and Natural History group ($t(132)=0.16, p=.87$).
Participants recalled on average 10 (out of a possible 14) forward and 10 (out of 14) backward digit sequences. Participants in the Modafinil Placebo group recalled significantly more forward digit sequences than participants in the Open Placebo group \((t(129)=2.09, p=.039)\) but not those in the Natural History group \((t(132)=1.84, p=.067)\). Backward digit span was also significantly higher for participants in the Modafinil Placebo than the Open placebo group \((t(129)=2.05, p<.05)\), but not the Natural History group \((t(132)=0.15, p=.88)\).

On average 24 (out of a possible 30) targets were correctly detected in the CPT-AX. Performance in the CPT-AX (number of correct target detections, reaction times) did not differ between the three experimental groups \((all ps>.05)\).

Table 23: Descriptive placebo and nocebo related outcomes

<table>
<thead>
<tr>
<th>Outcomes (M, SD)</th>
<th>Modafinil Placebo ((n=66))</th>
<th>Open Placebo ((n=65))</th>
<th>Natural History ((n=68))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom related outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>2.65 (2.27)(^{1,2})</td>
<td>1.92 (2.24)(^{3})</td>
<td>1.68 (1.75)(^{2})</td>
</tr>
<tr>
<td>Side Effects</td>
<td>1.41 (1.97)(^{4})</td>
<td>0.27 (0.86)(^{4})</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Cognitive Enhancement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WDST Forward Digit Span</td>
<td>10.79 (2.04)(^{4})</td>
<td>9.97 (2.42)(^{4})</td>
<td>10.09 (2.33)</td>
</tr>
<tr>
<td>Backward Digit Span</td>
<td>10.41 (2.08)(^{5})</td>
<td>9.57 (2.59)(^{5})</td>
<td>10.35 (2.15)</td>
</tr>
<tr>
<td><strong>CPT-AX</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct target responses</td>
<td>25.94 (3.70)</td>
<td>24.46 (5.98)</td>
<td>25.54 (3.10)</td>
</tr>
<tr>
<td>RT in msec</td>
<td>175.06 (60.27)</td>
<td>195.96 (98.99)</td>
<td>171.61 (64.33)</td>
</tr>
<tr>
<td>Perceived Cognitive Enhancement</td>
<td>57.14 (12.15)</td>
<td>53.38 (12.22)</td>
<td>57.53 (14.73)</td>
</tr>
</tbody>
</table>

*Note.\(^{1,2,3,4}\) denote significant between group differences \((p<.05, two-sided)\), all other comparisons \(p>.05\); WDST=Wechsler Digit Span Test, CPT-AX=Continuous Performance Test-AX version, RT=reaction time, msec=milliseconds*

### 3.7.13 Placebo/nocebo effects without deception

Participants’ self-reported mental ability was not better in the Open Placebo than the Natural History group \((t(131)=1.76, p=.080)\). There was no difference in recalled forward \((t(131)=0.29, p=.80)\), and backward digits \((t(131)=1.90, p=.06)\) between the two groups. Participants in the Open Placebo group did not detect more CPT-AX targets correctly \((t(131)=1.31, p=.19)\) and were not faster in the correct detection of targets \((t(131)=1.69, p=.09)\).
A Mann-Whitney U-Test showed that participants in the Open Placebo Group did not report significantly more symptoms than participants in the Natural History group (Mann Whitney U=2139, z=0.33, p=.74), indicating that there was no “nocebo with deception”-effect.

**3.7.14 Participants' reactions to debriefing**

The experimenter informed participants about the use of deception and explained the rationale behind the study immediately after the experimental session ended. None of the participants expressed being concerned about the deception and the overwhelming majority of participants readily acknowledged the scientific importance of using deception in this study. Several participants mentioned that they had originally signed up to the study to “try out” real Modafinil and to find out more about Modafinil’s efficacy and safety. However participants knew from the start that they might not receive Modafinil (because of the possibility of being randomized to the placebo or natural history control arm). In addition, many participants stated that they were actually interested in finding out to which extent Modafinil’s cognition and concentration improving effect was due to a placebo effect. Participants who wanted to find out more about the efficacy and safety of Modafinil in non-clinical samples were pointed to existing publications on the topic.

**3.8 Discussion**

**3.8.1 Summary of findings**

This was one of the first studies to demonstrate differences in symptom reporting in participants randomized to deceptive placebo verus open-label placebo or no treatment. Participants who believed that they were given active Modafinil (Deceptive Placebo) reported significantly more symptoms than participants given open-label placebo or no pill. Participants who were told that they had received an active drug were more likely to attribute these symptoms as side effects to the medication than those who were correctly informed that it was a placebo. Symptom reporting was frequent in all three experimental groups, however the induction of symptoms via the visual stimuli did not produce a strong effect (i.e. induced symptoms were not more frequent than other symptoms).

In addition I also systematically examined the role of several psychological characteristics in nocebo responding. In particular, this was the first study to show that specific medication beliefs and general pharmaceutical schemas are associated with nocebo responding. Participants who had stronger Concerns and higher
Necessity beliefs about the study pill reported significantly more symptom and side effects. More negative pharmaceutical schemas (high perceived sensitivity to medicines, beliefs that pharmaceuticals are generally harmful) were also associated with increased symptom and side effect reporting in the Deceptive Placebo group. Negative affect, somatization and self-reported attention to bodily sensations predicted symptom reporting across all experimental groups. Pharmaceutical schemas and negative affect also predicted how many of these symptoms were consequently attributed as side effects to Modafinil. These findings support the postulated relationship between negative medication beliefs and side effect reporting.

Participants who believed pharmaceutical medicines to be more harmful and less beneficial and who perceived themselves as more sensitive to their effects expected their body to feel worse when taking Modafinil. This lends support to the claim that medication beliefs may affect nocebo responding by influencing side effect expectations. Although general pharmaceutical schemas were not associated with self-reported attention bodily changes, specific beliefs about the study pill did predict how closely participants monitored their bodily sensations during the trial: As predicted, those who had stronger concerns about the study pill reported paying closer attention to changes in bodily sensations. Somewhat surprisingly, perceptions of necessity for the study pill were also related to increased monitoring of bodily sensations.

There was also some evidence for a placebo effect on short term memory as measured by the digit span test in the Deceptive Placebo group (compared to Open Placebo). However there was no difference in sustained attention (CPT-X outcomes) or self-reported cognitive enhancement.

Participants in the Open Placebo group performed marginally worse in both the WDST and CPT-AX than participants in the Natural History group, indicating that there was no “placebo without deception” effect. There was also no evidence for a “nocebo without deception” effect, as participants in the Open Placebo group did not report significantly more symptoms than participants in the Natural History group.

3.8.2 Integration with previous literature

There have been repeated calls for the use of appropriate control groups to study nocebo effects in the past (Colloca & Miller, 2011; Enck et al., 2011), but
surprisingly few studies examining side effects to placebo have done so (Neukirch & Colagiuri, 2014). This study makes an important contribution to the literature on nocebo effects by showing that the expectation of taking an active drug (Deceptive Placebo condition) leads to increased symptom and side effect reporting compared to a Natural History and Open Placebo condition where there is no such expectation. The study clearly illustrates the need for appropriate control groups to assess the magnitude of nocebo effects. Simply labelling all symptoms reported by participants receiving pharmacologically inactive placebo as nocebo effects would largely overestimate nocebo effects. In fact the majority of participants in the Natural history group (69.1%) also reported symptoms and not all reported symptoms were subsequently labelled as side effects. This finding is in line with studies showing that symptoms are common even in healthy members of the general population (Hiller, Rief, & Brähler, 2006; Reidenberg & Lowenthal, 1968).

Current research on the role of psychological characteristics on nocebo effects (see Webster et al., 2016) is sparse and suffers from a lack of consistency. This study makes an important contribution to the field by systematically examining whether prospectively measured psychological variables (i.e. medication beliefs, negative affect, somatization) are associated with symptom reporting and attribution in participants randomized to placebo or no treatment. The role of medication beliefs in nocebo responding has been theoretically acknowledged in the past (Faasse & Petrie, 2013; Horne, 1999). Yet this was the first study to show that medication beliefs were associated both with the detection and attribution of symptoms as side effects following deceptive placebo administration. Findings of the study suggest that the effect of medication beliefs is specific to the medication taking context, whereas somatization and negative affect were also associated with increased symptom reporting when no medication was given. My findings further confirmed the importance of negative affectivity in symptom (Mora, Halm, Leventhal, & Ceric, 2007; Watson & Pennebaker, 1989) and side effect reporting to active medication (Foster et al., 2008; Rabin, Ward, Leventhal, & Schmitz, 2001) and placebo. A previous study with asthmatic patients showed for example that individuals with higher negative affectivity reported greater airway obstruction (Put et al., 2004) after inhaling from a placebo inhaler, described as bronchoconstrictor. As one would expect from the literature on medically explained symptoms (Rief & Broadbent, 2007), somatization was also associated with increased symptom reporting, but not the attribution of these symptoms as side effects.
In contrast to previous studies (Kaptchuk et al., 2010; Kelley, Kaptchuk, Cusin, Lipkin, & Fava, 2012), I did not find evidence for the claim that placebos can be effective without deception. My study did however differ in several important aspects: In contrast to other studies where placebos were described as having powerful effects on the body and mind, I used a more standard definition that was more in line with typical descriptions of placebos in randomized controlled trials (Bishop et al., 2012). It is obvious that the former description is more likely to induce positive expectations (as well as a potential demand effect (Roscoe et al., 2006), see below), which are known to influence placebo effects. In addition, whereas the goal of the open-placebo “treatment” in the previous studies was symptom relief (reducing negative effects) the goal of the “treatment” in this study was to enhance cognitive performance (increasing a positive effect). It is also important to note here that most of the previous studies on the open-placebo effect used subjective outcome measures, whereas I measured cognitive enhancement using standardized and arguably more objective measures (WDS, CPT-AX). It is conceivable that at least some participants in the earlier studies on the “placebo without deception”-effect felt compelled to go along with the researchers’ suggestions of symptoms improvement.

3.8.3 Strengths and limitations

My study design has some clear strengths, but like all research has some limitations that may affect the validity of findings. The study design allowed me to examine both placebo (cognitive enhancement) and nocebo effects within the same study. Two different control groups (Natural History and Open Placebo) were used and not only symptom reporting, but also the attribution of symptoms as side effects was examined. However further analysis is required to examine differences between symptoms that were attributed as side effects and those that were not. In addition, I used both subjective (perceived mental ability) and objective placebo and nocebo outcome measures (WDS, CPT-AX, scratching), reducing the likelihood of reporting bias. Using the same randomization code in both placebo conditions, allowed the experimenter to remain blind to the allocation in these conditions (but not the Natural History Group). Although this technique and the computerized administration of measures reduced the likelihood of experimenter-effects, it cannot be completely ruled. I served as experimenter for all participants and was therefore aware of the hypotheses of the study. Participants in this study were healthy and not taking any medication, ruling out any concomitant pharmacological effects. Despite this advantage it is not certain that the findings can be generalized to patients. In
addition, students who volunteer for a study to assess drug safety have potentially more positive attitudes towards medicines and perceive themselves as less vulnerable to negative medication effects.

### 3.8.4 Clinical implications

Findings from the study have potential clinical application. Side effects, be they due to pharmacological or nocebo related factors, are likely to reduce adherence. This may lead to a loss in treatment benefit, which may consequently affect morbidity and mortality (Chisholm-Burns & Spivey, 2011). Given the association between medication beliefs and both adherence and side effects it may be helpful if clinicians speak to patients about their concerns and perceptions of sensitivity to medicines when prescribing treatment. The BMQ and PSM may serve as a templates to aid discussion. In addition, the findings suggest that interventions to modify unfounded concerns about the harmfulness of medications (Petrie et al., 2012) and personal sensitivity may be effective in reducing non-specific side effects.
Chapter 4: Medication beliefs predict the attribution of an unrelated symptom as a medication side effect (Study 3)

4.1 General overview and study aims

The two previous studies illustrated that individuals with stronger concerns and more negative pharmaceutical schemas tend to report more side effects when taking active medication (Study 1) or a mere placebo (Study 2). Several putative underlying mechanisms linking medication beliefs to side effects (e.g. expectations, somatic focus and attribution of symptoms) were identified in Study 2. In the placebo study (Study 2) the tendency to attribute symptoms as side effects was increased for people with stronger concerns about the study pill, higher perceived sensitivity to medicines and stronger harm beliefs. A placebo pill was used to examine the role of medication beliefs in side effect attribution in the previous study. It is yet to be shown whether these effects might be relevant for active medication and would affect non-adherence. But it seems reasonable to assume that individuals who attribute a symptom to the medication rather than the disease or other medication-unrelated factors (e.g. common ‘everyday’ symptom, natural fluctuation, emotions, etc.) would be more inclined to discontinue treatment (see also 1.5.2).

The current study starts to examine these questions by using an analogue scenario design to probe whether medication beliefs are associated with the misattribution of a common ‘everyday’ symptom as a side effect to a fictitious asthma medication and whether this in turn influences behavioural intentions to stop treatment. Demonstrating an association between medication beliefs and the misattribution of common symptoms as side effects would thus add to our understanding of mechanisms underlying the relationship between medication beliefs, side effects and medication taking behaviours (see Research Question 2).

Please note that findings from the study presented in this chapter have been published in the Journal of Psychosomatic Research (Heller et al., 2015) and some figures and tables are reproduced from this previous publication.

4.2 Theoretical background

Many patients will experience a large number of symptoms that resemble medication side effects (Barsky et al., 2002). As already outlined in the Introduction (see 1.5.2), even people without any underlying disease commonly report
symptoms that could be mistaken for side effects to medication (Khosla, Bajaj, Sharma, & Mishra, 1992; Meyer, Troger, & Rohl, 1996; Reidenberg & Lowenthal, 1968). One of the first studies examining the frequency of common symptoms in healthy volunteers was conducted by Reidenberg and Lowenthal (1968). In this study 81% of 414 healthy individuals reported having experienced symptoms in the previous three days. The five most commonly reported symptoms were fatigue, nasal congestion, inability to concentrate, bleeding gums and headaches. A replication study conducted almost 30 years later (Meyer et al., 1996) showed almost identical findings: fatigue, nasal congestion, inability to concentrate, bleeding gums and headache all featured again as the most commonly reported symptoms. Such symptoms could potentially be misattributed as side effects by someone taking medication.

Further support for the idea that some patients may falsely attribute common symptoms as side effects comes from studies examining side effects to placebo. An early review of side effects in the placebo arm of RCTs (Pogge, 1963), examining data from 67 RCTs (with 14 different types of medications) found that side effects relating to the central nervous system (CNS, e.g. dizziness, fatigue) and gastrointestinal symptoms (e.g. dry mouth, constipation) were the most prevalent. Most of the 38 side effects identified in this review were common physical symptoms. In a review of placebo side effects in RCTs for anti-depressant medication (Winfried Rief, et al., 2009), the vast majority of identified side effects were also common physical symptoms, with CNS (e.g. fatigue, drowsiness, dizziness, insomnia) and gastro-intestinal symptom clusters (e.g. dry mouth, constipation, abdominal pain, nausea and diarrhoea) again predominant.

In addition, a recent study analysing information about side effects for 15 commonly prescribed drugs (e.g. simvastatin, metoprolol) from various sources (e.g. regulatory agency, patient websites, patient leaflets) showed that many common symptoms are also frequently listed as side effects to active medication (Tan et al., 2014). For example back pain, fatigue, headache, muscle pain and joint pain were listed as symptoms in all 15 of the examined drugs. The authors compared this to results from a previous population based survey, that assessed the prevalence of common symptoms in New Zealand (Petrie, Faasse, Crichton, & Grey, 2014). All of the above listed side effects were reported by more than 20% of the participants in this survey.
Taken together these findings suggest that common symptoms are not only frequent but also phenomenologically similar to side effects, raising the possibility that some patients may falsely label them side effects. Yet so far little is known what drives individuals to attribute these common symptoms as side effects. I postulate that the tendency to falsely label common symptoms as side effects will be increased for participants with more negative beliefs about medicines (see also Chapter 1).

I decided to test the role of medication beliefs in the misattribution of common symptoms using an analogue scenario based approach. Participants were given a scenario where they had to imagine they were taking an asthma medication and then experiencing a headache (not listed as a side effect in the patient leaflet). Although this was an analogue study, I wanted to make the scenario presented as concrete and believable to participants as possible. I therefore chose a common disease, asthma (Asher et al., 2006), in the hope that participants who were recruited through convenience online sampling were familiar with the disease. Headache was selected because it is a common ‘everyday’ symptom and side effect (Reidenberg & Lowenthal, 1968; Stovner, Zwart, Hagen, Terwindt, & Pascual, 2006; Tan et al., 2014). In addition, several studies have shown that patients with asthma reported headache as a side effect to placebo (Löfdahl et al., 1999; Wise et al., 2009). A fictitious asthma medication (named “Molair”) was chosen in order to rule out familiarity effects.

In addition, I also systematically varied information about this fictitious medication, presenting it as either highly or moderately effective or having either frequent or rare side effects. It is likely that such information about an unfamiliar drug influences individuals ‘concerns and perceptions of necessity and concerns: One would for example expect to find increased concerns and greater side effect expectations for participants randomized to high side effect frequency information.

4.3 Hypotheses

I hypothesized that participants with negative medication beliefs would be more likely to misattribute the headache symptom as a side effect and to subsequently intend to stop the medication. I also explored whether the hypothesized relationships were similar for participants with and without self-reported previous asthma diagnosis and persisted when controlling for negative affect as a potential confounder.
In addition, I tested whether changing descriptions of the efficacy and side effect frequency of the fictitious asthma drug changed specific medication beliefs and examined whether the relationship between medication beliefs and symptom misattribution/behavioural intentions was robust across this information variation.

4.4 Method

Data was collected online with Qualtrics survey software in three consecutive waves. Within each wave, participants were randomized to one of two descriptions of efficacy or side effect frequency of the fictitious medication Molair (see section 4.4.2.2 below). In all waves participants completed validated measures of medication beliefs and the symptom attribution vignette. Negative affect was assessed in wave three only.

4.4.1 Participants

4.4.1.1 Inclusion and exclusion criteria

Participants were included if they were over 18 years of age. Individuals with and without self-reported past asthma diagnosis were eligible to participate. Only one response was allowed per participant (across the three waves) to ensure independence of responses. This was achieved by excluding repeat entries from the same IP address.

4.4.1.2 Recruitment

Participants were recruited via the Crowdflower crowdsourcing platform (https://www.crowdflower.com). Crowdflower allows researchers to advertise surveys to subscribers from various online job boards (like Amazon MTurk, Crowd Guru, DailySurveyPanet, etc.). Subscribers receive a small monetary reward (around $0.30 in this study) for participating in these surveys. A small proportion (n=8) of participants in wave three were recruited via an online research website (Psychological Research on the Net) from where they were redirected to the online survey link. Online sampling and data collection has demonstrated good reliability in studies of decision-making, personality and health (Buhrmester, Kwang, & Gosling, 2011; Ritter, Lorig, Laurent, & Matthews, 2004; Shapiro, Chandler, & Mueller, 2013). For example Goodman and colleagues (Goodman, Cryder, & Cheema, 2012) replicated standard experiments on decision making biases (e.g. loss aversion, present bias, certainty effect) in both MTurk participants and community/student participants with almost no significant differences in effect size between the samples. With this type of online recruitment it is however impossible to compute a
response rate (i.e. it is not possible to know how many people saw the survey advertisement, but decided not to participate).

### 4.4.2 Materials

#### 4.4.2.1 Asthma information

Participants read information about asthma (see Appendix H), which was structured according to Leventhal’s Common Sense Model of illness representations (Diefenbach & Leventhal, 1996; Leventhal et al., 1992). It contained information about asthma causes (airway inflammation and sensitization), known asthma triggers (e.g. exercise, pollen), likely consequences of asthma and provided brief information about asthma management (cure/control e.g. medicines and lifestyle changes). It also listed typical asthma symptoms (identity e.g. difficulty breathing, wheezing) and provided information about the episodic nature of asthma symptoms (timeline).

#### 4.4.2.2 Molair patient information leaflet

Participants were randomized to one of four written patient information leaflets (PILs) of the fictitious asthma drug Molair (see Appendix I). Molair was modelled on the existing asthma medication Montelukast (Committee & Britain, 2012), an oral leukotriene receptor antagonist, which is commonly used for the treatment and prevention of asthma and seasonal allergic rhinitis.

All four PIL versions contained the same information about Molair’s mechanism of action (blocking the action of leukotrienes) and contained the same list of eight side effects (rash, dizziness, itch, muscle or joint pain, abdominal pain, yellowing of the skin, fatigue, flu like symptoms) in randomized order. All listed side effects were based on published side effects of Montelukast. Please note that headache (the target-symptom to probe misattribution) was not listed as one of Molair’s side effects.

Information about Molair’s efficacy and the frequency of side effects differed according to the PIL version:

1) The “High Efficacy PIL” stated that Molair is highly effective with ‘86.6% of patients reporting a strong improvement in daytime asthma symptoms’ and contained no information about the frequency of side effects.
2) The “Moderate Efficacy PIL” stated that Molair is less effective, ‘53.2% of patients reported a small improvement’ and contained no information about the frequency of side effects.

3) The “Low Side Effect Frequency PIL” contained general efficacy information “Molair can be effective in preventing asthma symptoms.” and stated that side effects were rare, occurring “in less than 1 in 100 people”.

4) The “High Side Effect Frequency PIL” contained general efficacy information stating that “Molair can be effective in preventing asthma symptoms.” and indicated that side effects were frequent, occurring “in more than 45 out of 100 people”.

The information was in line with published data on the efficacy of Montelukast (Creticos, 2003; Diamant, Mantzouranis, & Björner, 2009; Virchow & Bachert, 2006) and reported side effect rates to Montelukast relative to placebo (rxlist.com for low frequency) and placebo in randomized controlled trials (for high frequency) (Mitsikostas, Mantonakis, & Chalarakis, 2013; Papadopoulos & Mitsikostas, 2012; Stathis et al., 2013).

4.4.3 Measures

4.4.3.1 Symptom misattribution and behavioural intention measures

Participants read the following scenario: “Imagine you are suffering from asthma. You have been taking one 4mg tablet of Molair every day for the last two weeks. At the beginning of the third week you get a headache.”

After reading this vignette participants were asked the following two questions:

1) Symptom misattribution:

“What do you think is the most probable reason for this?” Participants had a choice between five different options (side effect of Molair, onset of a cold, eyestrain, stress, no particular reason). Symptom misattribution was defined as indicating “side effect of Molair” as most likely reason for the headache symptom.

2) Behavioural intention to stop treatment:

Participants indicated which action(s) they would take following the start of the headache. Participants could select any of the following actions: stop taking
Molair, speak to a doctor or pharmacist, take over the counter painkiller, rest, none. Participants were allowed to select as many options as they wished and were allowed to specify other reasons in an additional textbox. Behavioural intention was operationalized as selecting “stop taking Molair”.

4.4.3.2 Beliefs about Medicines Questionnaire

Participants’ beliefs about pharmaceutical medicines in general were assessed with the standard BMQ-General (see section 1.3.2.1). Participants’ beliefs about Molair were assessed with an adapted version of the BMQ-Specific (see Appendix L) which was administered after participants read the Molair PIL. Participants were asked to imagine that they personally had asthma and had been prescribed Molair, before indicating the extent to which they agreed with statements other people had made about Molair. All BMQ-Specific and BMQ-General subscales showed good internal consistency (see Table 24).

Table 24: Internal consistency BMQ subscales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Number of items</th>
<th>Cronbach’s alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ General Overuse</td>
<td>4</td>
<td>.77</td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>4</td>
<td>.76</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>4</td>
<td>.91</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>5</td>
<td>.88</td>
</tr>
<tr>
<td>BMQ Specific Concern</td>
<td>6</td>
<td>.84</td>
</tr>
</tbody>
</table>

Note. BMQ=Beliefs about Medicines Questionnaire

4.4.3.3 Perceived Sensitivity to Medicines Scale

The PSM scale (Horne et al., 2013b) was used (see section 1.3.2.2) to assesses participants’ beliefs about their personal sensitivity to medicines. The internal reliability was excellent (Cronbach’s α=.91).

4.4.3.4 Measures to assess fidelity of PIL information variations (Efficacy and Side Effect VAS)

Two sets of visual analogue scales (VAS) were used to test whether the PIL variations changed perceptions of Molair (see Appendix J). Four VAS measured participants expectations of side effects (e.g. “How frequently do you think people in general develop side effects when taking Molair?” rated from 0=never to 100=always). Three VAS were used to measure efficacy perceptions (e.g. “How effective do you think Molair is in general for the prevention of asthma symptoms?” rated from 0=not effective at all to 100=extremely effective). Mean scores were computed for both sets of VAS. Internal consistency was high for both sets of VAS, with Cronbach’s αs of .88 and .90 respectively.
4.4.3.5 Positive and Negative Affect Schedule (PANAS)

State Negative Affect was assessed with the short form of the PANAS (Mackinnon et al., 1999) with instructions to focus on current feelings. Ten negative (e.g. distressed, upset) adjectives were rated on 5-point Likert scales (1=not at all to 5=extremely). State Negative Affect (State NA\textsubscript{PANAS}) scores were computed by averaging scores for all negative adjectives. Internal consistency was high (Cronbach’s $\alpha=.95$).

4.4.3.6 State and Trait Anxiety Inventory (STAI)

The STAI Form X (Spielberger, Gorsuch, & Lushene, 1970) was used to measure State (State NA\textsubscript{STAI}: 20-State Negative Affect items e.g. “I am tense.”) and Trait Negative Affect (Trait NA\textsubscript{STAI} 20-items e.g. “I worry too much over something that doesn’t matter.”). Items were rated on 4-point Likert scales (from 1=almost never to 4=almost always). Subscale scores were computed by averaging state and trait item scores. Internal consistency for both subscales was excellent (both Cronbach’s $\alpha=.91$).

4.4.3.7 Demographics and reported asthma diagnosis

Participants were asked to state their gender, age, country of residence, first language and to indicate whether they had ever been diagnosed with asthma (henceforth ‘reported asthma diagnosis’).

4.4.4 Procedures

The UCL Research Ethics Committee classified the study as exempt from REC approval (anonymous online survey of a non-sensitive nature).

Data was collected using Qualtrics online software. Participants first read the consent form and indicated whether they agreed (or did not agree) to participate in the study by ticking the relevant response option. Participants then completed the PANAS and STAI (wave 3 only, see Figure 29), PSM and BMQ-General. Next they received information about asthma and were randomized to receive the different PILs using the computerized block randomization function in Qualtrics. The order of side effects in the PILs was determined through simple computerized randomization in Qualtrics.

After reading the information about Molair, participants completed the Efficacy and Side Effect VAS and BMQ-Specific. Finally, they completed the symptom misattribution and behavioural intention measure, and demographic
questions. After completing the study, participants received a short written
debriefing statement. It took participants on average 14 minutes to complete the
study.
Figure 29: Overview of procedures

**Efficacy – PIL variation**
Wave 1 (N=201)

**Side effect risk - PIL variation**
Wave 2 (N=249)
(As Wave 2, but with affect measures)

PSM, BMQ-General, Asthma Information

Randomisation to Molair PIL

- **n=98**
  - High Efficacy PIL
  - Molair is highly effective in preventing asthma symptoms

- **n=103**
  - Moderate Efficacy PIL
  - Molair is moderately effective in preventing asthma symptoms

- **n=245**
  - Low Side Effect Frequency PIL
  - Molair only rarely (in less than 1 out of 100 people) causes side effects

- **n=244**
  - High Side Effect Frequency PIL
  - Molair frequently (in more than 45 out of 100 people) causes side effects

Efficacy and Side Effect VAS, BMQ-Specific, Symptom Misattribution and Behavioural Intention Measures, Demographics and Reported Asthma Diagnosis

*Note.* PANAS=Positive and Negative Schedule; STAI=Stat Trait Anxiety Inventory; PSM=Perceived Sensitivity to Medicines Scale; BMQ=Beliefs about Medicines Questionnaire; PIL=Patient Information Leaflet, VAS=Visual Analogue Scale; Figure reproduced from Heller et al. (2015)
4.4.5 Statistical considerations

4.4.5.1 Sample size

The sample size needed to detect an association between medication beliefs and symptom misattribution was calculated using GPower version 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009). An estimated odds ratio of 1.57, based on the reported association between BMQ Concern scores and side effect reports in a large US online sample (Shiyanbola & Farris, 2010) was used to ascertain that 251 participants were needed to detect this univariate association with 80% power and a two-tailed alpha error probability of .05. Please note that the ordering of studies in this thesis does not reflect their chronological order. Odds ratios from the two previously presented studies (Studies 1-2) were not available at the time the sample size calculation was conducted.

4.4.5.2 Statistical analysis

Pearson correlations were used to examine associations between general and specific medication beliefs and perceived sensitivity to medicines. Independent t-tests assessed whether PIL variations changed Side Effect /Efficacy VAS ratings and specific beliefs about Molair.

Univariate logistic regression, t-tests and chi-square tests were used to explore whether symptom misattribution and behavioural intention were associated with general and specific medication beliefs, affect, demographic variables, reported asthma diagnosis, and PIL variations. Hierarchical logistic regression models tested for the effect of medication beliefs on both outcomes when controlling for PIL variations, affect and demographics in the models.

Moderation analysis (Hayes, 2013) was used to test whether the relationship between medication beliefs and both outcomes was similar for people with and without reported asthma diagnosis and across PIL variations. Results of logistic regression models are reported using odds ratios (ORs), which reflect the change in odds of the outcome associated with a 1-unit change in the predictor. ORs above 1 indicate increased odds of the outcomes, ORs below 1 indicate decreased odds of the outcomes. An OR of 1.5 constitutes a small, 3.5 a medium, and 9 a large effect size (Vacha-Haase & Thompson, 2004). Classification tables and the Hosmer Lemeshow Test (HLT) were used to assess model fit.
4.5 Results

4.5.1 Survey completion rates and data exclusions

In total 782 responses were recorded in Qualtrics across the three waves. Repeated responses from the same computer (n=26), responses from underage participants (n=2), and responses with missing data on the two main dependent variables were excluded (n=64). Medication beliefs did not differ between completers and non-completers (all ps>.05). Responses from 690 participants (wave 1=201, wave 2=249, wave 3=240) were retained.

4.5.2 Demographic characteristics and reported asthma diagnosis

Approximately two-thirds of respondents were female and around a third reported a past asthma diagnosis. Participants were mainly US residents (all other countries <1) and native English speakers (see Table 25). There were no significant differences in baseline characteristics between the different PIL conditions (see Table 25).

4.5.3 Medication beliefs reported asthma diagnosis

Independent t-tests demonstrated no significant differences between participants with and without reported asthma diagnosis in general and specific medication beliefs (ps>.05). Participants with a reported asthma diagnosis did however perceive themselves as more sensitive to the effects of medicines (M=2.72, SD=1.05) than those without (M=2.47, SD=0.97; t(685)= 3.05, p<.01).

4.5.4 Inter-correlations medication belief scales

Participants who had stronger concerns about Molair perceived pharmaceutical medicines as more harmful and over-prescribed by doctors (see Table 26). Participants with stronger benefit beliefs showed reduced concerns about Molair and stronger beliefs in its necessity. Perceptions of higher personal sensitivity to medicines were significantly positively correlated with beliefs that medicines are fundamentally harmful and overprescribed as well as Concerns about Molair (all ps<.01, see Table 26).
Table 25: Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>Wave 1 Efficacy information variation (N=201)</th>
<th>Wave 2 Side effect likelihood variation (N=249)</th>
<th>Wave 3 Side Effect Likelihood variation with affect measures (N=240)</th>
<th>Waves 1-3 combined (N=690)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years mean (SD)</strong></td>
<td>34.8 (12.6)</td>
<td>36.2 (11.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>37.27 (14.2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>36.16 (12.8)</td>
<td>p=.127</td>
</tr>
<tr>
<td><strong>Gender n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>77 (38.3)</td>
<td>73 (29.3)</td>
<td>86 (36.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>236 (34.3)</td>
<td>p=.106</td>
</tr>
<tr>
<td>Female</td>
<td>124 (61.7)</td>
<td>176 (70.7)</td>
<td>153 (64.0)</td>
<td>453 (65.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Race n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White American</td>
<td>124 (61.7)</td>
<td>169 (67.9)</td>
<td>147 (61.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>440 (63.9)</td>
<td>p=.156</td>
</tr>
<tr>
<td>White British/ Irish</td>
<td>17 (8.5)</td>
<td>20 (8.0)</td>
<td>12 (5.0)</td>
<td>49 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>14 (7.0)</td>
<td>25 (10.0)</td>
<td>27 (11.3)</td>
<td>66 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Indian/Pakistani/Bangladesi</td>
<td>18 (9.0)</td>
<td>11 (4.4)</td>
<td>15 (6.3)</td>
<td>44 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>28 (13.9)</td>
<td>24 (9.6)</td>
<td>38 (15.9)</td>
<td>90 (13.1)</td>
<td></td>
</tr>
<tr>
<td><strong>First Language n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>191 (95.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>234 (94.4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>220 (91.7)</td>
<td>645 (93.8)</td>
<td>p=.226</td>
</tr>
<tr>
<td><strong>Country of residence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States n (%)</td>
<td>200 (99.5)</td>
<td>226 (91.9)</td>
<td>222 (94.1)</td>
<td>648 (94.9)</td>
<td>p=.219</td>
</tr>
<tr>
<td>Asthma n (%)&lt;sup&gt;d&lt;/sup&gt; reported diagnosis</td>
<td>73 (36.3)</td>
<td>69 (27.7)</td>
<td>81 (34.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>223 (32.4)</td>
<td>p=.123</td>
</tr>
</tbody>
</table>

*Note.* <sup>a</sup> 1 missing value; <sup>b</sup> 2 missing values; <sup>c</sup> 4 missing values; <sup>d</sup> self-reported past asthma diagnosis; SD=standard deviation; p-values refer to Chi-Square tests between waves (with the exception of age: Univariate ANOVA); Table reproduced from Heller et al. (2015)
Table 26: Inter-correlations medication belief scales

<table>
<thead>
<tr>
<th></th>
<th>General Benefit</th>
<th>General Harm</th>
<th>General Overuse</th>
<th>PSM</th>
<th>Molair Necessity</th>
<th>Molair Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>r</strong></td>
<td>(n=690)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Benefit</td>
<td>1</td>
<td>-.256**</td>
<td>-.148**</td>
<td>.023</td>
<td>.260**</td>
<td>-.101**</td>
</tr>
<tr>
<td>General Harm</td>
<td>1</td>
<td>.632**</td>
<td>.247**</td>
<td>-.018</td>
<td>.371**</td>
<td></td>
</tr>
<tr>
<td>General Overuse</td>
<td>1</td>
<td>.198**</td>
<td>.139**</td>
<td>.045</td>
<td>.382**</td>
<td></td>
</tr>
<tr>
<td>PSM</td>
<td>1</td>
<td></td>
<td>.139**</td>
<td>.259</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molair Necessity</td>
<td>1</td>
<td></td>
<td>.109**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molair Concern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Note. **p<.01 (two-tailed); PSM=Perceived Sensitivity to Medicines Scale

4.5.5. Medication beliefs and side effect expectations

Pearson correlations were used to explore whether medication beliefs were associated with participants’ expectations of side effects. Both pre-existing pharmaceutical schemas (BMQ-General and PSM scales, assessed at baseline) and specific beliefs following the Molair PIL information were significantly associated with side effect expectations: Participants who believed pharmaceutical medicines as generally more harmful ($r=.288$) and overused ($r=.197$) and who had greater perceived sensitivity to medicines ($r=.258$) and concerns about Molair ($r=.477$) had increased side effect expectations. Beliefs that pharmaceutical medicines are generally beneficial ($r=-.179$) and Molair Necessity beliefs ($r=-.144$, all $ps<.01$) were associated with decreased side effect expectations.

4.5.6 Medication beliefs and negative affect (state/trait)

Pearson correlations were used to explore whether medication beliefs were associated with state and trait negative affect (measured in wave three only). Participants who reported stronger perceived sensitivity to medicines scored higher on state negative affect as assessed with both the STAI$_{state}$ ($r=.217$) and PANAS NA ($r=.266$) as well as trait negative affect (STAI$_{trait}$ $r=.293$). Beliefs that medicines are generally harmful only showed significant positive associations with trait negative affect ($r=.219$; all $ps<.01$). Those who believed medicines as more beneficial in general had reduced state negative affect (STAI$_{state}$ $r=-.250$, $p<.01$; PANAS NA $r=-.151$; $p<.01$), but not trait negative affect (STAI$_{trait}$ $r=-.069$). Concerns about Molair were only associated with increased PANAS$_{NA}$ scores ($r=.257$; $p<.01$).
4.5.7 Between-group comparisons of medication beliefs and Efficacy/Side Effect VAS

Participants who were randomized to read the “High Efficacy” PIL had significantly higher necessity beliefs than those randomized to the “Moderate Efficacy” PIL ($t(199)=2.60$, $p<.01$). Molair Concerns were higher for participants who saw the “High Side Effect Frequency” PIL compared to the “Low Side Effect Frequency” PIL ($t(487)=2.59$, $p<.05$, see Table 27 for group means).

All PIL variations affected Efficacy and Side Effect VAS in the expected direction: Side Effect VAS scores were higher in the “High Side Effect Frequency” than in the “Low Side Effect Frequency” PIL conditions, and Efficacy VAS scores were higher in the “High Efficacy” than in the “Moderate Efficacy” PIL condition (all $ts>6.2$, $ps<.001$, see Table 27 for means).

Table 27: Specific medication beliefs and expectations by PIL variation

<table>
<thead>
<tr>
<th></th>
<th>High Efficacy PIL (n=98)</th>
<th>Moderate Efficacy PIL (n=103)</th>
<th>Low SE Frequency PIL (n=245)</th>
<th>High SE Frequency PIL (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molair Necessity; M (SD)</td>
<td>3.06 (0.78)</td>
<td>2.77 (0.73)</td>
<td>3.03 (0.85)</td>
<td>2.89 (0.84)</td>
</tr>
<tr>
<td></td>
<td>$t(199)=2.60, p&lt;.01$</td>
<td></td>
<td>$t(487)=1.89, p=.06$</td>
<td></td>
</tr>
<tr>
<td>Molair Concern; M (SD)</td>
<td>2.94 (0.78)</td>
<td>2.99 (0.78)</td>
<td>2.90 (0.83)</td>
<td>3.10 (0.83)</td>
</tr>
<tr>
<td></td>
<td>$t(199)=0.42, p=.68$</td>
<td></td>
<td>$t(487)=2.59, p&lt;.05$</td>
<td></td>
</tr>
<tr>
<td>Efficacy VAS; M (SD)</td>
<td>71.43 (17.41)</td>
<td>54.54 (20.32)</td>
<td>70.28 (16.13)</td>
<td>66.65 (17.04)</td>
</tr>
<tr>
<td></td>
<td>$t(199)=6.16, p&lt;.001$</td>
<td></td>
<td>$t(487)=2.42, p&lt;.05$</td>
<td></td>
</tr>
<tr>
<td>Side Effect VAS; M (SD)</td>
<td>35.47 (23.03)</td>
<td>41.33 (21.99)</td>
<td>39.54 (24.47)</td>
<td>52.79 (22.51)</td>
</tr>
<tr>
<td></td>
<td>$t(199)=1.85, p=.07$</td>
<td></td>
<td>$t(487)=6.23, p&lt;.001$</td>
<td></td>
</tr>
</tbody>
</table>

Note. PIL=Patient Information Leaflet; SE=Side Effect, VAS=Visual Analogue Scale

4.5.8 Symptom misattribution and behavioural intention frequencies

Around a fourth of participants ($n=170, 24.6\%$) misattributed the headache as a side effect and 69 (40.6\%) of these said that they would stop taking Molair as a result. Univariate logistic regression showed that misattribution significantly increased behavioural intention to stop the treatment (OR=8.02, 95\% CI[4.69, 10.69], $p<.001$).

Frequencies of symptom misattribution were similar in the different PIL conditions ($\chi^2(3)=3.80, p=.29$), ranging from 20.4\% ($n=21$) in the “Moderate Efficacy PIL” condition to 28.7\% ($n=70$) in the “High Efficacy PIL” condition. There was also no difference in behavioural intention between PIL conditions ($\chi^2(3)=0.37, p=.95$). Participants who reported an asthma diagnosis did not differ in rates of symptom
misattribution (n = 57, 25.56%) and behavioural intention (n=25, 11.21%) from those who did not (n=113, 24.30% and n=44, 9.50 % respectively; both p>.48).

Symptom misattribution and behavioural intention rates were similar for men and women. There was a significant effect of age, with older participants being less likely to attribute the headache as a side effect and subsequently intend to stop the medication (see Table 28). Participants who had stronger side effect expectations were significantly more likely to misattribute the headache as a side effect (OR=1.02; 95%CI [1.02;1.03], p<.001) and to subsequently intend to stop taking Molair (OR=1.02; 95%CI [1.01;1.03], p<.001).

### 4.5.9 Regression analyses examining the association between medication beliefs and symptom misattribution/behavioural intention

Univariate logistic regression models were used to explore whether misattribution and behavioural intention were associated with medication beliefs (BMQ-General, BMQ-Specific, PSM). Participants who had more negative beliefs about pharmaceuticals in general and Molair in specific were more likely to misattribute headache as a side effect and intend to stop taking Molair: General Harm, General Overuse and Molair Concerns increased the odds of symptom misattribution and behavioural intention. General Benefit and Molair Necessity reduced the odds of both outcomes. PSM was not associated symptom misattribution and behavioural intentions (see Table 28).
Figure 30: Hierarchical logistic regression models predicting symptom misattribution and behavioural intention to stop medication

Note. *p<.05, **p<.01, ***p<.001; adjusted for PIL variation, gender, age and self-reported past asthma diagnosis; PSM=Perceived Sensitivity to Medicines Scale; OR=Odds Ratio, CI=95% Confidence Interval
Table 28: Univariate logistic regression models predicting symptom misattribution and behavioral intention to stop treatment

<table>
<thead>
<tr>
<th>Univariate Predictors</th>
<th>Symptom misattribution</th>
<th>Behavioural intention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>General Medication Beliefs^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Benefit</td>
<td>0.72** [0.57, 0.91]</td>
<td>0.53*** [0.39, 0.73]</td>
</tr>
<tr>
<td>General Harm</td>
<td>1.90*** [1.53, 2.37]</td>
<td>2.72*** [2.00, 3.71]</td>
</tr>
<tr>
<td>General Overuse</td>
<td>1.74*** [1.39, 2.18]</td>
<td>1.56** [1.13, 2.14]</td>
</tr>
<tr>
<td>Specific Medication Beliefs^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molair Necessity</td>
<td>0.72** [0.58, 0.89]</td>
<td>0.70* [0.51, 0.84]</td>
</tr>
<tr>
<td>Molair Concern</td>
<td>1.52*** [1.21, 1.89]</td>
<td>1.78*** [1.28, 2.47]</td>
</tr>
<tr>
<td>PSM</td>
<td>1.02 [0.86, 1.21]</td>
<td>1.25 [0.98, 1.59]</td>
</tr>
<tr>
<td>Affect^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>State NA_PANAS</td>
<td>1.01 [0.98, 1.05]</td>
<td>1.03 [0.99, 1.08]</td>
</tr>
<tr>
<td>State NA_STAI</td>
<td>1.02 [0.99, 1.05]</td>
<td>1.02 [0.97, 1.06]</td>
</tr>
<tr>
<td>Trait NA_STAI</td>
<td>1.02 [1.00, 1.05]</td>
<td>1.02 [0.98, 1.06]</td>
</tr>
<tr>
<td>Demographic factors^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.98* [0.97, 1.00]</td>
<td>0.96* [0.94, 0.98]</td>
</tr>
<tr>
<td>Gender^c</td>
<td>0.81 [0.57, 1.16]</td>
<td>0.61 [0.37, 1.00]</td>
</tr>
</tbody>
</table>

Note. OR=Odds ratio; CI=confidence interval; PSM=Perceived Sensitivity to Medicines; NA=Negative Affect; PANAS= Positive and Negative Affect Schedule, STAI = State Trait Anxiety Inventory, ^a N=690, ^b N=240 (data available for wave 3 only); ^c reference category=male; *p<.05, **p<.01, ***p<.001; Table reproduced from Heller et al. (2015)

Two hierarchical logistic regression models were constructed to test whether negative general and specific medication beliefs predicted symptom misattribution and behavioural intention when entering all medication belief scales jointly into the model (see Table 29 and Figure 30). Demographics (age, gender), reported asthma diagnosis and PIL variations were included as control variables in step 1. General medication beliefs and PSM were entered in step 2 and specific medication beliefs in step 3. In both models, age, but none of the other control variables, was significantly associated with either outcome. In the symptom misattribution model, general medication beliefs significantly improved prediction, and adding the specific medication belief block further improved prediction. In the full model, General Harm and Molair Concerns increased symptom misattribution, while Molair Necessity reduced symptom misattribution. The effect of General Overuse was significant at step 2, but not at step 3. In the behavioural intention model, both the general and specific medication belief step significantly improved prediction. In the full model, General Harm, Molair Necessity and Molair Concerns independently predicted behavioural intention. General Benefit was associated with reduced behavioural intention at step 2, but not at step 3. Both models had adequate fit as indicated by non-significant Hosmer Lemeshow Tests (HLT).
Using wave 3 data, we built hierarchical logistic regression models for both outcomes, controlling for negative affect in the first step and adding general and specific medication beliefs jointly in the second step. In the model predicting symptom misattribution, the affect block was not significant ($\chi^2(3) = 3.68, p = .30$), while step 2 (general and specific medication beliefs and PSM) improved the model considerably ($\chi^2(6) = 13.51, p < .05$; full model $\chi^2(9) = 17.20, p < .05$). Molair Necessity was the only significant predictor of misattribution (OR = 0.55, 95% CI [0.36, 0.85]). The model had adequate fit as shown by a non-significant HLT and accounted for 77.6% correct classification of cases. In the equivalent model predicting behavioral intention, the affect block ($\chi^2(3) = 2.01, p = .57$) was not significant, while the medication belief block significantly improved prediction ($\chi^2(6) = 18.92, p < .01$). Only General Harm (OR = 3.79, 95% CI [1.62, 8.90]) was a significant predictor. The full model ($\chi^2(9) = 20.92, p < .05$) had adequate fit (HLT $p > .05$) and accounted for 90.0% correct classification of cases.

4.5.10 Tests for interaction effects

Hierarchical logistic regression models predicting symptom misattribution and behavioural intention were constructed for each medication belief. In these models the medication belief, PIL variation and their interaction term were entered in consecutive steps. No significant interaction effects between PIL variations and medications beliefs were detected ($p > .05$), indicating that the relationship between medication beliefs and both outcomes was similar for participants who saw the different PILs.

A similar set of regression models was constructed to test for interaction effects between medication beliefs and reported asthma diagnosis in predicting these outcomes. In each model the medication belief (e.g. General Harm), asthma diagnosis and the interaction term (e.g. General Harm x asthma diagnosis) were entered in consecutive steps. None of the interaction terms was significant ($p > .05$), indicating medication beliefs have similar effects for individuals with and without reported asthma.
Table 29: Multivariate hierarchical logistic regression models predicting symptom misattribution and behavioural intention to stop medication

<table>
<thead>
<tr>
<th>Step 1: PIL variation, demographics and asthma diagnosis</th>
<th>Symptom misattribution</th>
<th>Behavioural intention</th>
</tr>
</thead>
<tbody>
<tr>
<td>X² Block:</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>PIL variation</td>
<td>1.04</td>
<td>[0.94, 1.16]</td>
</tr>
<tr>
<td>Gender</td>
<td>0.84</td>
<td>[0.59, 1.22]</td>
</tr>
<tr>
<td>Age</td>
<td>0.98*</td>
<td>[0.97, 1.00]</td>
</tr>
<tr>
<td>Reported asthma diagnosis</td>
<td>0.94</td>
<td>[0.65, 1.36]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2: General Medication Beliefs and PSM</th>
<th>Symptom misattribution</th>
<th>Behavioural intention</th>
</tr>
</thead>
<tbody>
<tr>
<td>X² Block:</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>PIL variation</td>
<td>1.01</td>
<td>[0.91, 1.13]</td>
</tr>
<tr>
<td>Gender</td>
<td>0.86</td>
<td>[0.59, 1.27]</td>
</tr>
<tr>
<td>Age</td>
<td>0.98*</td>
<td>[0.97, 1.00]</td>
</tr>
<tr>
<td>General Harm</td>
<td>1.57**</td>
<td>[1.16, 2.12]</td>
</tr>
<tr>
<td>General Benefit</td>
<td>0.88</td>
<td>[0.67, 1.14]</td>
</tr>
<tr>
<td>General Overuse</td>
<td>1.40*</td>
<td>[1.05, 1.89]</td>
</tr>
<tr>
<td>PSM</td>
<td>0.90</td>
<td>[0.74, 1.09]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3: Specific Medication Beliefs</th>
<th>Symptom misattribution</th>
<th>Behavioural intention</th>
</tr>
</thead>
<tbody>
<tr>
<td>X² Block:</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>PIL variation</td>
<td>1.02</td>
<td>[0.91, 1.14]</td>
</tr>
<tr>
<td>Gender</td>
<td>0.86</td>
<td>[0.58, 1.26]</td>
</tr>
<tr>
<td>Age</td>
<td>0.98*</td>
<td>[0.97, 1.00]</td>
</tr>
<tr>
<td>General Harm</td>
<td>1.55**</td>
<td>[1.14, 2.11]</td>
</tr>
<tr>
<td>General Benefit</td>
<td>0.98</td>
<td>[0.74, 1.30]</td>
</tr>
<tr>
<td>General Overuse</td>
<td>1.28</td>
<td>[0.95, 1.73]</td>
</tr>
<tr>
<td>PSM</td>
<td>0.90</td>
<td>[0.74, 1.09]</td>
</tr>
<tr>
<td>Molair Necessity</td>
<td>0.74*</td>
<td>[0.58, 0.94]</td>
</tr>
<tr>
<td>Molair Concern</td>
<td>1.30*</td>
<td>[1.00, 1.68]</td>
</tr>
</tbody>
</table>

X² Total model: | OR | 95% CI |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>X²(10)=55.88, p&lt;.001</td>
<td>X²(10)=71.90, p&lt;.001</td>
</tr>
</tbody>
</table>

Hosmer Lemeshow Test: | OR | 95% CI |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>X²(8)=10.22, p=.25</td>
<td>X²(8)=6.44, p=.60</td>
</tr>
</tbody>
</table>

Correct classification (%): 75.8 90.2

Note: OR= odds ratio; CI= confidence interval; PSM=Perceived Sensitivity to Medicines Scale; PIL= Patient Information Leaflet a reference category: high efficacy information, b reference category: male, c reference category: self-reported past asthma diagnosis; *p<.05, **p<.01, ***p<.001; N=690; Table reproduced from Heller et al. (2015).
4.6 Discussion

4.6.1 Summary of findings

The overall aim of this study was to explore whether the misattribution of symptoms could explain the association between medication beliefs and side effects (see Research Question 2). This study used an analogue scenario approach to show that misattribution of symptoms as side effects is likely to be common and can be predicted by medication beliefs. About a quarter of participants in this large online study misattributed headache (a symptom that had not been listed in the patient information leaflet) as a side effect. As hypothesized, the odds of misattributing the headache symptom as a side effect were increased for participants who had more negative beliefs about pharmaceutical medicines in general and the specific asthma medication Molair: Participants were more likely to misattribute the headache as a side effect if they initially believed pharmaceutical medication to be generally harmful (General Harm), over-prescribed by doctors (General Overuse), less beneficial (General Benefit), and if they had stronger concerns and more doubts about need for Molair. Also in line with predictions, misattributing the headache symptom as a side effect increased the odds of behavioural intentions to stop Molair. Behavioural intentions were again predicted by participants’ medication beliefs: Participants were more likely to intend to stop Molair following the headache symptom if they had increased General Harm and General Overuse beliefs and stronger Concerns about Molair. Those who viewed pharmaceutical medicines as more beneficial in general and had stronger Molair necessity beliefs were less likely to intend to stop treatment.

The size of the associations between medication beliefs and symptom misattribution/behavioural intentions in this study were small to moderate (Cohen, 1988), with univariable odds ratios ranging from 1.52 to 2.76. An odds ratio of 1.52 for the association of Molair Concerns and symptom misattribution indicates that for every 1 unit increase in Molair Concerns, the odds that the headache symptom is misattributed as a side effect is multiplied by 1.52 (or in other words the predicted odds are increased by 52%). It rests to show whether these effect sizes could be replicated outside this analogue approach, but findings from this study suggest that medication beliefs contribute to a considerable increase in the number of symptoms misattributed as side effects.

Changing descriptions of Molair’s efficacy and the frequency of side effects changed participants expectations and specific beliefs about Molair as intended:
Participants who read that Molair was highly effective in treating asthma symptoms had significantly greater efficacy expectations and Molair necessity beliefs compared to those who were told it was only moderately effective. This suggests that providing patients with information highlighting the efficacy of their prescribed medication may increase perceptions of personal need for treatment. This is important as patients with greater necessity beliefs tend to be more adherent to their treatment (Horne et al., 2013a). On the other hand, participants who were randomized to the high frequency side effect leaflet had greater side effect expectations and more concerns about Molair.

Moderation analysis showed that the relationship between medication beliefs and symptom misattribution and behavioural intention was not affected by manipulations of side effect and efficacy descriptions in the PIL. The relationship between medication beliefs and both outcomes was also similar for participants with and without self-reported past asthma diagnosis, suggesting that the findings may generalize to patient groups and across different medications.

Participants with more negative pharmaceutical schemas (high harm beliefs and perceived sensitivity to medicines) and concerns about Molair showed increased state negative affect. But I demonstrated that medication beliefs predicted symptom misattribution when controlling for negative affect as a potential confounder.

Perceived sensitivity to medicines (PSM) was unrelated to misattribution and behavioural intentions. However, correlations between PSM and both general and specific medication beliefs were consistent with theoretical predictions. As expected from an analogue approach with a hypothetical medication, correlations between the medication belief scales were small to moderate in scale (Cohen, 1988), yet statistically significant and in the predicted direction.

As in Study 2, medication beliefs were also related to participants expectations of side effects. Participants who started out with more negative beliefs about pharmaceutical medicines in general (high General Harm and General Overuse beliefs and low Benefit beliefs) and who perceived themselves as more sensitive to medicines showed increased side effect expectations.

Taken together these findings suggest that medication beliefs do indeed play a role in the attribution of common symptoms as side effects. Findings from the study suggest that participants with more negative medication beliefs are more likely
to err towards attributing unrelated symptoms as side effects. This is likely to have important consequences for medication taking behaviours by increasing behavioural intentions to stop treatment.

4.6.2 Integration with previous literature

The associations of medication beliefs with symptom misattribution and intention to stop treatment detected in this study mirror the associations between medication beliefs, side effect reporting and adherence to medication in the clinical literature. Patients with concerns about their medication are typically less adherent, while patients with stronger beliefs in the personal necessity of medication tend to be more adherent (see 1.3.1.1). Findings from this study are also consistent with the previous studies also showing that patients with stronger concerns about their medication (Aikens & Klinkman, 2012; Nestoriuc et al., 2010; Shiyanbola & Farris, 2010) and more negative beliefs about medicines in general (Bautista et al., 2011) report more side effects (see also literature review section 1.3.3).

Misattribution of symptoms as medication side effects may help to understand part of the relationships between medication beliefs, side effect reports and adherence. Patients often experience a range of disease or common symptoms and sensations from normal bodily function (Barsky et al., 2002; Pennebaker, 1982). If they have negative beliefs about medicines, they may misattribute these symptoms as side effects, thereby reinforcing negative beliefs, reducing adherence, and increasing future symptom misattribution (see also Figure 6).

Symptom misattribution is of course only one of several (not mutually exclusive) processes that might explain the association between negative medication beliefs and side effect reporting in clinical groups. I have already explored several other putative processes (expectations, somatic focus) in the previous study (see Study 2). The finding that individuals’ representations of pharmaceuticals influenced expectations of side effects was replicated in the current study. But I feel that symptom attribution is particularly important as it mentally links symptoms to the medication and it is this mental link that is likely to influence subsequent medication taking behaviour. Research informed by the Common Sense Model of illness representations, suggest that the causal attribution of symptoms (cause component in the illness representation model) is an important predictor of coping behaviour (Leventhal, Nerenz, & Straus, 1982). But while the attribution of a symptom to an illness would more likely encourage medication
taking, attribution of the symptom to the medication seems to reduce behavioural intentions to continuation of the medication.

I have also illustrated in the previous chapter that medication beliefs are part of a complex of psychological factors that may affect side effect reporting. Individuals with high negative affect report more symptoms (Mora et al., 2007; Van Diest et al., 2005; Watson & Pennebaker, 1989) and side effects (Davis et al., 1995; Foster et al., 2008). Concerns about medication have also been associated with negative affect (Gonzalez et al., 2007). Negative affect could therefore potentially confound the relationship between medication beliefs and side effect attributions. This was not confirmed by my analysis, where the relationship between negative medication beliefs and concerns and side effect misattribution was independent of negative affect.

4.6.3 Strengths and limitations

Convenience online sampling allowed me to survey a large number of participants for this study, but may have resulted in biased sampling, i.e. an over- or underrepresentation of particular groups (Paolacci, Chandler, & Ipeirotis, 2010). For example, relatively few participants were from an older age segment (e.g. >65). Younger participants are less likely to have been pre-exposed to medical conditions and medication use. In addition, the type of online sampling used in this study carries the risk of a potential self-selection sampling bias. It was not possible to determine how many participants elected to not take part in the survey after reading the study description on the crowdsourcing websites. It is therefore possible that those who chose to participate in the study differed from those that declined to participate in relevant characteristics (e.g. general interest in medicine related studies, medication beliefs, etc.).

Associations between medication beliefs and symptom misattribution/behavioural intentions to stop treatment were similar for participants with and without self-reported asthma, but the external validity of the finding is limited. It is for example not clear whether these findings generalize to clinical settings, where patients have a medically confirmed diagnosis, co-morbid conditions, take active medication and experience illness symptoms.

The vignette approach allowed me to unambiguously test symptom misattribution (i.e. it was clear whether headache was a side effect or not). A similar vignette approach has been used to study symptom attribution in patients with
medically unexplained symptoms using (Kolk, Hanewald, Schagen, & Gijsbers van Wijk, 2002), strengthening confidence in the validity. In the extensively used Symptom Interpretation Questionnaire (Robbins & Kirmayer, 1991), patients read about various common symptoms and are asked to select between different causal explanations. Patients who attribute these symptoms more to somatic and psychological factors tend to report more symptoms than patients who make normalizing attributions (Robbins & Kirmayer, 1991).

It is also possible that participants may not have fully understood the information they received about the hypothetical drug or paid sufficient attention to the material. Research on health literacy suggests however that patients’ understanding of health information is also far from perfect in general practice (Powers, Trinh, & Bosworth, 2010). In addition, the manipulation of efficacy and side effect frequency were effective despite their relative subtlety, suggesting that participants did generally understand and pay attention to the presented information. It will nevertheless be interesting to explore in future studies whether patients who do not fully understand (or chose not to read) patient information rely more on their underlying general attitudes and beliefs when making symptom attributions. Future studies should also explore whether excluding participants who complete the survey suspiciously quickly (also refered to as speeding (Greszki, Meyer, & Schoen, 2014)) or who give non-differentiated (identical) ratings to a series of statements (so called straightlining (Zhang & Conrad, 2014)) would change the observed relationships.

4.6.4 Clinical implications

Despite its limitations, this study extends our understanding of side effect attributions and the role of general and specific beliefs about medicines in this process. The findings have potential clinical implications. Understanding patients’ medication beliefs may help identify patients at risk of misattributing unrelated symptoms as side effects and aid the interpretation of side effect reports in RCTs and clinical practice. If there is no clear pharmacological rationale for certain side effects and if similar symptoms are highly prevalent in the general population (see section 4.2) doctors may want to explore patients’ beliefs about their treatment and pharmaceutical medicines in general. My findings also imply that interventions to address negative medication beliefs and to educate patients about potential
attribution biases may be successful at reducing symptom misattribution. This will be examined in detail in Chapter 6 of this thesis.

4.6.5 Summary

Taken together the findings suggest that the misattribution of symptoms as side effects can explain part of the association between medication beliefs and side effects (see Research Question 2) and that this may negatively affect medication taking behaviour. Yet it needs to be shown whether this effect can be replicated and further research is needed to ascertain psychological processes linking medication beliefs to symptom misattribution.
Chapter 5: Pharmaceutical schemas and memory for side effect information (Study 4)

5.1 General aims of the study

Findings from the Modafinil placebo study (Study 2) and the previous analogue online study (Study 3) illustrate the importance of medication beliefs in the attribution of symptoms as side effects. The present study explores in more detail the psychological processes linking medication beliefs to the attribution of symptoms as side effects (see Research Question 2). In particular, I will examine whether individuals’ background beliefs about pharmaceuticals (i.e. pharmaceutical schemas, see also section 1.3.1.2) influence how people process and remember information about side effects. The study is based on the idea that the attribution of a symptom as a medication side effect will be more accurate when people accurately remember the information they have been given about the specific side effects that are known to be associated with the particular medication. Memory researchers have long been aware that people are not blank slates and that prior knowledge and beliefs influence how people remember new information (Hirt, Lynn, Payne, Krackow, & McCrea, 1999). It is thus plausible that individuals’ pharmaceutical schemas affect memory for side effect information and subsequent side effect attribution.

5.2 General study background

We know that patients’ memory for treatment information (Barsky, 2002; Weinman, 1990), including side effects (Tarn & Flocke, 2011), is poor. It is however yet unclear whether there are any systematic biases underpinning poor memory for side effect information. As outlined above, I propose here that schematic representations of pharmaceuticals influence how well individuals remember information about side effects.

This claim is supported by the extensive literature on the role of schemas in memory (Anderson & Bower, 2014; Graesser & Nakamura, 1984; Hastie & Kumar, 1979). Schemas generally facilitate the meaningful organization of new information, thereby increasing the number of available cues to retrieve stored information. People thus tend to remember information better if it can be assimilated in an active schema (Koriat, Goldsmith, & Pansky, 2000). But schemas can also lead people to make errors when remembering specific information, as information in the pre-
existing schema can be confused with the new information, and information which conflicts with the existing schema may not be encoded accurately (Brainerd & Reyna, 2002; Roediger & McDermott, 1995). The effect of schemas on false memory has for example been demonstrated with the Deese-Roediger-McDermott-paradigm (Roediger & McDermott, 1995): Individuals who were asked to recall a list of thematically related words (e.g. tired, dream, bed, duvet…) falsely recalled and recognized unlisted words (e.g. sleep, night) that were part of the activated schema.

Thus, schemas can be a two-edged sword: on the one hand helping people to remember information (increasing the amount of remembered information), on the other hand increasing the risk of false memory (i.e. reducing accuracy). In this study I will therefore not only look at the number of side effects participants correctly remember and recognize from the patient leaflet, but also examine the recall and recognition of side effects that have not been listed in the patient information leaflet (false alarms).

This is to my knowledge the first empirical study to examine whether pharmaceutical schemas, (as operationalized with the BMQ-General and PSM) are associated with memory for side effects. There is however evidence for the role of illness schemas in memory for illness symptoms: Students who were given bogus feedback that they had high blood pressure (“well above average for people their age”) remembered having experienced more hypertension-related symptoms in the past three months (e.g. fast heartbeat, dizziness, palpitations) than participants given bogus feedback about normal blood pressure (“about average for people their age”) (Baumann, Cameron, Zimmerman, & Leventhal, 1989). Another study examining the role of illness schemas in memory for symptoms (Bishop & Converse, 1986) showed that participants remembered more symptoms of fictitious patients if the symptoms were highly prototypic (e.g. sneezing nasal congestion, nasal discharge, itchy nose, teary eyes for hay fever) versus moderately prototypic for a disease (i.e. if the set contained some irrelevant symptoms).

Both recall and recognition memory for side effect information will be examined in this study. Recall involves the retrieval and reproduction of remembered information from memory, while recognition memory relates to the capacity to compare new information to information in memory (Zechmeister & Nyberg, 1982). Schemas have been shown to influence both recall and recognition (Graesser & Nakamura, 1984) and both types of memory could be important in the
perception and attribution of symptoms as side effects: To recognize whether a new symptom (e.g. headache) is a side effect, patients need to compare it with the information they hold in memory about known side effects of the medication. Recalling information about specific side effects may influence patients’ expectations of experiencing these side effects. There is limited evidence for this from an experimental placebo study: Patients who were warned about only one (versus four side effects) of a novel “sleeping pill”, did not only remember the single side effect better (83% versus 35% of participants recalled the side effect), but were also somewhat more likely to report this side effect, although this trend was only marginally significant (Colagiuri et al., 2012).

It is plausible that pharmaceutical schemas influence memory not only by facilitating retrieval of side effect information, but also through attentional processes. Individuals who are more concerned about potential harm of pharmaceuticals and who perceive themselves as more sensitive to pharmaceuticals may pay greater attention (operationalized in the present study through reading times) to side effect information, making it more likely that the information is encoded. At the same time, there is some evidence that patients who are concerned about side effects may in some cases avoid information about side effects. One patient, who participated in a qualitative study assessing patients’ views of written patient information of the arthritis drug methotrexate (Hayden, Neame, & Tarrant, 2015) brought this to the point:

“I think you can worry yourself reading things [...] if you read the leaflets in the tablets - any tablet – you wouldn’t take them, would you? Because they all have side effects, haven’t they?” (Hayden et al., 2015; page 6).

An analogue scenario approach, using the same fictitious asthma drug (“Molair”) and same ‘attribution’-symptom (“headache”) as in the previous study (Study 3) was chosen for the present study. I again systematically varied the information participants were given about Molair. But this time I either included or omitted information about the efficacy of Molair. Patient information leaflets tend to contain mostly risk information (e.g. side effects, warnings about contraindications and interactions with other drugs) (Kitching, 1990). Benefits of treatment (e.g. efficacy information) are rarely mentioned, although patients often wish to receive more information about the benefits they could reasonable expect from their medication (Hayden et al., 2015). There is some evidence that perceptions of benefit and risk are not independent. Research on risk perception for example
suggests that people typically perceive products (including asthma and other
prescription drugs (Slovic, Peters, Grana, Berger, & Dieck, 2007)) that offer greater
benefits as less risky (Alhakami & Slovic, 1994). Making benefits more salient could
thus be potentially effective in decreasing perceived risk and reducing the likelihood
that unrelated symptoms are attributed as medication side effects. On the other
hand there is a clinical impression that patients often perceive medicines as a two-
edged sword, believing that greater potency of medicines comes at the price of
greater adverse effects (Horne, 2003).

5.3 Hypotheses

The following research questions and hypotheses were examined. In line
with findings from Study 3 I hypothesized that individuals with more negative pre-
eexisting pharmaceutical schemas (e.g. beliefs that medicines are generally harmful,
high perceived sensitivity to their effects) would show an increased tendency to
attribute the unrelated headache symptom as a side effect. I further tested whether
pre-existing negative pharmaceutical schemas influenced recall and recognition, as
well as reading times for side effect information. Better memory for side effects from
the leaflet was expected to reduce the likelihood that an unlisted symptom was
attributed as a side effect. In addition, I explored whether the inclusion of efficacy
information had an effect on perceived risk and side effect attribution.

5.4 Method

5.4.1 Participants and recruitment

Adults (18 and over) with and without self-reported asthma were recruited
via the Crowdflower crowdsourcing platform (see also Study 3), from where they
were directed to the Qualtrics online study. Participants received $0.30 for
participating in this study. Only one survey submission from the same IP address (in
this study or Study 3) was permitted to ensure independence of responses.

5.4.2 Measures and materials

5.4.2.1. Beliefs about Medicines Questionnaire-General

The standard version of the Beliefs about Medicines Questionnaire-General
(BMQ-General) (Horne et al., 1999) was used to assesses individuals' beliefs about
pharmaceutical medicines as a class of treatment. Internal consistency of all BMQ-
General scales was good (see Table 30).
5.4.2.2 Perceived Sensitivity to Medicines Scale

The standard 5-item version of Perceived Sensitivity to Medicines Scale (PSM) (Horne et al., 2013b) was used to assess participants' beliefs about their personal sensitivity to the positive and negative effects of medicines. Internal consistency was again excellent (see Table 30).

Table 30: Internal consistency medication belief measures

<table>
<thead>
<tr>
<th>Scale</th>
<th>Number of items</th>
<th>Cronbach’s alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMQ General Overuse</td>
<td>4</td>
<td>.75</td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>4</td>
<td>.77</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>4</td>
<td>.76</td>
</tr>
<tr>
<td>PSM</td>
<td>5</td>
<td>.91</td>
</tr>
</tbody>
</table>

Note. BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale

5.4.2.3 Demographics and self-reported asthma diagnosis

Participants indicated their age, gender, ethnicity, country of residence, and whether they had ever been diagnosed with asthma and previously taken asthma medication.

5.4.2.4 Asthma information

As in Study 3 participants read information about asthma, structured according to Leventhal’s common sense model of illness representation (Diefenbach & Leventhal, 1996). It included information about asthma causes and triggers, symptoms and their episodic nature, likely consequences, and asthma management (see section 4.4.2.1 and Appendix H).

5.4.2.5 Molair Patient Information Leaflets

Participants read one of two possible patient leaflets of the fictitious asthma medication Molair (see Appendix K), modelled on the existing asthma drug Montelukast. The Qualtrics block randomization function was used to randomize participants to leaflet conditions.

- Both information leaflets provided information about Molair’s mechanism of action (leukotriene receptor agonist) on the first page. Possible side effects (rash, dizziness; yellowing of the skin, itch, fatigue, abdominal pain, joint pain, muscle pain) were listed on a separate page. Side effects were similar to those listed in Study 3. However in order to facilitate the coding of correctly recalled symptoms I took out “flu like symptoms” (as it is not clear whether specific flu symptoms like fever would count as correct recall) and listed muscle and joint pain as separate side effects. The order of side effects was randomised.
The “Efficacy information” leaflet contained an additional page outlining Molair’s efficacy (based on a clinical trial of Montelukast (Virchow & Bachert, 2006)) presented before the side effect information: “A recent clinical trial (with 5855 asthma patients) has shown the effectiveness of Molair in adults. Following a 4-6 week treatment with Molair 86.6% percent of patients reported a strong improvement in day-time asthma symptoms and 88.7% a strong improvement in night-time asthma symptoms.”

5.4.2.6 Reading times for side effect information

The Qualtrics page timing function was used to assess how long participants spent on the side effect information page. The page timing function allows researchers to measures the time (in seconds) participants spend on a survey page before advancing to the next survey page (by clicking on the continue button).

5.4.2.7 Efficacy and side effect expectations

As in Study 3, three 100-point VAS were used to measure perceptions of efficacy and four 100-point VAS were used to measure side effect expectations (as in Study 3, see Appendix J). Internal consistency for both sets of VAS was high (Cronbach’s α of .88 and .90 respectively).

5.4.2.8 Recall task

Participants were asked to type all the side effects they could remember from the leaflet in a text box. There was no time limit for the recall task. I coded responses as correct if they matched or were synonyms of listed side effects (e.g. tiredness for fatigue). All other entries of unlisted side effects were coded as incorrect. Correct Side Effect Recall and Incorrect Side Effect Recall scores were computed by counting correct and incorrect responses respectively.

5.4.2.9 Recognition task

The recognition memory task was modelled on the yes-no signal detection paradigm (Commons, Nevin, Davison, & Davidson, 2013). Participants saw a table with 16 symptoms: eight side effects from the leaflet and eight new symptoms (see Figure 31). The Qualtrics choice randomization function was used to randomize the order of symptoms.

Listed side effects and new symptoms were matched in word length (t(14)=.560, p=.586). A post-test with n=33 participants, recruited as per the main
study via Crowdflower, was conducted to test whether listed side effects and new symptoms differed in perceived severity (rated from 1=not at all to 7=extremely). It showed that new symptoms and listed side effects did not differ in severity ($t(32)=.08, p=.941$).

Participants were asked to indicate (yes/no) whether each symptom had been listed in the leaflet. Correct Side Effect Recognition andIncorrect Side Effect Recognition scores were computed by counting the number of correctly and incorrectly recognized side effects.

Figure 31: Overview SDT-classification recognition task

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes, it was listed</th>
<th>No, it was not listed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Correct Hit</td>
<td>Miss</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellowing of the skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td>False Alarm</td>
<td>Correct Rejection</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tight chest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In addition, I computed recognition memory indices in line with Signal Detection Theory (SDT) (Green & Swets, 1966; McNicol, 2005). According to SDT, whether a participant responds that a symptom was listed in the leaflet will depend both on the memory strength or familiarity of the symptom and the participant’s general tendency to guess that a symptom was listed (Response Bias, see Figure 32 below).
Signal detection theory assumes that the memory strength of both the listed side effects and new symptoms is normally distributed. On average the previously listed side effects should have a higher memory strength (i.e. distribution of the listed items is more to the right) than the new symptoms, but there is some overlap (i.e. some new symptoms may appear as familiar as some of the originally listed side effects). The further apart the distributions, the better a participant can discriminate between previously listed symptoms and new symptoms (see sensitivity $d'$ in Figure 32). All items have certain memory strength, but whether a participant responds that an item is from the previously memorized list will also depend on the threshold (or response bias $c$) participants set for responding that an item was previously listed. A participant with a lower threshold (i.e. dotted line in Figure 32 would move to the left) would be more likely to respond that an item had been previously listed in the leaflet. This increases of course the chances of falsely classifying new symptoms as listed side effects (see Figure 32), but would reduce the chances of missing previously memorized side effects.

To compute these signal detection measures responses were classified as follows: Responses were coded as Correct Hits (responded listed, when listed), Correct Rejections (responded new, when new), Misses (responded new, when listed), and False Alarms (responded listed, when new). False Alarm rates (number of False Alarms/number of new symptoms) and Correct Hit rates (number of correct hits/number of listed side effects). From these Response Bias (tendency to guess
that a symptom was listed) and Side Effect Recognition Sensitivity (ability to discriminate between listed side effects and new symptoms, see Figure 32) were calculated:

- **Side Effect Recognition Sensitivity** was operationalized as the difference between the z-scores of the Correct Hit and False Alarm rates (Stanislaw & Todorov, 1999). As outline above, low Recognition Sensitivity could arise if a participant strategically responds all items were from the memorized list, resulting in a perfect Correct Hit rate and maximum False Alarm rate. Higher Side Effect Recognition Sensitivity indicates better discrimination between previously listed side effects and new symptoms.

- **Response Bias** was computed by summing the z-score corresponding to the False Alarm and the Correct Hit rate and multiplying the result by -1/2. (Macmillan, 1993). Higher Response Bias scores indicate more conservative responding i.e. decreased willingness to guess that an item was from the original list.

### 5.4.2.10 Symptom attribution vignette

Participants read the following vignette: "Imagine you are suffering from asthma. You have been taking one 4mg tablet of Molair every day for the last two weeks. At the beginning of the third week you get a headache." Headache was not listed as one of Molair’s side effects in the leaflet. Recognizing that attribution is not necessarily binary (yes/no) and probably more probabilistic in nature I decided to use a visual analogue scale to measure side effect attribution. Participants were asked to indicate on 100-point visual analogue scales how likely they thought that six different factors (side effect of Molair, eye strain, stress, beginning of a cold, lack of sleep, no particular reason; order randomized) caused the headache (from 0= very unlikely to 100=very likely).

---

2 Extreme Correct Hit and False Alarm rates of 0 and 1, which would result in infinite parameter estimates, were adjusted. Rates of 0 were replaced with 0.5/n and rates of 1 with (n-0.5)/n, where n is the number of listed and new symptoms respectively (Macmillan & Kaplan, 1985).
5.4.3 Procedures

The study was categorized as exempt from ethical approval by the UCL Research Ethics Committee. Data was collected online with Qualtrics survey software. Participants gave informed consent, completed the PSM and the BMQ-General, read the asthma information and were randomized to leaflet conditions using the Qualtrics block randomization function. Participants then completed the Side effect and Efficacy Expectation VAS and the Recall and Recognition Tasks (fixed order). Finally participants completed the Symptom Attribution Vignette, Demographics and Self-Reported Asthma Diagnosis questions and received a short written debriefing statement.

5.4.4 Statistical considerations

5.4.4.1 Sample size

Sample size was calculated with GPower version 3.1 (Faul et al., 2009), based on previously published data (Heller et al., 2015), showing that 244 participants were required to predict side effect attribution in a multivariate linear regression model with four predictors.

5.4.4.2 Statistical analyses

Pearson correlations were used to explore relationships between pharmaceutical schemas, side effect attribution, and memory outcomes. The frequency and distribution of memory outcomes (Correct Side Effect Recall, Incorrect Side Effect Recall, Recognition Sensitivity, Criterion Bias) was examined. Incorrect Side Effect Recall was rare and outcomes were dichotomized (any incorrect recall yes/no). Associations between pharmaceutical schemas and dichotomized Incorrect Side Effect Recall were examined using logistic regression. Linear regression modelling was used to model associations between pharmaceutical schemas and side effect attribution and all other memory related outcomes. Hierarchical linear regression modelling was used to explore the amount of variance explained by pharmaceutical schemas in these outcomes when controlling for leaflet condition, asthma diagnosis, gender and age. Putative associations between pharmaceutical schemas and reading times for side effect information and between memory outcomes and side-effect attribution were examined using correlational analysis and linear regression. Correct recall and recognition sensitivity were examined as potential mediators in the relationship between pharmaceutical schemas and side effect attribution using bootstrapped confidence intervals (1000 bootstrap samples) of the estimated indirect effect using
the PROCESS Macro for SPSS (Hayes, 2012). Differences in expectations, side-effect attribution and memory outcomes between participants randomized to the different leaflet conditions were examined with independent t-tests.

5.5 Results

5.5.1 Survey completion rates and data exclusions

Responses from the same IP address (n=29), and responses with incomplete outcome data (n=33) were excluded. Pharmaceutical schemas did not differ between completers and non-completers (p>.12). Data from 260 participants was retained.

5.5.2 Demographic characteristics and reported asthma diagnosis

Participants were predominantly white (74.2%), female (58.8%), US residents (94.1%) without a reported asthma diagnosis (77.7%) (see Table 31).

Table 31: Overview sample characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=260</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years mean (SD)</td>
<td>34.7 (11.6)</td>
</tr>
<tr>
<td>Gender n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>153 (58.8)</td>
</tr>
<tr>
<td>Ethnicity n (%)</td>
<td></td>
</tr>
<tr>
<td>White American</td>
<td>177 (68.1)</td>
</tr>
<tr>
<td>White British/ Irish</td>
<td>16 (6.2)</td>
</tr>
<tr>
<td>Black</td>
<td>13 (5.0)</td>
</tr>
<tr>
<td>Indian/Pakistani/Bangladeshi</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>First Language n (%)</td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>242 (93.1)</td>
</tr>
<tr>
<td>Residence n (%)</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>241 (94.1)</td>
</tr>
<tr>
<td>Asthma n (%)</td>
<td></td>
</tr>
<tr>
<td>reported diagnosis</td>
<td>58 (22.3)</td>
</tr>
<tr>
<td>taken asthma medication</td>
<td>52 (20.0)</td>
</tr>
</tbody>
</table>

5.5.3 Descriptive memory outcomes

Participants recalled on average only 2 of the 8 listed PIL side effects (Correct Side Effect Recall, Table 32). Around a fourth of participants (24.3%) recalled at least one unlisted side effect (Incorrect Side Effect Recall). Correct and Incorrect Side Effect Recall were significantly negatively correlated (r=-.134, p<.05), indicating that participants who recalled more side effects correctly committed less recall errors. Participants recognized on average five listed (M=5.45, SD=1.87) and two unlisted side-effects (M=2.08, SD=2.00). Over three quarters of participants (75.4%) “recognized” at least one unlisted side effect. Mean Side Effect Recognition
Sensitivity was 1.24 (SD=1.12). The mean Response Bias (M=0.09, SD=0.48) was above 0, indicating that participants were unwilling to guess that side effects were from the leaflet.

5.5.4 Inter-correlations between pharmaceutical schemas

There were small to moderate correlations between the individual measures assessing pharmaceutical schemas (see Table 32). For example, participants, who believed pharmaceutical medicines to be more harmful, perceived pharmaceuticals as significantly less beneficial and overprescribed by doctors and perceived themselves as more sensitive to their effect (all \( ps < .01 \)).

5.5.5 Pharmaceutical schemas and side effect expectations

Pearson correlations were used to explore whether medication beliefs were associated with participants’ expectations of side effects. Participants who believed pharmaceutical medicines as more harmful (\( r = .363 \)) and overused (\( r = .160 \)) in general and who had greater perceived sensitivity to medicines (\( r = .385 \)) had increased side effect expectations. Beliefs that pharmaceutical medicines are generally beneficial (\( r = -.289, \) \( ps < .01 \)) were associated with decreased side effect expectations.

5.5.6 Pharmaceutical schemas and side effect attribution

Exploratory analyses showed that participants rated the headache symptom as more likely to be a side effect of Molair if they believed medicines to be more harmful, overused, and less beneficial and perceived themselves as more sensitive to medicines (see Table 32). Demographic factors, leaflet condition and self-reported asthma diagnosis showed no association with side effect attribution (all \( ps > .05 \)). A multivariate linear regression model with BMQ-General scales and PSM entered jointly in the model explained 16.8% of variance in side effect attribution (\( F(4) = 14.09, p < .001 \)). Both PSM (\( \beta = .172 \)) and General Harm (\( \beta = .296, ps < .01 \)) remained significant predictors in the multivariate model, while General Benefit was only marginally significant (\( \beta = -.100, p = .096 \)).
Table 32: Correlations between pharmaceutical schemas, side effect attribution and memory outcomes

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSM</td>
<td>1</td>
<td>34**</td>
<td>-.13</td>
<td>.28**</td>
<td>.28**</td>
<td>-.07</td>
<td>.08</td>
<td>-.03</td>
<td>.06</td>
<td>2.6 (1.0)</td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>1</td>
<td>-.32**</td>
<td>.57**</td>
<td>.38**</td>
<td>-.27**</td>
<td>-.01</td>
<td>-.27**</td>
<td>.13*</td>
<td>2.5 (0.8)</td>
<td></td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>1</td>
<td>-.16**</td>
<td>-.22**</td>
<td>.16**</td>
<td>-.04</td>
<td>.16*</td>
<td>.22**</td>
<td>3.8 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Overuse</td>
<td>1</td>
<td>.22**</td>
<td>.03</td>
<td>-.02</td>
<td>.07</td>
<td>.22**</td>
<td>3.4 (0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side Effect Attribution</td>
<td>1</td>
<td>-.23**</td>
<td>-.02</td>
<td>-.20**</td>
<td>-.02</td>
<td>39.6 (26.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct Side Effect Recall</td>
<td>1</td>
<td>-.13*</td>
<td>.72**</td>
<td>.03</td>
<td>2.2 (1.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorrect Side Effect Recall</td>
<td>1</td>
<td>.21**</td>
<td>-.16**</td>
<td>0.3 (0.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognition Sensitivity</td>
<td>1</td>
<td>.07</td>
<td>1.2 (1.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criterion Bias</td>
<td>1</td>
<td>1</td>
<td>0.10 (0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. ** p<.01; * p<.05 (two-tailed); PSM=Perceived Sensitivity to Medicines Scale; BMQ=Beliefs about Medicines Questionnaire*
5.5.7 Pharmaceutical schemas and memory for side effect information

5.5.7.1 Correct Side Effect Recall

Exploratory analyses (see Table 32) showed that there were significant correlations between BMQ-General Benefit and Harm beliefs and Correct Side-Effect Recall. Stronger beliefs in the harmfulness of pharmaceuticals were associated with reduced Correct Side Effect Recall ($r=-.273$), whereas stronger perceived benefits of pharmaceuticals were associated with increased Correct Side Effect Recall ($r=.164$, $p<.01$). Perceived Sensitivity to Medicines (PSM) and beliefs that medicines are overprescribed by doctors (BMQ-General Overuse) were not associated with Correct Side-Effect Recall. Figure 33 illustrates differences in Correct Side Effect Recall for participants scoring in the lower and upper 50th percentile (Median split) on the General Harm and General Benefit scales.

Figure 33: Mean Correct Side Effect Recall by BMQ-General Harm and Benefit beliefs

![Graph showing mean correct side effect recall by BMQ-General Harm and Benefit beliefs.](image)

Note. **$p<.01$; SE= Side Effect; Low=lower 50th percentile, high=upper 50th percentile

A hierarchical regression model was then constructed to test for the amount of variance in Correct Side Effect Recall explained by pharmaceutical schemas, when controlling for age, gender, asthma diagnosis and leaflet condition (see Table 33, Model A). In this model both control variables ($R^2$ step 1 = .066, $p<.01$) and pharmaceutical schemas ($R^2$ change step 2 = .082, $p<.001$) significantly improved prediction. General Harm beliefs remained a significant predictor ($\beta = -.340$, $p<.001$) in the multivariate model. Probably owing to relatively high inter-correlations
between beliefs (see Table 32), General benefit beliefs failed to reach significance in the full model.

Table 33: Hierarchical regression models predicting Correct and Incorrect Side Effect Recall

<table>
<thead>
<tr>
<th></th>
<th>Model A</th>
<th>Model B</th>
<th>Model C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correct Side Effect Recall</td>
<td>Recognition Sensitivity</td>
<td>Response Bias</td>
</tr>
<tr>
<td>Step 1</td>
<td>△R²</td>
<td>β</td>
<td>△R²</td>
</tr>
<tr>
<td>Leaflet Condition</td>
<td>.066**</td>
<td>-.028</td>
<td>.101***</td>
</tr>
<tr>
<td>Asthma¹</td>
<td></td>
<td>-.056</td>
<td></td>
</tr>
<tr>
<td>Gender²</td>
<td>.183**</td>
<td></td>
<td>.187**</td>
</tr>
<tr>
<td>Age</td>
<td>.146*</td>
<td></td>
<td>.226***</td>
</tr>
<tr>
<td>Step 2</td>
<td>.082***</td>
<td>.087***</td>
<td></td>
</tr>
<tr>
<td>General Harm</td>
<td>-.340***</td>
<td>-.367***</td>
<td></td>
</tr>
<tr>
<td>General Benefit</td>
<td>.048</td>
<td>.038</td>
<td>.238***</td>
</tr>
<tr>
<td>General Overuse</td>
<td>.202**</td>
<td></td>
<td>.191*</td>
</tr>
<tr>
<td>PSM</td>
<td>-.014</td>
<td>.013</td>
<td>.003</td>
</tr>
<tr>
<td>Total R²</td>
<td>.147***</td>
<td>.188***</td>
<td></td>
</tr>
</tbody>
</table>

Note. ***p<.001; **p<.01; *p<.05; PSM=Perceived Sensitivity to Medicines Scale, ¹,²reference category= reported asthma diagnosis, male

5.5.7.2 Incorrect Side Effect Recall

Exploratory analyses showed no associations between pharmaceutical schemas and the number of incorrectly recalled side effects (see Table 32). Univariate logistic regression models predicting dichotomized Incorrect Recall also found no associations with pharmaceutical schemas or control variables (all confidence intervals of ORs contained zero).

5.5.7.3 Recognition Sensitivity

Exploratory correlational analyses showed that General Harm and General Benefit beliefs were significantly associated with participants’ ability to discriminate side effects from the leaflet from new unlisted symptoms (Recognition Sensitivity). Stronger General Harm beliefs were associated with reduced Recognition Sensitivity (r=-.256, p<.01), stronger beliefs in the benefits of medicines were associated with increased Recognition Sensitivity (r=.160, p<.05).

A hierarchical linear regression model, with all control variables entered in the first step and pharmaceutical schemas entered in the second step (see Table 33, Model B) showed that recognition sensitivity was better for women and older participants, with control variables accounting for around 10% of variance in Recognition Sensitivity. Adding pharmaceutical schemas to the model significantly improved prediction, accounting for an additional 8.7% of variance (see Table 33, Model B).
5.5.7.4 Response Bias

Exploratory analysis (see Table 32) showed that General Harm ($r=.126; p<.05$), General Benefit ($r=.215, p<.001$) and General Overuse beliefs ($r=.223, p<.001$), were associated with higher Response Bias, indicating that participants with this belief set were less likely to guess that a symptom was from the leaflet. A hierarchical linear regression model (again with control variables entered in Step 1 and pharmaceutical schemas entered in step 2) found that control variables were not associated with Response Bias ($R^2=.012, p>.05$), whereas pharmaceutical schemas accounted for 10% of variance (see Table 33, Model C).

5.5.8 Memory for side effect information and side effect attribution

Univariate linear regression models tested whether more accurate memory for side-effects from the leaflet reduced attribution of an unlisted symptom as a side effect. As predicted, Correct Side Effect Recall ($\beta=-.234$) and Recognition Sensitivity significantly reduced side-effect attribution ($\beta=-.207, ps<.001$). Response Bias ($\beta=-.019, p=.762$) and Incorrect Side Effect Recall ($\beta=-.017, p=.789$) were not associated with side-effect attribution.

5.5.9 Mediation analysis

Mediation analysis was used to examine whether the effect of pharmaceutical schemas on side effect attribution was mediated by memory for side-effect information. We only tested for mediation effects for General Harm and Benefit beliefs, as there were no direct effects of either PSM or Overuse on Correct Side Effect Recall and Recognition Sensitivity (see also Table 32). A mediation model with General Harm beliefs as predictor, Correct Side Effect Recall as mediating variable and side effect attribution as outcome (see Figure 34 a), showed that Correct Side Effect Recall significantly mediated the effect of General Harm beliefs on side effect attribution (indirect effect ab=1.23; 95% CI [0.20; 2.65]; $R^2$ mediation effect size=.03; 95% CI [.01, .07]). The direct effect of Harm beliefs on attribution remained significant ($c'=.10; 95\% \text{ CI } [7.00, 14.51], p<.001$), suggesting partial mediation.

An equivalent mediation model was constructed for General Benefit beliefs (see Figure 34 b). In this model Correct Recall again significantly mediated the relationship with the bootstrapped confidence interval of the indirect effect again excluding zero (indirect effect ab=-1.36; 95% CI [-.2.98; -.0.38]; $R^2$ mediation effect size=.01; 95% CI [.002, .032]). As in the previous model, the direct effect of Benefit
beliefs on attribution was significant ($c'=-7.53$, 95% CI [-12.37, -2.69], $p<.01$). Findings were similar when using recognition sensitivity as a mediator, with both confidence intervals of the indirect effect excluding zero.

Figure 34: Mediation models

Note: ***$p<.001$; **$p<.01$; *$p<.05$; BMQ=Beliefs about Medicines Questionnaire

5.5.10 Pharmaceutical schemas and reading times

Participants who believed medicines to be more harmful ($\beta=-.128$) and who perceived themselves as more sensitive to their effects ($\beta=-.138$, $p<.05$) spent less time reading side-effect information (all other BMQ-scales $p>$.05). Older participants spent longer reading side-effect information ($\beta=.292$, $p<.001$), but there was no difference between men and women ($\beta=.03$, $p=.61$) and participants with or without self-reported asthma ($\beta=.03$, $p=.66$) or any of the other control variables.

5.5.11 Testing for differences between leaflet conditions

Demographic characteristics were similar in both leaflet conditions ($p>$.05). Participants in the efficacy information leaflet condition rated Molair as significantly
more effective than participants in the no efficacy information condition ($t(258)=2.17$, $p<.05$; see Table 4 for means). There was no significant difference in side effect expectations, memory outcomes or side-effect attribution between the two groups (all $t$s<1, $ps>.05$, see Table 34).

Table 34: Expectations and memory outcomes by leaflet condition

<table>
<thead>
<tr>
<th>Variable</th>
<th>Efficacy Information ($n=133$)</th>
<th>No Efficacy Information ($n=127$)</th>
<th>Total ($N=260$)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expectations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side Effect VAS; $M(SD)$</td>
<td>44.19 (23.25)</td>
<td>41.81 (22.71)</td>
<td>43.03 (22.98)</td>
<td>.405</td>
</tr>
<tr>
<td>Efficacy VAS; $M(SD)$</td>
<td>70.79 (18.08)</td>
<td>66.27 (15.40)</td>
<td>68.58 (16.94)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td><strong>Memory Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct SE Recall $M(SD)$</td>
<td>2.24 (1.68)</td>
<td>2.18 (1.60)</td>
<td>2.21 (1.63)</td>
<td>.764</td>
</tr>
<tr>
<td>Correct SE Recognition $M(SD)$</td>
<td>5.44 (2.00)</td>
<td>5.45 (1.74)</td>
<td>5.45 (1.87)</td>
<td>.931</td>
</tr>
<tr>
<td>Incorrect SE Recall $M(SD)$</td>
<td>0.27 (0.52)</td>
<td>0.35 (0.67)</td>
<td>0.31 (0.36)</td>
<td>.411 $^a$</td>
</tr>
<tr>
<td>Incorrect SE Recognition $M(SD)$</td>
<td>2.10 (2.00)</td>
<td>2.07 (1.92)</td>
<td>2.08 (2.00)</td>
<td>.820</td>
</tr>
<tr>
<td><strong>Side effect attribution</strong></td>
<td>$M(SD)$</td>
<td></td>
<td></td>
<td>.816</td>
</tr>
<tr>
<td></td>
<td>39.23 (27.54)</td>
<td>39.98 (24.89)</td>
<td>39.60 (26.23)</td>
<td></td>
</tr>
</tbody>
</table>

Note. SE=Side effect; VAS=Visual Analogue Scale; $^a$ Chi-square-test; all other tests independent samples $t$-test (all two-sided)

5.6 Discussion

5.6.1 Summary of findings

The study replicated findings from the previous analogue study (Study 3) by showing that more negative pharmaceutical schemas increased the likelihood that an unrelated symptom (not listed in the patient leaflet) was attributed as a side effect. Participants who believed pharmaceutical medicines to be more harmful and less beneficial in general were more likely to attribute the headache symptom as a side effect. But while participants’ perceptions of higher personal sensitivity to medicines only marginally increased side effect attribution in Study 3, there was a clear effect of increased side effect attribution in this study. Taken together these findings lend support for the postulated role of medication beliefs in the attribution of symptoms as side effects (see Research Question 2).

But the study went beyond a mere replication of the previous findings, by showing that medication beliefs influenced how participants processed and remembered information about side effects. Participants who perceived pharmaceuticals as more harmful recalled fewer of the side effects that were listed
in the patient leaflet and were less able to discriminate between listed and new side effects in the recognition memory task (Recognition Sensitivity). Participants who believed medicines to be generally more beneficial (higher BMQ-General Benefit) recalled more side effects correctly and showed better Recognition Sensitivity. As predicted, better memory for listed side effects decreased the likelihood that an unlisted symptom was attributed as a side effect. The relationship between pharmaceutical schemas and side effect attribution was partially mediated by memory for side effect information.

Including additional efficacy information in the patient leaflet increased individuals’ expectations of the drug’s efficacy, but did not influence side effect expectations, memory for side effect information or side effect attribution.

5.6.2 Integration with previous literature

Previous studies have shown poor memory for medical information (Barsky, 2002; Ley, 1979), but few have examined potentially modifiable psychological factors related to memory (Watson & McKinstry, 2009) and linked memory for side effects to symptom attribution decisions. As outlined in the introduction of this chapter, there is evidence that illness schemas influence the recall of illness symptoms (Baumann et al., 1989), but this is the first study to demonstrate an association between pharmaceutical schemas and memory for side effects. Perhaps contrary to clinical intuition, more negative pharmaceutical schemas were associated with poorer memory for side effect information (reduced Correct Side Effect Recall and Recognition Sensitivity).

Possible reasons for this unexpected finding include the avoidance of information and gist-based encoding: Participants with stronger harm beliefs spent less time on the page of the patient leaflet that contained the side effect information. This is in line with studies showing that anxious people may avoid anxiety inducing stimuli (Cisler, Bacon, & Williams, 2009; Onnis, Dadds, & Bryant, 2011) and qualitative studies documenting instances where patients actively avoid information about side-effects. As side effect information can be frightening some patients may choose to avoid this information altogether in order not to demotivate themselves from taking their treatment (Hayden et al., 2015). Information about side-effects may also have simply confirmed participants’ negative general preconceptions about medicines, leading them to scrutinize information less carefully or to encode mainly
the general gist of the information (Brainerd & Reyna, 2002; Reyna & Brainerd, 1995); i.e. long list of relatively mild side effects. Participants perceptions of the harmfulness of pharmaceuticals in general were associated with reduced recognition sensitivity (indicating more false alarms), speaking to the possible role of gist-based memory strategies (Roediger & McDermott, 1995).

After completing the medication belief measures, some participants were randomized to receive efficacy information as part of the patient leaflet, According to the affect heuristic (Slovic, Finucane, Peters, & MacGregor, 2007), higher efficacy perceptions should lead to more positive feelings about the treatment and reduced risk perceptions. The inclusion of efficacy information in the leaflet significantly increased efficacy expectations in this study. However, risk perceptions, side effect attribution and memory outcomes were not affected by the efficacy manipulation. It is possible that the manipulation, which consisted of showing a short additional paragraph in an online patient leaflet, was too weak to raise efficacy expectations enough in order to impact risk perception. Further studies are needed to test whether patients may benefit from more balanced patient information leaflets that include both risk and benefit information. However findings from the placebo and clinical literature speak to the possible benefit of mentioning drug effectiveness by increasing patients’ expectations (Benedetti, 2010; Enck et al., 2013; von Blanckenburg, Schuricht, Albert, Rief, & Nestoriuc, 2013)

The study also highlights the importance of memory for side effect information in symptom attribution. People are more likely to make appropriate symptom attribution decisions if they correctly remember side effect information. Better memory for factual side effect information may reduce the likelihood that noisy common background symptoms (Reidenberg & Lowenthal, 1968) or symptoms of the disease (Thiwan et al., 2009) are reported as side effects. The misattribution of these unrelated symptoms as side effects to the medication may have serious consequences by reducing adherence to necessary treatment.

5.6.3 Strengths and limitations

The study has several strengths and limitations. The analogue study approach, using a fictitious (but realistic) medication allowed me to control for previous experience with the medication and to unambiguously operationalize what constitutes an unrelated side effect. Recall and recognition memory was similar for participants with and without self-reported past asthma diagnosis, speaking to the potential generalizability of findings. It was beyond the scope of this preliminary
online study to assess other potentially important variables (e.g. health anxiety, somatization, illness representations, and previous side effect experience). Recall and recognition memory were measured in a within-subjects design. It is therefore possible that recognition of side effect information was influenced by previous recall. A replication of the findings, varying recall and recognition between subjects, is needed. Future studies should also test whether pharmaceutical schemas are only associated with reduced memory for side effect information and not memory in general. This could for example be achieved by including a standardized memory test like the Wechsler Digit Span Test (Wechsler, 2008) in the study design.

Given that pharmaceutical schemas were not experimentally manipulated in this study, it is possible that individuals with more negative pharmaceutical schemas differed systematically on memory-relevant attributes such as educational background and need for cognition from participants with more positive schemas. Further studies could test whether there was a specific effect of schemas on memory rather than through these factors, by attempting to modify pharmaceutical schemas and examining whether this affects memory for side effects. However, changing peoples’ ingrained beliefs about pharmaceuticals is not straightforward, particular in an online setting. Even relatively intensive interventions (e.g. individual sessions with a nurse (Chapman et al., 2015)) to change beliefs about prescribed medications and improve adherence have had mixed success (Chapman et al., 2015; Petrie et al., 2012; Zwikker et al., 2014). In the following chapter I will present a feasibility study, which explores whether short online interventions can indeed be effective in changing pharmaceutical schemas. It was however beyond the scope of this intervention study to test putative effects on memory for side effect information.

The role of attentional processes in the association between medication beliefs and memory for treatment information also merits further investigation. The finding that participants with more negative medication beliefs spent less time reading side effect information rests on online data, where a range of uncontrolled variables may have affected reading time. Examining the role of medication beliefs on attention in a more controlled lab setting or potentially using eye tracking technology may help to further explore this question.

As in the previous study, participants were recruited through convenience sampling. This raises again questions about a possible selection bias (see also section 4.6.3). A further limitation is that the study failed to explicitly examine potential speeding and straightlining response patterns (McHorney, Zhang, Stump, & Zhao, 2012), which may have affected general data quality.
Above all, it is very important to keep in mind that analogue studies have only limited external validity. It is plausible that individuals would process information about a new medication differently if there was more at stake, i.e. if they were prescribed this new medication by a doctor to manage an existing illness. A replication of the findings in clinical samples, prescribed real medication, with a range of mild to severe side effects is therefore highly warranted.

5.6.4 Clinical implications

The study has several clinical implications. Research on the use of patient information in the UK suggests that over 70% of patients read at least part of the patient leaflet, especially if they are first-time users. The side effect section was identified as the most commonly read section (Raynor, Silcock, Knapp, & Edmondson, 2007). However, the majority of interviewed patients in the study indicated that they did not look at the leaflet again after initial reading. This suggests that patients do indeed rely on their memory for side effects when evaluating symptoms.

We know that memory for patient information is generally poor (Kessels, 2003). The present study suggests that giving patients even carefully designed patient information may not be sufficient to ensure that this information is correctly remembered. Past efforts to improve recall of medical information have primarily focused on the presentation of the information itself (e.g. written versus oral (Weinman, 1990), use of pictures (Houts, Doak, Doak, & Loscalzo, 2006), the clarity and complexity of wording (Bradshaw, Ley, & Kincey, 1975) or use of mind maps and acronyms (Thickett & Newton, 2006). These strategies are clearly important, but practitioners and designers of patient information should also take individual differences in pre-existing beliefs about medicines into account when communicating treatment information. Treatment decision support tools (O'Connor et al., 1999) and patient leaflets may benefit from including information that addresses known but unfounded concerns about the treatment. The study also demonstrates the need to develop targeted interventions to modify medication beliefs as this may increase patients’ readiness to engage with treatment information, reduce symptom attribution errors and related adherence problems.
5.6.5 Conclusion

Despite the limitations inherent in an analogue study design, the findings provide new knowledge about the psychological processes linking medicines information to the attribution of symptoms as medication side effects (see Research Question 2) by showing that pre-existing pharmaceutical schemas affect both the quantity and accuracy of memory for side effect information and highlight the need to consider the patient’s perspective when communicating treatment information.
Chapter 6: Feasibility study exploring intervention components to change medication beliefs (Study 5)

6.1 General aims of the study

Findings from the previous studies lend support to the postulated relationship between medication beliefs and side effects. Individuals who started out with more negative beliefs about medicines subsequently reported more side effects in response to active medication (Study 1) and placebo (Study 2) (see Research Question 1). In addition, I provided first insights into the putative processes underlying this association (see Research Question 2): More negative medication beliefs were associated with increased side effect expectations (Studies 2-4), greater monitoring of bodily changes following deceptive placebo treatment (Study 2) and a tendency to attribute ambiguous sensations (Study 2) or a common unrelated symptom (Studies 3-4) as side effects.

These findings are clinically important as patient reported side effects have been shown to compromise quality of life and to reduce adherence to necessary treatment in clinical samples (see section 1.2). This was confirmed in Study 1, where side effects decreased adherence and persistence with prescribed treatment. These associations were also apparent in Studies 3 and 4, where I showed that misattributing the unrelated headache symptom as a side effect starkly increased behavioural intentions to stop treatment.

This chapter addresses the outstanding question of whether it is possible to change medication beliefs (see Research Question 3). Given the association of medication beliefs with both side effects and adherence, interventions to modify treatment beliefs may be effective in improving outcomes for patients. The aim of the present feasibility study is thus to explore whether interventions that modify negative general beliefs about pharmaceuticals can reduce side effect attributions and behavioural intentions to stop treatment.

6.2 General theoretical background

There have been repeated calls to develop effective interventions to modify treatment beliefs in order to improve patient outcomes (Butler et al., 2004; Murphy, Bartholomew, Carpentier, Bluethmann, & Vernon, 2012; Ponieman, Wisnivesky, Leventhal, Musumeci-Szabo, & Halm, 2009), but systematic evidence on how to best modify treatment beliefs is sparse.
To date there is no systematic review of interventions to modify treatment beliefs. The majority of interventions identified by a literature search focused on psychoeducational strategies, e.g. presenting facts and information to increase perceived necessity for a specific treatment and to reduce patients’ concerns about negative treatment effects (Chapman et al., 2015; Karamanidou, Weinman, & Horne, 2008; Magadza, Radloff, & Srinivas, 2009; O’Carroll, Chambers, Dennis, Sudlow, & Johnston, 2014; Petrie et al., 2012; Zwikker et al., 2014). According to the taxonomy of behaviour change techniques (BCTs) developed by Michie and colleagues (Michie, Johnston, Abraham, Francis, & Eccles, 2013) most of the interventions would correspond to providing “information about health consequences (Item 5.1)” and increasing the “salience of consequences (Item 5.2)”. For example in one of the interventions patients with asthma were told that “taking their preventer medication every day protects them from asthma symptoms” (Petrie et al., 2012).

Findings concerning the efficacy of published interventions is mixed, with some studies showing significant differences between the intervention and control group in reducing concerns and increasing necessity beliefs (Magadza et al., 2009; O’Carroll et al., 2014; Petrie et al., 2012), others failing to do so (Chapman et al., 2015; Zwikker et al., 2014). In some of these studies, general medication beliefs, although not the main focus of the intervention, improved as well (Magadza et al., 2009). Potentially there may be further studies that were not published (or did not mention effects of the intervention on medication beliefs) because of non-significant findings (Easterbrook, Gopalan, Berlin, & Matthews, 1991), making it difficult to get a complete picture of previous intervention approaches and their effectiveness in changing medication beliefs.

There is of course also always the risk that interventions were not adequately implemented (Chapman et al., 2015), meaning that potentially effective interventions may not have changed beliefs. However, the literature on attitude and behaviour change shows that fact-based educational strategies have their limitations (Maio & Haddock, 2009). Public health campaigns have ensured that most smokers are accurately aware of the negative health consequences of smoking (Brownson et al., 1992), but this knowledge does not always translate into any attitude or behaviour change. There is even a risk that warnings about potential health consequences can have unintended negative effects. An early lab experiment showed for example that participants reading the statement “Warning by
HM government. Smoking can damage your health.” had a stronger desire to smoke than those not receiving this warning (Hyland & Birrell, 1979).

Similarly providing information to reduce concerns about treatment is not always effective and can at times backfire: A nationally representative US survey (Nyhan & Reifler, 2015) showed for example that 43% of survey respondents held the false belief that they could contract the flu from receiving influenza vaccination. An intervention that provided corrective information about this myth was effective in reducing this false belief and alleviating concerns about vaccination safety. However, it also significantly reduced behavioural intentions to vaccinate among participants who started out with stronger concerns about vaccine side effects. Similar findings have been reported (Nyhan, Reifler, Richey, & Freed, 2014) from a study trying to debunk the myth that the measles, mumps and rubella (MMR) vaccine causes autism, where intent to vaccinate also decreased.

Interventions that focus on informing patients that their prescribed medication is safe may thus not be enough to fundamentally reduce patients’ concerns about side effects and improve adherence, in particular if the underlying general beliefs about pharmaceuticals remain negative. Instead of attempting to reduce concerns about side effects of a specific medication, this study focused on changing underlying background beliefs about pharmaceuticals (pharmaceutical schemas). Pharmaceutical schemas are thought to influence beliefs about specific medications (Horne, 2003) (see also section 1.3.1.3). It is therefore plausible that reducing negative pharmaceutical schemas could be effective in ameliorating perceptions of specific medicines. The focus on general medication beliefs also allowed me to pre-test intervention components in a convenience sample of mainly healthy participants.

Secondly, I will explore whether strategies beyond the prevalent psychoeducational approach may be effective in changing pharmaceutical schemas. All of the proposed intervention techniques are grounded in social cognitive models of attitude/belief change. Similar techniques have been suggested within the BCT taxonomy (Michie et al., 2013) to foster health promoting attitudes and behaviour (e.g. credible expert source, cognitive dissonance). Given that medication beliefs are cognitions (Horne, 1997, 2003), cognition-focused intervention techniques were deemed a good fit.
6.3 Design considerations

The Medical Research Council’s (MRC) guidance on intervention development (Craig et al., 2008) stresses the importance of pilot and feasibility testing. I therefore decided to pre-test a range of possible interventions for potential inclusion in a future complex intervention to modify general medication beliefs. Although multiphase optimization of interventions and systematic pre-testing of intervention components is highly recommended (Collins, Murphy, Nair, & Strecher, 2005), it is often compromised by time, monetary and recruitment constraints. Recruiting pre-test participants through convenience online sampling (as in Studies 3 and 4) and delivering the intervention online allowed me to avoid some of these issues. Online-interventions have become increasingly popular in general (Griffiths, Lindenmeyer, Powell, Lowe, & Thorogood, 2006) and have for example proved effective in reducing alcohol consumption (White et al., 2010), increasing adherence to a recommended diet-regimen (Sainsbury, Mullan, & Sharpe, 2013) and reducing symptoms of depression in a community sample (Christensen, Griffiths, & Jorm, 2004).

I decided to use a pre-post randomized control group design to examine the effect of the intervention components on general medication beliefs (primary outcome). But we have seen from the vaccination intervention studies (Nyhan & Reifler, 2015; Nyhan et al., 2014) that changing unhelpful beliefs is not necessarily effective in changing behavioural intentions. I thus decided to also examine potential consequences of belief change, namely a reduction in the misattribution of unrelated symptoms as side effects and behavioural intentions to stop treatment. A vignette scenario approach (comparable to Studies 3 and 4) was used to assess the effect of the intervention on these secondary outcomes. This further allowed me to examine whether I could replicate previously identified associations between medication beliefs and side effect attribution/behavioural intention. However, in order to explore the generalizability of previous findings, I changed the fictitious medication to an oral over-the-counter anti-histamine (previously leukotriene receptor antagonist) for the treatment of hay fever (previously asthma). Hay fever (allergic rhinitis) is a type of inflammation that occurs when the immune system overreacts to inhaled allergens (e.g. seasonal pollen and moulds) (Wheatley & Togias, 2015). Symptoms include sneezing, airflow obstruction, itching and excess nasal secretion (Valet & Fahrenholz, 2009). Like asthma, hay fever is fairly common in the general population, suggesting that most people should be familiar with the illness. The National Centre for Health Statistics estimates that 8% of the adult
population suffer from allergies or hay fever in the US. (http://www.cdc.gov/nchs/fastats/allergies.htm). The Health Survey for England estimated a 15% prevalence rate for hay fever in the UK in 2001 (Gupta, Sheikh, Strachan, & Anderson, 2007). In addition, the target attribution symptom was changed from headache to nausea. Nausea is a commonly reported side effect to placebo (De La Cruz et al., 2010; Klosterhalfen et al., 2009) and is frequently listed as a side effect to active medication (Tan et al., 2014).

6.4 Theoretical background and content of interventions

As already outlined above, all intervention components were based on social cognitive models of attitude and belief change. Detailed accounts of the theoretical models informing the different interventions and an overview of the content and procedures of the interventions are presented below. I am fully aware that descriptions of intervention content and procedures would more naturally sit in the method section. Yet, given the number of different theoretical accounts used in the intervention development, I decided to present the information about the specific interventions along with their theoretical background in order to facilitate understanding. Table 36 provides a brief overview of the proposed interventions and their theoretical background.

6.4.1 Cognitive Dissonance Theory

Interventions 1 and 2 were informed by cognitive dissonance theory (Festinger, 1962; Festinger & Carlsmith, 1959). Cognitive dissonance theory predicts that individuals will change their attitudes and beliefs if they voluntarily and without external coercion advocate a counter-attitudinal position. Defending counter-attitudinal beliefs is thought to lead to an aversive motivational state (i.e. dissonance) if there is little external justification for doing so (e.g. no external pressure, no financial incentive). Individuals subsequently change their beliefs or attitudes in order to reduce the aversive experience of dissonance, which is associated with psychological discomfort and physical arousal (Croyle & Cooper, 1983; Elliot & Devine, 1994; Losch & Cacioppo, 1990). A meta-analysis examining evidence from 16 dissonance based interventions showed that relative to untreated controls, cognitive dissonance interventions resulted in greater reduction in eating disorder (ED) risk factors, ED symptoms, future risk for onset of EDs, and mental health utilization, with some effects persisting over a three year follow-up (Stice, Shaw, Becker, & Rohde, 2008). Cognitive dissonance based interventions have
also been shown to be effective in changing other health behaviours (e.g. sexual risk behaviour (Eitel & Friend, 1999) and smoking (Simmons & Brandon, 2007).

Several dissonance based intervention techniques have been developed (Freijy & Kothe, 2013). For the present study the counter-attitudinal essay task (or induced compliance paradigm) was chosen. The counter-attitudinal essay task (Janis & King, 1954), where individuals freely write a short essay defending a counter-attitudinal perspective, has been used in numerous studies of attitude and belief change (Maio & Haddock, 2009). It has proved effective in changing attitudes and beliefs about marihuana smoking (Nel, Helmreich, & Aronson, 1969), alcohol consumption (Croyle & Cooper, 1983), prejudice toward blacks (Leippe & Eisenstadt, 1994), and even students’ attitudes towards tuition fee increases (Elliot & Devine, 1994). The content and procedures of the two cognitive dissonance interventions are outlined below.

6.4.1.1 Counter-attitudinal essay about benefits of medicines (Intervention 1)

Participants were invited to write a short essay arguing that the benefits of medicines outweigh the risks. They were told that they could freely decide whether or not to write the essay and that there were no negative consequences for not doing so. In addition, participants were informed that their arguments might be used as basis for discussion in patient focus groups aimed at improving adherence. This was included as cognitive dissonance tends to be stronger if the counter-attitudinal act has potential consequences (e.g. if students essays about fee increases are shown to the university board voting on fee increases (Elliot & Devine, 1994)). Please note that writing this essay would not constitute a counter-attitudinal act for participants with initially favourable attitudes towards medicines. Writing a belief-congruent essay is not expected to lead to dissonance, but may strengthen individuals’ initial favourable attitudes by making them more accessible (Powell & Fazio, 1984). There was no time limit for typing the essay in the provided text-box, but the Qualtrics page timing function was used to measure writing times. A validated three item psychological discomfort scale (Elliot & Devine, 1994) was used to assess whether the intervention resulted in cognitive dissonance: Participant had to rate on 7-point Likert scales (from 1=does not apply at all to 7=applies very much) whether they felt uncomfortable, uneasy and bothered.
6.4.1.2 Counter-attitudinal essay about the lack of harm of medicines (Intervention 2)

Intervention 2 followed the same procedures as Intervention 1, but participants were asked to write a short essay arguing that medicines are safe and not harmful.

6.4.2 Elaboration Likelihood Model of persuasion

Persuasive health communication is a cornerstone of public health campaigns (Hornik, 2002), but is unfortunately not always sufficiently informed by theory (Fishbein & Yzer, 2003). As argued above, fact based psychoeducational strategies are not necessarily effective in changing beliefs and behaviour. The idea behind Interventions 3 and 4 was to create persuasive messages to convince people that pharmaceuticals are generally beneficial and not harmful, but to firmly ground the messages and their delivery in a well-established persuasion framework. One of the most prominent and best validated models of persuasion (Zimbardo & Leippe, 1991) is the Elaboration Likelihood Model (ELM) by Petty and Cacioppo (Petty & Brinol, 2010; Petty & Cacioppo, 1986). The ELM postulates that there are two distinctive routes to persuasion:

A) a central route, where individuals engage in more effortful elaborative processing of arguments (e.g. evaluating the quality of the arguments)

B) a peripheral route where people rely on heuristic cues (e.g. number of pro versus con arguments, credibility of the message source) (Petty & Cacioppo, 1986).

Persuasion can result both from central and peripheral processing, but belief/attitude change resulting from more elaborate processing is more enduring, resistant and predictive of behaviour (Petty & Brinol, 2010; Petty, Haugtvedt, & Smith, 1995). The two ELM interventions (Interventions 3 and 4) were designed to achieve more sustained belief change via the central route, but heuristic cues for persuasion under low elaboration conditions were also included.

A) Central route to persuasion

Several factors that have proved effective in increasing elaborate processing of information and facilitating persuasion were incorporated in the intervention (see Table 35).

- Personal relevance of the issue (Johnson & Eagly, 1989; Petty, Cacioppo, & Goldman, 1981) was made salient by highlighting that medicines are the most
common and universally used health interventions and that most people will use medicines at some point in their lives.

- In order to increase the perceived importance of the task (Chaiken & Maheswaran, 1994) participants were told that careful reading of the arguments was crucial for the validity of study results and were informed that they had to answer questions about the arguments later on.

- Message comprehensibility is key to ensure that messages are adequately processed. People typically only skim over complex and incomprehensible information or ignore it altogether (Eagly & Warren, 1976). Readability of the messages was assessed with readability software (https://readability-score.com) and messages were optimized for comprehensibility. Final Flesch Kinkaid readability scores ranged from 50-65, corresponding to a reading age of 13-15 year olds or the readability of an average broadsheet (Williamson & Martin, 2010).

- Elaborate processing of arguments is only effective if the quality of presented arguments is high (Petty & Cacioppo, 1986). Messages should be credible and supported by expert knowledge and data and not easily falsifiable (i.e. not be inconsistent with prior experiences or personal observations) (Crano, 2010). Where possible, empirical data from published studies was used in generating the arguments (see Appendix N for sample arguments).

I followed Petty and Cacioppo’s advice (Petty & Cacioppo, 1986) to determine the quality of the generated arguments through a pre-test. Participants (N=67, recruited from subject pool comparable to the main study) were asked to freely list the thoughts that came to mind when reading each of several arguments about pharmaceutical medicines. This thought-listing technique has proved effective in determining argument quality in the past (Petty & Cacioppo, 1986). Pre-test participants were shown eight arguments outlining the benefits (pros) of medicines and eight arguments acknowledging problems and risks related to pharmaceutical medicines (cons). In addition, participants rated the strength of each argument on a 9-point Likert scale (from 1 = not strong at all to 9 = extremely strong). The 6 strongest pro medication arguments as well as 3 low strength con arguments were included in the intervention.

- Con arguments were included, as two-sided arguments increase credibility by making the persuader appear less biased (Crowley & Hoyer, 1994).
People do not easily give up existing beliefs and attitudes (Crano, 2010) and sometimes failed persuasion attempts can strengthen or polarize initial attitudes (see also section 6.2). Two-sided arguments can help to reduce resistance to persuasion and attitude polarization (Petty & Cacioppo, 1986), as people feel they are given a more balanced account of the topic.

Table 35: Intervention components based on the Elaboration Likelihood Model of persuasion

<table>
<thead>
<tr>
<th>Central Route to Persuasion</th>
<th>Peripheral Route to Persuasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal Relevance</td>
<td>Credibility of message source</td>
</tr>
<tr>
<td>Task Importance</td>
<td>Number of arguments (6 pro, 3 con)</td>
</tr>
<tr>
<td>Readability</td>
<td>Length of arguments (pro longer)</td>
</tr>
<tr>
<td>Argument Quality</td>
<td></td>
</tr>
<tr>
<td>credible</td>
<td></td>
</tr>
<tr>
<td>convincing</td>
<td></td>
</tr>
<tr>
<td>supported by expert knowledge and data</td>
<td></td>
</tr>
<tr>
<td>not easily falsifiable</td>
<td></td>
</tr>
<tr>
<td>two-sided (pros and cons)</td>
<td></td>
</tr>
</tbody>
</table>

B) Peripheral route to persuasion

Several factors that can increase persuasion via the peripheral route were incorporated in the intervention (see Table 35).

- The mere **number of arguments** for an attitudinal position may serve as a cue for the amount of supporting evidence (Haugtvedt & Petty, 1992). Participants saw six pro-medications arguments, but only three con-arguments (two of which contained some kind of refutation (e.g. “Almost all medicines have side effects, but many side effects are due to human error”). The predominance of pro arguments was also graphically illustrated by showing participants a table summarizing pro and con arguments (see Figure 35).

- **Message length** may also serve as a heuristic cue for the amount of supporting evidence (Wood, Kallgren, & Preisler, 1985). Pro arguments were thus constructed to be relatively longer than con arguments.

- People are more easily persuaded by messages if they believe that the message come from a **credible** and unbiased **source** (Michie, Johnston, Francis, Hardeman, & Eccles, 2008; Petty & Cacioppo, 1984; Pornpitakpan, 2004). Two different message sources were used in the ELM based interventions. Participants read pro and con arguments about pharmaceutical medicines either presented by an independent medical expert (Intervention 3) or a patient representative (Intervention 4). Past research has shown that patients trust doctors (followed by pharmacists) most in providing information about medicines (Donohue, Huskamp,
Wilson, & Weissman, 2009; Marrie, Salter, Tyry, Fox, & Cutter, 2013). Since the rise of internet and social media platforms there is however also a growing trend for patients to seek information and advice about treatments from fellow patients (Beusterien, Tsay, Gholizadeh, & Su, 2013; McGregor et al., 2014). The content and procedures of the two ELM-based interventions are outlined below.

6.4.2.1 Two-sided persuasive arguments presented by medical expert (Intervention 3)

Participants were told that they would read parts of a speech about the benefits and risks of medicines. They were informed that the speech was by a professor from Harvard Medical School and that the speaker was a world-renowned medical expert with a proven publication record in medical and pharmaceutical journals. After some information about the relevance of the topic and the importance of the task, participants were shown a series of nine argument about the pros and cons of medicines. One argument was presented per screen. At the end participants saw a picture summarizing the presented arguments (see Figure 35) and were asked to briefly list the thoughts that went through their mind when reading the arguments (thought-listing task).

Figure 35: Summary of pro-and con arguments

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Medicines save lives</td>
<td>1 Pharmaceutical companies make misleading claims about efficacy</td>
</tr>
<tr>
<td>2 Medicines increase life expectancy</td>
<td>2 Medicines are too unspecific</td>
</tr>
<tr>
<td>3 Medicines reduce disability and improve quality of life</td>
<td>3 Medicines have risks</td>
</tr>
<tr>
<td>4 Medicines have societal benefits</td>
<td></td>
</tr>
<tr>
<td>5 Medicine safety is carefully monitored</td>
<td></td>
</tr>
<tr>
<td>6 New medicines have fewer side effects</td>
<td></td>
</tr>
</tbody>
</table>

6.4.2.2 Two-sided persuasive arguments presented by patient representative (Intervention 4)

As per Intervention 3, but participants were told that the presented arguments were from a speech given by a patient representative. They learned
about the speaker's own medical condition (heart disease) and were told that the speaker had volunteered as an advocate for patient rights at many different health organizations.

6.4.3 Availability heuristic

The next three interventions (Interventions 5-7) were informed by research on the role of heuristic inferences in judgement and decision making. Participants were invited to generate arguments why medicines are beneficial and/or harmful. Self-generated arguments are especially effective in inducing attitude change (Briñol, Tormala, & Petty, 2013). Participants who had to generate arguments about the dangers of smoking changed their attitudes more than participants who passively received similar arguments (Janis & King, 1954). Letting individuals generate arguments against their initial attitudinal position is however only effective if it feels easy to generate these arguments (Wänke, Bohner, & Jurkowitsch, 1997). According to the availability heuristic people infer the strength of their attitude from the ease with which they can generate attitude supporting evidence (Kahneman, Slovic, & Tversky, 1982). If it feels difficult to come up with arguments, individuals are likely to infer that there are not many or not many valid arguments to support this particular attitudinal position. This in turn decreases the strength of the attitudinal position and the confidence with which the attitude is held. Ease of argument generation can be experimentally manipulated by varying the number of arguments participants are instructed to generate. Given that it typically feels more difficult to come up with a greater number of arguments, participants who were asked to generate fewer arguments changed their attitude more: People rated themselves as more assertive if they had to recall 6 (versus 12) examples of their own assertive behaviours (Schwarz et al., 1991). People thought they cycled less frequently if they had to generate 8 (versus 3) examples of past bicycle use (Aarts & Dijksterhuis, 1999). Participants who had to generate 3 (versus 7) arguments in favour of public transport, were more favourable towards public transport (Wanke, Bless, & Biller, 1996). The content and procedures of the three availability heuristic based interventions are outlined below.

6.4.3.1 Generate harm and benefit arguments (Intervention 5)

Participants were invited to generate eight arguments explaining why medicines are harmful. They were encouraged to take their time to complete the task and were told that it was important to come up with the indicated number of arguments. Participants were provided with eight numbered textboxes to enter their
responses. As a manipulation check, participants had to rate how difficult it was to generate the arguments (from 1=not difficult at all to 9=extremely difficult) and how much confidence they had in their arguments (from 1=none at all to 9=very much). Participants were then invited to generate three arguments why medicines are beneficial and to rate difficulty and confidence as before. The number and content of generated arguments was examined for all availability heuristic based interventions.

6.4.3.2 Generate harm arguments (Intervention 6)
As above, but participants had to generate only eight arguments why medicines are harmful.

6.4.3.3 Generate benefit arguments (Intervention 7)
As above, but participants were invited to generate only three arguments why medicines are beneficial.

6.4.4 Social Identity Theory
Social identity theory (Tajfel, 1982) assumes that when people categorize themselves as a member of a particular in-group, the in-group serves as a reference for social comparison. People often adopt the prototypic in-group attitudes and beliefs as their own. Agreement from others that are seen as similar to oneself is thought to enhance attitude certainty. Disagreement from similar others on the other hand leads to subjective uncertainty and motivates people to address the disagreement (Wood, 2000). These basic principles have been applied to persuasion: individuals typically find messages from in-group members more persuasive than by messages from out-group members (Turner, Hogg, Oakes, Reicher, & Wetherell, 1987). In a similar vein, individuals are more influenced by in-group consensus (“8 out of 10 people in in-group say that…”) than by out-group consensus information (Stangor, Sechrist, & Jost, 2001). Exposure to in-group consensus that differs from one’s own views violates the general expectation that one’s opinions are widely held and may thus motivate attitude and belief change. (Ross, Greene, & House, 1977). The content and procedures of the two social identity theory based interventions is outline below.

6.4.4.1 Consensus information about lack of harm (Intervention 8)
Basic demographic information (age, gender, country of residence), which was measured at the beginning of the study, was used to personalize consensus
information presented to participants using the Qualtrics text piping function. Participants read the following message (see square brackets for in-group personalization): “We are interested in finding out how people think about medicines. We regularly conduct studies on the internet to ask people for their opinion. In our last study 89% (413 out of 464) of [female/male] participants aged [age range] living in the [country of residence] stated that they found medicines generally safe and low risk.” Participants also saw an info-graphic (see Figure 36) that visually summarized the consensus information. Participants’ surprise, indicating disconfirmation of previously held beliefs, was assessed on a 9-point Likert scale (from 1=not surprised at all to 9=extremely surprised).

Figure 36: Infographic safety consensus information

In addition, participants read anonymized quotes (see Figure 37) from participants from a previous qualitative pre-test study. The pre-test study had been conducted to inform construction of arguments for the two ELM-based interventions (see section 6.4.2). After reading this information participants were asked to describe in a few sentences why they thought that “people like you living in [country of residence] are so confident that medicines are safe and pose little risk”.

6.4.4.2 Consensus information about benefits (Intervention 9)

As above, but the consensus information was changed to “agree that the benefits of medicines outweigh the risks” and medication benefit themed quotes (again real quotes from pre-test participants, see Figure 38) were presented. The percentages, which were loosely based on pre-test response data, were kept the same in order to compare the efficacy of both messages.

6.4.5 Debiasing

The tendency to attribute unrelated symptoms and ambiguous sensations as side effects could be conceptualized as a decision making bias: When in doubt about the aetiology of a symptom, individuals with negative medication beliefs err towards “blaming” the drug. There is surprisingly little agreement on the best strategies to reduce decision making biases (Milkman, Chugh, & Bazerman, 2009),
but warning individuals about the possibility of bias can in some instances reduce bias (Fischhoff, 1982). There is some evidence that this strategy can be effective in health settings. Individuals who received explanations about the nocebo response versus a biological explanation for symptoms during exposure to sub-audible windfarm sound (infrasound), showed lower symptom reporting following infrasound exposure (Crichton & Petrie, 2015).

However a study in participants with self-reported sensitivity to mobile phones did not find an effect of warning participants about potential bias (Nieto-Hernandez, Rubin, Cleare, Weinman, & Wessely, 2008). Participants in this double-blind study were exposed to two testing sessions, one involving a mobile phone signal, the other a sham signal. Symptoms were as likely to occur during sham than actual signal exposure (Rubin, Hahn, Everitt, Cleare, & Wessely, 2006), but giving participants individual feedback about their inability discriminate active from sham signals was not sufficient to change attributions or symptoms.

In my de-biasing intervention participants read information about the frequency of side effects in patients receiving placebo and learned about the possibility of misattributing unrelated symptoms as side effects. If convincing, this intervention may lead participants to questions whether all of the medication side effects they have personally experienced (or witnessed/read about) were actually due to pharmacological effects. This may in turn reduce beliefs that pharmaceutical medicines are harmful in general. Thus in contrast to the previous interventions, medication beliefs were not the primary intervention target.

**6.4.5.1 Forewarning about potential bias (Intervention 10)**

Participants first read some general information about statins and their efficacy in lowering the incidence of heart attacks and strokes. Participants also learned that many patients discontinue statin treatment because of side effects. They were then presented with findings from a recent meta-analysis examining the frequency of side effects in statin trials (Finegold, Manisty, Goldacre, Barron, & Francis, 2014). Participants learned that all statin side effects (apart from a slight increase in type 2 diabetes) documented in this study were equally likely in patients receiving placebo or statin treatment. A graph (see Figure 39) illustrated this visually for six common statin side effects.
The misattribution of common symptoms as medication side effects was then discussed as a possible explanation for this finding. Symptom misattribution was illustrated with the example of back pain. Participants read that back pain is very common in the general population (Andersson, 1999), with even higher prevalence rates in the elderly, who also happen to be more likely to use statins. The misattribution of back pain as a statin side effect was graphically illustrated (see Figure 40). Participants’ cognitive responses to the information about side effects to placebo and symptom misattribution were assessed with a thought listing task (Petty & Cacioppo, 1986). Participants were encouraged to freely state what went through their mind when reading this information. This served as a check to assess whether the information induced positive rather than negative responses or counter-arguing.

Figure 39: Graphical illustration of side effects frequencies in patients taking statins or placebo

Figure 40: Graphical illustration of symptom misattribution
6.4.6 Control intervention – control essay task

One single control intervention (Intervention 11), comparable in length and task difficulty to the active interventions (but unrelated to medicines), was chosen as comparator condition to all active interventions.

Participants in the control intervention were invited to write a short essay about the pros and cons of working from home. As in the cognitive dissonance essay tasks (Interventions 1 and 2), participants typed their essay directly in the provided text-box.

6.5 Hypotheses

The following hypotheses were examined: I hypothesized that participants in the intervention groups would have more positive beliefs about medicines in general (stronger beliefs that medicines are beneficial, reduced harm beliefs) after the intervention compared to baseline. In addition I predicted significant between-group differences (intervention versus control) in these beliefs. I further hypothesized that participants in the intervention groups would have more positive beliefs (weaker concerns, stronger necessity beliefs) about the novel fictitious anti-histamine medication than those randomized to the control intervention. Participants in the intervention groups were expected to show a decreased tendency to attribute the nausea symptom as a side effect and to subsequently intend to stop treatment than participants in the control group.

6.6 Methods

6.6.1 Study design

The study used a pre-post randomized control group design, with balanced allocation to conditions. Qualtrics online software was used to deliver interventions and collect outcome data.

6.6.2 Participants

Participants were recruited via the Crowdflower crowdsourcing platform (see Studies 3 and 4), from where they were redirected to the Qualtrics study link. Participation was restricted to UK and US residents over 18 years (as specified in Crowdflower recruitment settings). Only one entry per IP address was allowed to ensure independence of responses. Participants received $1 for their participation.
6.6.3 Randomization to interventions

The Qualtrics block randomization function was used to randomize participants to one of the ten active interventions or the control intervention (see Figure 42 for sample sizes and Table 36 for a summary of the interventions).

Table 36: Overview of interventions

<table>
<thead>
<tr>
<th>Intervention #</th>
<th>Theory</th>
<th>General Task</th>
<th>Specific Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cognitive Dissonance</td>
<td>Write Essay about…</td>
<td>why benefits of medicines outweigh risks.</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>why medicines are safe and not harmful.</td>
</tr>
<tr>
<td>3</td>
<td>Elaboration Likelihood Model</td>
<td>Read two-sided arguments from…</td>
<td>a medical expert.</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>a patient representative.</td>
</tr>
<tr>
<td>5</td>
<td>Availability heuristic</td>
<td>Create specific number of arguments:</td>
<td>8 medication harm, 3 medication benefit</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>8 medication harm</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>3 medication benefit</td>
</tr>
<tr>
<td>8</td>
<td>Social Identity Theory</td>
<td>Read in-group consensus information</td>
<td>lack of harm of medicines</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>benefits of medicines outweigh risks</td>
</tr>
<tr>
<td>10</td>
<td>Debiasing</td>
<td>Read information about…</td>
<td>side effects to placebo and symptom misattribution</td>
</tr>
<tr>
<td>11</td>
<td>Control</td>
<td>Write Essay about…</td>
<td>pros and cons of working from home</td>
</tr>
</tbody>
</table>

6.6.4 Measures and materials

6.6.4.1 Xymex patient information leaflet

Participants were shown the patient information leaflet of the fictitious anti-histamine medication Xymex (see Appendix M). Xymex was modelled on over the counter oral anti-histamine treatment. Oral anti-histamines are currently the treatment of choice to manage hay fever and related allergies (Ghouri, Hippisley-Cox, Newton, & Sheikh, 2008). The leaflet contained information about the active ingredient (promethazine hydrochloride), the mechanism of action, indications, counter-indications, mode and dose of administration and a list of side effects. Nausea was not listed as a side effect.

6.6.4.2 Outcome measures

As outlined before, not only immediate post intervention medication beliefs but also side effect attribution and behavioural intentions to stop treatment were
used as outcome measures. Table 37 provides an overview of measures and their internal consistency.

Table 37: Overview of primary and secondary outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Measure</th>
<th>Cronbach's alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcomes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harm and Benefit beliefs</td>
<td>Post-intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMQ-General Harm</td>
<td>.80</td>
</tr>
<tr>
<td></td>
<td>BMQ-General Benefit</td>
<td>.82</td>
</tr>
<tr>
<td>Secondary Outcomes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific beliefs about Xymex</td>
<td>BMQ-Specific Scales</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specific Concerns</td>
<td>.81</td>
</tr>
<tr>
<td></td>
<td>Specific Necessity</td>
<td>.86</td>
</tr>
<tr>
<td>Symptom attribution</td>
<td>Symptom Attribution VAS</td>
<td>-</td>
</tr>
<tr>
<td>Behavioural intentions</td>
<td>Behavioural Intention VAS</td>
<td>-</td>
</tr>
<tr>
<td>Other measures:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMQ-General Overuse</td>
<td>.82</td>
</tr>
<tr>
<td></td>
<td>PSM</td>
<td>.90</td>
</tr>
</tbody>
</table>

*Note: BMQ=Beliefs about Medicines Questionnaire, PSM=Perceived Sensitivity to Medicines Scale, VAS=Visual Analogue Scale*

The aim of the study was to inform the development of effective belief change interventions in the hope that this would improve adherence. The focus of this intervention approach relied on modifying medication beliefs, which were consequently chosen as the primary outcome measure. It is however important to acknowledge that adherence is a complex behaviour and likely to be influenced by a variety of factors beyond medication beliefs. Medication beliefs would therefore constitute only one of several potential intervention targets in an effective complex adherence intervention.

### 6.6.4.2.1 Beliefs about Medicines Questionnaire (BMQ)

The BMQ-General (Horne et al., 1999) (see also section 1.3.2.1), which was administered pre- and post-intervention, was used to assess participants’ beliefs about pharmaceutical medicines in general. The BMQ-Specific (Horne et al., 1999) was administered after participants had completed the interventions and read the Xymex patient information leaflet. Specific Concerns about Xymex were assessed with six items (e.g. “Having to take Xymex worries me.”). Beliefs in the Specific Necessity for Xymex were assessed with five items (e.g. “My life would be impossible without Xymex.”).
6.6.4.2.2 Perceived Sensitivity to Medicines Scale (PSM)

The PSM (see section 1.3.2.2) was administered pre- and post-intervention to assess participants’ perceptions of personal sensitivity to medicines. Internal consistency for all pre-and post-intervention medication beliefs scales was good (see Table 37 for Cronbach’s alphas of individual scales).

6.6.4.2.3 Symptom attribution and behavioural intention measures

Participants read the following vignette: “Image that you have hay fever and have been taking a daily 25mg tablet of Xymex for a week. After a week of taking Xymex you experience symptoms of nausea (i.e. sensations of discomfort in the upper stomach with an involuntary urge to vomit).”

Participants were asked to rate on 100-point VAS (from 0=not likely at all to 100=extremely likely) how likely they thought that the following factors caused the nausea symptoms: *Xymex side effect*, food intolerance, stomach infection, stress. Participants were given the opportunity to specify (in an open text-box) and rate another reason.

Participants were then shown another set of 100-point VAS (scale anchors as above) asking them to rate how likely they would take the following actions: *stop taking Xymex*, take Xymex less frequently, speak to a pharmacist, consult a doctor, take an anti-emetic drug. Participants were also given the possibility to specify another action (in an open text-box) and to rate this option.

6.6.4.3 Other measures

6.6.4.3.1 Positive and Negative Affect Schedule (PANAS)

State Negative Affect was assessed pre- and post-intervention using the short form of the PANAS (58) with instructions to focus on current feelings. Ten negative (e.g. distressed, upset) adjectives were rated on 5-point Likert scales (1=not at all to 5=extremely). State Negative Affect scores were computed by averaging scores for all negative adjectives at the respective time point. Internal consistency was high at both time points (Cronbach’s αs .95 and .95 respectively).

6.6.4.3.2 Demographics

Participants were asked to indicate their gender, age group, first language, ethnic background and country of residence.
6.6.3.3 Hay fever/ allergy and previous anti-histamine use

Participants were asked to indicate (yes/no) whether they had ever suffered from hay fever or a related allergic illness. Participants who answered yes were prompted to specific whether they were currently suffering from the condition. All participants were asked to indicate (yes/no) whether they had used over the counter anti-histamine medication in the past. Common UK and US anti-histamine brands (e.g. Actifed, Benadryl, Claritin) were listed as examples.

6.6.5 Procedures

The study was classified as exempt from ethical approval by the UCL Research Ethics Committee. The survey and interventions were administered via Qualtrics online survey software. Participants saw a written online consent form outlining the study procedures and their rights as research participants (e.g. anonymity of responses, right to withdraw without loss of benefit). Consent was given by ticking “I agree to participate” on the electronic consent form.

Figure 41: Overview Study Procedures

<table>
<thead>
<tr>
<th>Consent, Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Measures: BMQ-General, PSM, PANAS</td>
</tr>
<tr>
<td>Randomization to Interventions/Control</td>
</tr>
<tr>
<td>1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>Follow-Up: BMQ-General, PSM, PANAS</td>
</tr>
<tr>
<td>Xymex Patient Information Leaflet</td>
</tr>
<tr>
<td>BMQ-Specific, Symptom attribution and behavioural intention measures</td>
</tr>
<tr>
<td>Control measures, Debriefing</td>
</tr>
</tbody>
</table>

*Note. BMQ=Beliefs about Medicines Questionnaire; PSM=Perceived Sensitivity to Medicines Scale; PANAS=Positive and Negative Affect Schedule, 11-10=Interventions 1 to 10; C=Control group*
After providing informed consent participants completed the demographic questions and the baseline BMQ-General, PSM and PANAS measures (see Figure 41 for an overview of study procedures). Participants were then randomized to one of the ten active interventions or the control intervention using the Qualtrics block randomization function. BMQ-General, PSM and PANAS scores were reassessed after the intervention. Participants then read the patient information leaflet of the fictitious anti-histamine medication Xymex and completed the BMQ-Specific. After reading the Xymex vignette, participants completed the symptom attribution/behavioural intention and control measures and received a short written debriefing. Participants were redirected to the Crowdflower platform after exiting the Qualtrics survey, where they were given the opportunity to provide the researcher general feedback about the study.

6.6.6 Analytical considerations

6.6.6.1 Sample size

Because this was a feasibility study, it was only powered for single comparisons (with control group) and not for all potential comparisons between conditions. Sample size was calculated with GPower version 3.1 (Faul et al., 2009). The effect size estimate (d=0.56) was based on findings from a study by Magadza et al. (Magadza et al., 2009), in which general harm beliefs were successfully modified through a psychoeducational intervention. Power calculations showed that 52 participants per condition were required to achieve 80% power with an alpha error probability (two-sided) of .05, resulting in a total sample size of 572 (11x52).

6.6.6.2 Statistical analyses

Inter-correlations between BMQ-General (pre-post intervention) and BMQ-Specific scales were examined to assess whether measures fitted theoretical predictions (e.g. associations between General Harm and Specific Concerns (Horne, 2003), associations between General Harm and PSM (Horne et al., 2013b), see also section 1.3.1). Differences in pre-intervention medication beliefs and demographic factors were examined with one-way ANOVAs and Chi-Square tests. The magnitude of pre-post intervention differences in medication beliefs was examined with paired-samples t-tests. The same control group was used for all between group comparisons. The overall effectiveness of the beliefs change interventions (change in medication beliefs pre-post intervention, reduction in side effect attribution, behavioural intentions to stop treatment) was examined using analysis of covariance and independent t-tests. The general effect of medication
beliefs on side effect attribution and behavioural intentions was explored using linear regression analysis. Confidence intervals for mean differences and effect size estimates are reported.

6.6.6.3 Assessment of compliance with instructions

In some (but not all) interventions participants were asked to perform specific tasks (e.g. write essay [Interventions 1, 2 and 11], list a pre-specified number of arguments [Interventions 5-7]). I examined the extent to which participants followed the specific instructions given. In addition, the overall stance of the cognitive dissonance essays [Interventions 1 and 2] was coded by an independent research assistant on a scale ranging from 1=highly positive (only positive arguments) to 5=highly negative (only negative arguments).

6.6.6.4 Exploration of qualitative data

After some interventions, i.e. ELM [Interventions 3 and 4], SIT [Interventions 8 and 9] and Debiasing [Intervention 10] participants were given the opportunity to write down what went through their minds during the intervention (see thought-listing technique, section 6.4.2). Text from all the thought-listing tasks was exported from Qualtrics into a word-processor. The general valence of the comments was examined and comments were searched for clues regarding the effectiveness of the intervention and for barriers to persuasion. Representative quotes will be presented. Given the exploratory nature of this task, no explicit qualitative data-analysis framework was used (Spencer, Ritchie, & O’Connor, 2003).

6.7 Results

6.7.1 Data exclusions and attrition

Responses from 605 participants were downloaded from Qualtrics. Data from participants with duplicate IP addresses (n=6), who declined consent (n=5), or who reported being non US/UK residents (n=10) was excluded, resulting in a total sample of 585. All participants confirmed being over 18 years of age. Only eight of the 580 participants that participated in the intervention, did not complete the post-intervention measures. Drop-outs rates were comparable between intervention and control conditions (see Figure 42).
6.7.2 Sample and baseline characteristics

Participant characteristics for the whole sample are depicted in Table 38. Participants were relatively young and more likely to be female. The vast majority of participants were native English speakers. Over a fifth of participants from both the US and UK indicated that they were currently suffering from hay fever.

Chi-Square tests were used to test for baseline differences in demographic characteristics between intervention groups. There was no significant difference in gender, age group, native English language, past and present hay fever diagnosis, or previous anti-histamine use between intervention groups ($p_s > .20$). One-way ANOVAs with Dunnett’s post hoc tests (comparing all other groups with control group) showed that participants’ beliefs about medicines in general, perceived sensitivity to medicines and negative affectivity did not differ between experimental groups before the intervention (all $p_s > .05$).
Table 38: Sample characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%) total sample</th>
<th>N=585</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>272 (46.5)</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>313 (53.5)</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤21</td>
<td>31 (5.3)</td>
<td></td>
</tr>
<tr>
<td>22-34</td>
<td>267 (45.6)</td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>127 (21.7)</td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>103 (17.6)</td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>49 (8.4)</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>8 (1.4)</td>
<td></td>
</tr>
<tr>
<td>country</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>204 (34.9)</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>381 (65.1)</td>
<td></td>
</tr>
<tr>
<td>language</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native English speaker</td>
<td>563 (96.2)</td>
<td></td>
</tr>
<tr>
<td>ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White British/Irish/American</td>
<td>437 (74.7)</td>
<td></td>
</tr>
<tr>
<td>Any other White background</td>
<td>49 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Black British/American</td>
<td>20 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Any other Black background</td>
<td>14 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Indian/Pakistani/Bangladeshi</td>
<td>11 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Any other Asian background</td>
<td>17 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>19 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>12 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (1.5)</td>
<td></td>
</tr>
<tr>
<td>hay fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>past</td>
<td>251 (42.9)</td>
<td></td>
</tr>
<tr>
<td>current</td>
<td>127 (21.7)</td>
<td></td>
</tr>
<tr>
<td>previous anti-histamine use</td>
<td>362 (61.9)</td>
<td></td>
</tr>
</tbody>
</table>

6.7.3 Inter-correlations between medication beliefs

Inter-correlations between medication belief scales (both pre-and post-intervention) fitted the theoretical model well (see section 1.3.1.3). Beliefs about medicines in general were associated with specific beliefs about Xymex as predicted (see Figure 43): Stronger beliefs that medicines are generally beneficial were related to stronger perceptions of necessity. Stronger beliefs that pharmaceutical medicines are harmful were associated with increased concerns about Xymex. Participants who perceived themselves as more sensitive to the effects of medicines had stronger concerns about Xymex and believed pharmaceutical medicines to be more harmful in general.
Figure 43: Inter-correlations beliefs about medicines scales

Note. **p < .01; BMQ = Beliefs about Medicines Questionnaire, \( r_{\text{pre/post}} \) = Pearson correlation between pre/post-intervention measures (across the whole sample)

6.7.4 Pre-post intervention differences in BMQ-General Harm and General Benefit

Paired-tests were conducted to test whether participants believed pharmaceutical medicines to be less harmful and more beneficial after the intervention compared to baseline (see Table 39 for summary of all pre-post comparisons and effect size estimates). Several interventions were effective in reducing harm beliefs: Participants who were asked to write an essay arguing that medicines are not harmful (Intervention 2: \( t(50) = 3.23, p < .001 \)), participants who read two-sided arguments by a patient representative about the benefit and risks of medicines (Intervention 4: \( t(52) = 2.54, p < .05 \)) and participants who saw in-group consensus information showing that the benefits of medicines outweigh the risks (Intervention 9: \( t(52) = 3.60, p < .001 \)) rated medicines as significantly less harmful after the intervention. Interestingly, reading two sided arguments (identical to those presented in Intervention 4) by a medical expert did not significantly change harm perceptions, but strengthened participants' beliefs that medicines are generally beneficial (Intervention 3: \( t(51) = 3.46, p < .001 \)). No other intervention had an effect on harm or benefit beliefs. As predicted, there was no significant change in either harm or benefit belief in the control condition, although harm beliefs marginally worsened in this condition (\( t(52) = 2.00, p = .052 \)).
6.7.5 Pre-post intervention differences in Perceived Sensitivity to Medicines

Participants who were asked to write an essay about the lack of harm of medicines had lower perceived personal sensitivity to medicines after the intervention (Intervention 2: t(48)=2.62, p<.05). There was also a significant reduction in perceived sensitivity to medicines for participants who saw the in-group consensus information about lack of harm of medicines (Intervention 8: t(52)=2.88, p<.01). None of the other interventions had a significant effect on perceived sensitivity to medicines (all ps>.05).

6.7.6 Pre-post intervention differences in Negative Affect

Paired t-tests were used to examine whether there were any changes in negative affect following the interventions. There was no significant change in all but one intervention condition. Participants who had to generate both 8 medication harm and 3 medication benefit arguments (Intervention 5) had significantly lower negative affect after (M=1.44, SD=0.80) than before the intervention (M=1.55, SD=0.84; t(53)=2.13, p<.05).

6.7.7 Between-group differences in BMQ-General Harm and General Benefit

Post-intervention General Harm and General Benefit beliefs in each intervention condition were compared to the control group, while adjusting for the baseline measures of these beliefs. Given that the study was not powered to detect differences between all possible conditions, these ANCOVAs were conducted per belief and per condition (see Table 40 for effect size estimates). Findings mirror results from the within-subject pre-post comparisons: Post-intervention General Harm beliefs were significantly lower for participants who were invited to write an essay about the lack of harm of medicines (Intervention 2: B=-.20, p<.011), who read two-sided persuasive arguments by a patient representative (Intervention 4: B=-.17, p<.01) and who saw in-group consensus information indicating that benefits of medicines outweigh potential harm (Intervention 9: B=-0.22, p<.001). Participants who read two-sided arguments about the benefits and risks of medicines by a medical expert, believed medicines to be significantly more beneficial than participants in the control group (Intervention 3: B=0.21, p<.01).
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Pre</th>
<th>Post</th>
<th>t(df)</th>
<th>p</th>
<th>Cohen's d^1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Cognitive Dissonance Essay:</strong> Benefits outweigh harms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.54 (0.74)</td>
<td>2.51 (0.70)</td>
<td>t(51)=0.55</td>
<td>.58</td>
<td>0.04</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.90 (0.57)</td>
<td>3.81 (0.77)</td>
<td>t(50)=0.70</td>
<td>.49</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>2 Cognitive Dissonance Essay:</strong> Medicines are not harmful</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.32 (0.78)</td>
<td>2.20 (0.82)</td>
<td>t(50)=3.23</td>
<td>&lt;.001</td>
<td>0.16</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.87 (0.70)</td>
<td>3.95 (0.79)</td>
<td>t(48)=1.67</td>
<td>.10</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>3 Elaboration Likelihood Model:</strong> Arguments by Medical expert</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.37 (0.89)</td>
<td>2.34 (0.87)</td>
<td>t(52)=0.70</td>
<td>.49</td>
<td>0.04</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.87 (0.70)</td>
<td>4.10 (0.67)</td>
<td>t(51)=3.46</td>
<td>&lt;.001</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>4 Elaboration Likelihood Model:</strong> Arguments by Patient Representative</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.79 (0.86)</td>
<td>2.66 (0.78)</td>
<td>t(52)=2.54</td>
<td>&lt;.05</td>
<td>0.15</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.87 (0.71)</td>
<td>3.82 (0.80)</td>
<td>t(51)=0.28</td>
<td>.78</td>
<td>0.03</td>
</tr>
<tr>
<td>**5 Availability heuristic: Generate 8 Harm arguments, 3 benefit arguments</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.63 (0.82)</td>
<td>2.63 (0.81)</td>
<td>t(53)=0.10</td>
<td>.92</td>
<td>0.01</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.75 (0.71)</td>
<td>3.83 (0.68)</td>
<td>t(51)=1.55</td>
<td>.13</td>
<td>0.12</td>
</tr>
<tr>
<td>**6 Availability heuristic: Generate 8 Harm arguments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.53 (0.80)</td>
<td>2.60 (0.83)</td>
<td>t(51)=0.94</td>
<td>.35</td>
<td>0.08</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.83 (0.62)</td>
<td>3.73 (0.62)</td>
<td>t(51)=1.47</td>
<td>.15</td>
<td>0.16</td>
</tr>
<tr>
<td>**7 Availability heuristic: Generate 3 benefit arguments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.48 (0.63)</td>
<td>2.48 (0.70)</td>
<td>t(52)=0.01</td>
<td>.99</td>
<td>0.00</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.79 (0.62)</td>
<td>3.76 (0.65)</td>
<td>t(50)=0.39</td>
<td>.58</td>
<td>0.04</td>
</tr>
<tr>
<td>**8 Social Identity Theory: In-group consensus medicines are not harmful</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.45 (0.93)</td>
<td>2.41 (0.92)</td>
<td>t(52)=0.63</td>
<td>.53</td>
<td>0.04</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.70 (0.82)</td>
<td>3.81 (0.80)</td>
<td>t(52)=1.51</td>
<td>.14</td>
<td>0.15</td>
</tr>
<tr>
<td>**9 Social Identity Theory: In-group consensus benefits outweigh risks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.53 (0.85)</td>
<td>2.38 (0.76)</td>
<td>t(52)=3.60</td>
<td>&lt;.001</td>
<td>0.18</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.96 (0.68)</td>
<td>3.89 (0.75)</td>
<td>t(52)=1.05</td>
<td>.30</td>
<td>0.10</td>
</tr>
<tr>
<td>**10 Debiasing: Information about symptom misattribution</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.47 (0.81)</td>
<td>2.43 (0.77)</td>
<td>t(53)=0.97</td>
<td>.34</td>
<td>0.06</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>3.81 (0.56)</td>
<td>3.76 (0.59)</td>
<td>t(51)=0.93</td>
<td>.36</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>11 Control Essay:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>2.39 (1.02)</td>
<td>2.47 (1.03)</td>
<td>t(52)=2.00</td>
<td>.05</td>
<td>0.08</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>4.04 (0.71)</td>
<td>4.03 (0.69)</td>
<td>t(51)=0.39</td>
<td>.70</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Note. ^1 Effect sizes were computed using effect size calculator for dependent t-test on [http://www.psychometrica.de/effect_size.html](http://www.psychometrica.de/effect_size.html); BMQ=Beliefs about Medicines Questionnaire
Table 40: ANCOVA post-intervention BMQ-General Benefit and General Harm

<table>
<thead>
<tr>
<th>Intervention versus control, controlling for baseline beliefs</th>
<th>B [95% CI]</th>
<th>t</th>
<th>p</th>
<th>partial η^2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Cognitive Dissonance Essay:</strong> Benefits outweigh harms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post BMQ General Harm</td>
<td>-0.10 [-0.23; 0.03]</td>
<td>1.52</td>
<td>.13</td>
<td>.02</td>
</tr>
<tr>
<td>Post BMQ General Benefit</td>
<td>-0.12 [-0.36; 0.13]</td>
<td>0.96</td>
<td>.34</td>
<td>.01</td>
</tr>
<tr>
<td><strong>2 Cognitive Dissonance Essay:</strong> Medicines are not Harmful</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-0.20 [-0.32; -]</td>
<td>3.68</td>
<td>&lt;.001</td>
<td>.12</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>0.10</td>
<td>1.28</td>
<td>.21</td>
<td>.02</td>
</tr>
<tr>
<td>**3 Elaboration Likelihood Model: Arguments by Medical expert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-0.12 [-0.24; 0.01]</td>
<td>1.85</td>
<td>.07</td>
<td>.03</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>0.21 [0.05; 0.36]</td>
<td>2.67</td>
<td>&lt;.01</td>
<td>.07</td>
</tr>
<tr>
<td><strong>4 Elaboration Likelihood Model: Arguments by Patient Representative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-0.17 [-0.30; -0.04]</td>
<td>2.68</td>
<td>&lt;.01</td>
<td>.07</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>0.01 [-0.16; 0.17]</td>
<td>0.06</td>
<td>.96</td>
<td>.00</td>
</tr>
<tr>
<td><strong>5 Availability heuristic: Generate 8 Harm arguments, 3 benefit arguments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-0.62 [-0.19; 0.06]</td>
<td>1.01</td>
<td>.31</td>
<td>.01</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>0.05 [-0.09; 0.18]</td>
<td>0.65</td>
<td>.52</td>
<td>.00</td>
</tr>
<tr>
<td><strong>6 Availability heuristic: Generate 8 Harm arguments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-0.00 [-0.16; 0.16]</td>
<td>0.01</td>
<td>.99</td>
<td>.00</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>-0.13 [-0.29; 0.30]</td>
<td>1.61</td>
<td>.11</td>
<td>.03</td>
</tr>
<tr>
<td><strong>7 Availability heuristic: Generate 3 benefit arguments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-0.08 [-0.20; 0.02]</td>
<td>1.28</td>
<td>.20</td>
<td>.02</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>-0.05 [-0.19; 0.10]</td>
<td>0.65</td>
<td>.52</td>
<td>.00</td>
</tr>
<tr>
<td><strong>8 Social Identity Theory: In-group consensus medicines are not harmful</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-0.12 [-0.27; 0.04]</td>
<td>1.52</td>
<td>.13</td>
<td>.02</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>0.06 [-0.12; 0.24]</td>
<td>0.63</td>
<td>.53</td>
<td>.00</td>
</tr>
<tr>
<td><strong>9 Social Identity Theory: In-group consensus benefits outweigh risks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-0.22 [-0.34; -0.11]</td>
<td>3.89</td>
<td>&lt;.001</td>
<td>.13</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>-0.06 [-0.23; 0.10]</td>
<td>0.78</td>
<td>.44</td>
<td>.01</td>
</tr>
<tr>
<td><strong>10 Debiasing: Information about symptom misattribution</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ General Harm</td>
<td>-0.12 [-0.25; 0.01]</td>
<td>1.90</td>
<td>.06</td>
<td>.03</td>
</tr>
<tr>
<td>BMQ General Benefit</td>
<td>-0.07 [-0.21; 0.08]</td>
<td>0.97</td>
<td>.33</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Note. BMQ=Beliefs about Medicines Questionnaire; compared to control, controlling for pre-intervention General Benefit/Harm*
6.7.8 Between group differences in specific beliefs about Xymex

Independent t-tests were used to examine whether participants in the intervention groups had more positive beliefs about Xymex after reading the patient leaflet than participants in the control group (see Table 41). Participants who were asked to write the cognitive dissonance essay (Intervention 2), had significantly lower concerns about Xymex than participants in the control group (t(98)=2.10, p<.05). All other comparisons were not statistically significant at alpha level of .05. There were however signs (see Table 41 for effect sizes) that participants had stronger necessity beliefs following Interventions 3 and 9, but the differences were not statistically significant. Results were similar when controlling for pre-intervention beliefs.

6.7.9 Beliefs about medicines and side effect attribution/behavioural intention to stop treatment

Univariate linear regression models were used to examine whether beliefs about medicines in general and specific beliefs about Xymex were associated with side effect attribution and behavioural intentions to stop treatment (across the whole sample). Participants who believed medicines to be more harmful in general (β=.198) and who had stronger concerns about Xymex (β=.386, ps<.001) were more likely to attribute the nausea symptom as a side effect of Xymex. Participants who believed medicines to be more beneficial (β=-.087, p<.05) were less likely to attribute the unrelated symptom as a side effect. Beliefs about the Necessity for Xymex were not associated with side effect attribution (p>.05).

Stronger harm beliefs (β=.242) and concerns about Xymex (β=.226, ps<.001) also increased participants intentions to stop treatment following the nausea symptom, while stronger beliefs in the benefits of pharmaceutical medicines (β=-.155, p<.001) and higher perceived necessity for Xymex (β=-.086, p<.05) reduced intentions to stop treatment. In multivariate regression models (with all BMQ-scales entered jointly), medication beliefs explained 16.6% of variance in side effect attribution (F(5)=23.67, p<.001) and 10.6% in behavioural intentions to stop treatment (F(5)=14.58, p<.001).

6.7.10 Between-group differences in side effect attribution/behavioural intention to stop treatment

Independent t-test were used to examine whether participants randomized to an active intervention were less likely to attribute an unrelated symptom as a side
effect and intended to stop treatment compared to participants in the control condition (see Table 42 for an overview of all comparisons and effect size estimates). Participants who learned about symptom misattribution in the debiasing intervention (Intervention 10) were less likely to attribute the unrelated nausea symptom as a side effect to Xymex ($B=-12.11$, $p<.05$).

There were several marginally significant effects of several other belief change interventions. For example, side effect attribution ($B=-10.16$, $p=.061$) and behavioural intentions to stop treatment ($B=-11.47$, $p=.080$) were marginally lower for participants who wrote the cognitive dissonance essay in Intervention 2 compared to the control essay. Side effect attribution was also marginally lower in the other cognitive dissonance condition (Intervention 1) and first Social Identity Theory condition (Intervention 8, see Table 42). Effect size estimates for these marginal effects would be considered small to moderate (Cohen’s $d>.30$), suggesting that the study was probably underpowered to detect differences with the control group (Field & Hole, 2003).
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mean difference [95% CI]</th>
<th>t (df)</th>
<th>p</th>
<th>Cohen’s d [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive Dissonance Essay:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefits outweigh harms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>-0.13 [-0.45; 0.20]</td>
<td>0.78 (100)</td>
<td>.44</td>
<td>0.15 [-0.24; 0.54]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>0.03 [-0.30; 0.36]</td>
<td>0.17 (100)</td>
<td>.87</td>
<td>-0.03 [-0.42; 0.36]</td>
</tr>
<tr>
<td>2 Cognitive Dissonance Essay:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines are not Harmful</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>-0.35 [-0.68; -0.02]</td>
<td>2.10 (98)</td>
<td>&lt;.05</td>
<td>0.42 [0.02; 0.81]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>0.00 [-0.34; 0.34]</td>
<td>0.00 (98)</td>
<td>.99</td>
<td>0.00 [-0.39; 0.39]</td>
</tr>
<tr>
<td>3 Elaboration Likelihood Model:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arguments by Medical expert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>0.01 [-0.29; 0.31]</td>
<td>0.05 (101)</td>
<td>.95</td>
<td>-0.01 [-0.40; 0.38]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>0.29 [-0.06; 0.60]</td>
<td>1.62 (101)</td>
<td>.11</td>
<td>0.32 [-0.71; 0.07]</td>
</tr>
<tr>
<td>4 Elaboration Likelihood Model:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arguments by Patient Representative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>0.11 [-0.22; 0.44]</td>
<td>0.67 (102)</td>
<td>.51</td>
<td>-0.13 [-0.52; 0.25]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>0.01 [-0.31; 0.33]</td>
<td>0.02 (102)</td>
<td>.96</td>
<td>-0.01 [-0.39; 0.38]</td>
</tr>
<tr>
<td>5 Availability heuristic: Generate 8 Harm arguments, 3 benefit arguments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>0.11 [-0.22; 0.43]</td>
<td>0.64 (102)</td>
<td>.53</td>
<td>-0.12 [-0.51; 0.27]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>0.00 [-0.34; 0.33]</td>
<td>0.02 (102)</td>
<td>.98</td>
<td>0.00 [-0.38; 0.39]</td>
</tr>
<tr>
<td>6 Availability heuristic: Generate 8 Harm arguments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>0.12 [-0.12; 0.44]</td>
<td>0.73 (101)</td>
<td>.47</td>
<td>-0.14 [-0.53; 0.24]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>0.03 [-0.32; 0.38]</td>
<td>0.15 (101)</td>
<td>.88</td>
<td>-0.03 [-0.42; 0.36]</td>
</tr>
<tr>
<td>7 Availability heuristic: Generate 3 benefit arguments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>-0.11 [-0.45; 0.24]</td>
<td>0.62 (102)</td>
<td>.54</td>
<td>0.12 [-0.26; 0.51]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>-0.13 [-0.46; 0.21]</td>
<td>0.76 (102)</td>
<td>.45</td>
<td>0.15 [-0.24; 0.53]</td>
</tr>
<tr>
<td>8 Social Identity Theory: In-group consensus medicines are not harmful</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>-0.08 [-0.43; 0.27]</td>
<td>0.47 (102)</td>
<td>.64</td>
<td>0.09 [-0.29; 0.48]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>0.11 [-0.25; 0.46]</td>
<td>0.60 (102)</td>
<td>.53</td>
<td>-0.12 [-0.50; 0.27]</td>
</tr>
<tr>
<td>9 Social Identity Theory: In-group consensus benefits outweigh risks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>-0.06 [-0.40; 0.27]</td>
<td>0.38 (102)</td>
<td>.71</td>
<td>0.07 [-0.31; 0.50]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>0.24 [-0.09; 0.57]</td>
<td>1.46 (102)</td>
<td>.15</td>
<td>-0.29 [0.67; 0.10]</td>
</tr>
<tr>
<td>10 Debiasing: Information about symptom misattribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMQ Specific Concerns</td>
<td>-0.13 [-0.47; 0.21]</td>
<td>0.75 (101)</td>
<td>.46</td>
<td>0.15 [-0.24; 0.53]</td>
</tr>
<tr>
<td>BMQ Specific Necessity</td>
<td>0.12 [-0.20; 0.44]</td>
<td>0.74 (101)</td>
<td>.46</td>
<td>-0.15 [-0.53; 0.24]</td>
</tr>
</tbody>
</table>

Note. BMQ=Beliefs about Medicines Questionnaire; independent t-tests intervention versus control
Table 42: Misattribution/behavioural intentions to stop treatment by intervention

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mean difference [95% CI]</th>
<th>t (df)</th>
<th>p</th>
<th>Cohen’s d [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive Dissonance Essay: Benefits outweigh harms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>-9.60 [-20.89; 1.71]</td>
<td>1.68 (100)</td>
<td>.10</td>
<td>0.33 [-0.06; 0.74]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>-10.20 [-23.15; 2.76]</td>
<td>1.56 (100)</td>
<td>.12</td>
<td>0.31 [-0.08; 0.70]</td>
</tr>
<tr>
<td>2 Cognitive Dissonance Essay: Medicines are not Harmful</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>-10.16 [-20.79; 0.48]</td>
<td>1.89 (98)</td>
<td>.06</td>
<td>0.38 [-0.02; 0.78]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>-11.47 [-24.33; 1.39]</td>
<td>1.77 (98)</td>
<td>.08</td>
<td>0.35 [-0.04; 0.75]</td>
</tr>
<tr>
<td>3 Elaboration Likelihood Model: Arguments by Medical expert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>0.47 [-10.01; 10.95]</td>
<td>0.09 (101)</td>
<td>.93</td>
<td>-0.02 [-0.40; 0.37]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>2.08 [-10.98; 15.14]</td>
<td>0.32 (101)</td>
<td>.75</td>
<td>-0.06 [-0.45; 0.32]</td>
</tr>
<tr>
<td>4 Elaboration Likelihood Model: Arguments by Patient Representative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>-1.36 [-12.13; 9.40]</td>
<td>0.25 (102)</td>
<td>.80</td>
<td>0.05 [-0.34; 0.43]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>-0.24 [-13.07; 12.59]</td>
<td>0.04 (102)</td>
<td>.97</td>
<td>0.01 [-0.38; 0.39]</td>
</tr>
<tr>
<td>5 Availability heuristic: Generate 8 Harm arguments, 3 benefit arguments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>-2.99 [-13.88; 7.91]</td>
<td>0.54 (102)</td>
<td>.59</td>
<td>0.11 [-0.28; 0.50]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>0.63 [-13.04; 14.39]</td>
<td>0.09 (103)</td>
<td>.93</td>
<td>-0.02 [-0.40; 0.37]</td>
</tr>
<tr>
<td>6 Availability heuristic: Generate 8 Harm arguments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>0.97 [-9.39; 11.32]</td>
<td>0.19 (101)</td>
<td>.85</td>
<td>-0.04 [-0.42; 0.35]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>7.90 [-1.54; 20.36]</td>
<td>1.26 (101)</td>
<td>.21</td>
<td>0.25 [-0.64; 0.14]</td>
</tr>
<tr>
<td>7 Availability heuristic: Generate 3 benefit arguments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>-0.22 [-10.94; 10.41]</td>
<td>0.05 (102)</td>
<td>.96</td>
<td>0.01 [-0.38; 0.39]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>2.16 [-11.85; 16.16]</td>
<td>0.31 (102)</td>
<td>.76</td>
<td>-0.06 [-0.44; 0.33]</td>
</tr>
<tr>
<td>8 Social Identity Theory: In-group consensus medicines are not harmful</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>-9.97 [-21.04; 1.11]</td>
<td>1.79 (102)</td>
<td>.087</td>
<td>0.35 [-0.03; 0.74]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>-4.11 [-17.11; 8.90]</td>
<td>0.63 (102)</td>
<td>.53</td>
<td>0.12 [-0.26; 0.51]</td>
</tr>
<tr>
<td>9 Social Identity Theory: In-group consensus benefits outweigh risks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>-0.10 [-10.85; 10.64]</td>
<td>0.02 (102)</td>
<td>.99</td>
<td>0.00 [-0.38; 0.39]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>0.85 [-11.86; 13.57]</td>
<td>0.13 (102)</td>
<td>.89</td>
<td>-0.03 [-0.41; 0.36]</td>
</tr>
<tr>
<td>10 Debiasing: Information about symptom misattribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect attribution</td>
<td>-12.11 [-23.39; -0.83]</td>
<td>2.13 (101)</td>
<td>&lt;.05</td>
<td>0.42 [0.03; 0.81]</td>
</tr>
<tr>
<td>Intentions to stop</td>
<td>-8.46 [-21.82; 4.90]</td>
<td>1.26 (101)</td>
<td>.21</td>
<td>0.25 [-0.14; 0.64]</td>
</tr>
</tbody>
</table>

*Note.* Independent t-tests intervention versus control
6.7.11 Other findings

6.7.11.1 Differences between anti-histamine users and non-users

Independent t-tests were used to examine whether previous anti-histamine use affected beliefs about the fictitious anti-histamine Xymex. Participants who had previously used anti-histamines (N=362) did not differ significantly in either Concerns (t(566)=-.03, p=.973) or Necessity Beliefs (t(566)=.145, p=.885) from those without previous anti-histamine exposure (N=206). Previous anti-histamine use also did not affect the likelihood that participants attributed the unrelated nausea symptom as a side effect to Xymex (t(566)=.048, p=.962) or behavioural intentions to stop treatment (t(566)=.557, p=.578).

6.7.11.2 Compliance with instructions

Six and eight participants decided not to write the cognitive dissonance essay in Interventions 1 and 2 respectively. Two participants failed to write the control essay in the control intervention. Only one participant in each availability heuristic intervention (Interventions 5, 6, 7) failed to list any arguments. In intervention 5, 79.2% of participants managed to generate 8 different risk arguments, 98.1% completed all 3 benefit arguments. In Intervention 7, 96.2% of participants listed all three benefit arguments. In Intervention 6 78.8% of participants generated 8 risk arguments.

6.7.11.3 General participant feedback

Participant feedback on Crowdflower was very positive with the majority of participants commenting that they found the study interesting and enjoyable. (“Interesting survey as I take prescription medication myself.” “A thought provoking survey.”). Three participants complained that the survey was too long or repetitive. One participant commented that the survey was “scary but worth the money”.

6.7.11.4 Induced dissonance (Interventions 1 and 2)

The majority of participants generated mainly positive arguments (i.e. arguments to show that medicines are beneficial and not harmful respectively), but many participants also included negative arguments (e.g. mentioned the risk of side effects and preferences for natural treatment alternatives and lifestyle changes).
Table 43: Overall stance of cognitive dissonance essays

<table>
<thead>
<tr>
<th>Overall stance</th>
<th>Intervention 1 Dissonance Benefit (n (%))</th>
<th>Intervention 2 Dissonance Harm (n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly positive (only positive arguments)</td>
<td>31 (60.8%)</td>
<td>26 (51.0%)</td>
</tr>
<tr>
<td>Positive (mostly positive)</td>
<td>9 (17.6%)</td>
<td>6 (11.8%)</td>
</tr>
<tr>
<td>Balanced (equally positive and negative)</td>
<td>4 (7.8%)</td>
<td>8 (15.7%)</td>
</tr>
<tr>
<td>Negative (mostly negative)</td>
<td>0</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Highly negative (only negative)</td>
<td>1 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>6 (11.8%)</td>
<td>8 (15.7%)</td>
</tr>
</tbody>
</table>

Average psychological discomfort, a proxy for cognitive dissonance, was low to moderate (M=2.30, SD=1.67 and M=2.49, SD=1.56 in Interventions 1 and 2 respectively), and did not differ significantly between the two dissonance interventions (t(98)=0.59, p=.56). In Intervention 1 there was a positive, but only marginally significant association between pre-intervention General Harm beliefs and psychological discomfort reported after writing the essay (r=.246, p=.08). Pre-intervention Benefit beliefs were not associated with discomfort (r=.07). In Intervention 2, the higher pre-intervention General Harm scores, the higher psychological discomfort (r=.339). The higher pre-intervention General Benefit Scores, the lower psychological discomfort (r=−.378, both ps<.01), suggesting that this intervention induced dissonance as expected.

6.7.11.5 Perceptions of ELM arguments (Interventions 3 and 4)

Many participants listed mostly positive thoughts after reading the two-sided arguments about the risks and benefits of medicines:

“I think that the pro’s outweigh the cons massively. Most of the cons were the same like having negative effects on your health, but I think the pro’s are much better. For example, medicines are assessed by drug regulation companies. This for me was the biggest point for the pro’s that swung myself in the favour of medicines, as if they’re tested then they must be safe and harmless. This made me feel more confident in medicines”. (male, white, UK resident, 45-54 years)

“The arguments seem to be overwhelmingly in favour, the "cons" seemed rather trivial in comparison to the pros. It's interesting that modern medicines are becoming more specific and directed so they work as required without causing as many side effects. We‘re a lot worse off without the medicines we already have and probably going to be even better off in the future.” (female, white, UK resident, 45-54 years)

The vast majority of entries contained both positive and negative thoughts:

“Hearing how many things have been eradicated brings a sense of hope. Medicine truly has helped save lives and improve the quality of life. There are dangers and I feel that
there needs to be thorough research as well as update info available to the public." (female, white, US resident, 45-54 years)

“No question drugs can be very beneficial. It can improve life style and life span. However I still worry about potential negative effects of the drugs.” (male, white, UK resident, 55-64 years)

A small number of expressed thoughts were entirely negative:

“I was just thinking about how much of the information could be propaganda from the pharmaceutical companies just wanting us to turn more to taking medications.” (male, Hispanic, US resident, 35-44 years)

“One thing that I was thinking about was all those commercials on TV that say "Did you or a loved one take xxxxxx? If so and they died and/or had children with birth defects, call us now" ... The side effects of a lot of pills are worse than what they treat. I want to know why so many people are taking pills. Anyone ever wonder what the cause is for people to be on so many medications?” (male, white, US resident, 22-34 years)

6.7.11.6 Harm and benefit arguments (Interventions 5, 6, 7)

Not surprisingly participants found it significantly easier to generate three benefit arguments (M=3.48, SD=2.11) than eight harm arguments (M=5.59, SD=2.53; t(209)=6.58, p<.001). But ease of argument generation led to only directionally higher confidence in the validity of benefit arguments (M=7.19, SD=1.67) compared to harm arguments (M=6.84, SD=1.94; t(209)=1.41, p=.16). An analysis of the content of the risk arguments showed that many participants simply listed several potential side effects (e.g. medications can cause liver damage, allergies, stomach problems, etc.) as risks. Similarly, many participants listed various positive specific treatment outcomes (e.g. improve pain, make joints work, help breathing) as medication benefits. Side effects were the most commonly mentioned harm argument, curing of disease the most commonly mentioned benefit argument.

6.7.11.7 Perceptions of consensus information (Interventions 8 and 9)

Participants were only moderately surprised about the consensus information concerning the lack of harm of medicines (Mean 4.19, SD=2.53; rated from 1=not surprised at all and 9=extremely surprised) and about the consensus information stating that benefits outweigh harms (Mean 3.59, SD=2.41).

Participants were asked to briefly state why they thought other in-group members held this opinion (see section 6.4.4). Many participants listed careful
testing and regulation (e.g. through FDA) and positive personal experience as explanations for other people’s perceived lack of harm (Intervention 8).

“The FDA make sure that all medicines are safe and effective before release. If something isn’t safe, effective or poses a general threat to the public it is recalled.” (male, white, US resident, 22-34 years)

“Medicines are well-regulated and generally responsibly prescribed in the UK.” (female, white, UK resident, 22-34 years)

“From personal experience - I’ve been prescribed medication in the past and it has helped me to get better, without giving me any bad side effects.” (male, white, UK resident, 22-34 years)

“I have never had a problem with them.” (female, white, UK resident, 35-44 years)

However a few comments concerned other people’s lack of understanding:

“They are just not well educated on medicine and just assume it’s safe and pose little risk.” (female, white, US resident, 22-34 years)

“Because that is what they are told, and like said in the tv show jericho ” people get the news they want”. (male, mixed race, US resident, 22-34 years)

Many participants listed positive personal or second hand experiences of efficacy, trust in prescribing doctors and scientific evidence from trials to explain the consensus that the benefits of medicines outweigh harms (Intervention 9).

“I've had asthma for many years and need my daily medication. Many people have a better quality of life because of their medicines. Some people are kept alive by their medication.” (female, white, UK resident, >65 years)

“Because their personal experience and knowledge of history have taught them so. It is obvious that various illnesses and conditions that used to be fatal can now be cured thanks to the development of various medicines. Not only have such drugs saved many lives, but they have also been used to manage conditions successfully, in order to, for example, extend life or make symptoms easier to cope with.” (female, white, UK resident, 22-34 years)

“I know people who have taken them and benefitted.” (female, white, UK resident, 35-44 years)

“Because we have a lot studies that prove or disprove their effectiveness.” (female, Asian, US resident, 22-34 years)
Again a few participants indicated that others were overly trusting:

“Because this is what we have been brainwashed into believing. If you're ill, go to the doctor and he'll give you some medicine to make it better. Sometimes the illness would clear up just as well without any medicine.” (female, white, UK resident, 45-54 years)

“People will believe anything doctors say, instead of doing their own research on medicines and their alternatives.” (female, white, US resident, 22-34 years)

6.7.11.8 Perceptions of debiasing information (Intervention 10)

Many participants agreed with the information about placebo side effects/symptom misattribution and related it to personal experiences:

“My thoughts were neutral and I thought what was said made sense that you would have those effects no matter what. I mean I have headaches and I’m tired and I get sore and everything all the time and I'm not taking any medicine and haven't for a long time.” (female, white, US resident, 35-44 years)

“I agree with many of these thoughts. When I start a new medicine, I pay close attention to reactions and what else is going on. Did my diet change? Was I more active? It could be many things and/or the medicine, so it is important to consider all changes and impacts.” (female, white, US resident, 45-54 years)

“I found this information extremely interesting. I have suspected this may have been the situation with members of my family that take medications. It appears that medications are used as the scapegoat for many common problems and give the person an excuse for stopping the medicine (that they may not have wanted to take in the first place).” (female, white, US resident, 55-64 years)

“I am on anti-depressives and a side effect is an increased risk of suicide. I am pretty sure it’s not, it’s just with them taking time to get into your system, when someone has gone through actually seeking help and it appears not to have any effect it can spiral you down. The increased risk is not a side effect, it’s purely a psychological state brought on by a perception in the mind.” (female, white, UK resident, 35-44 years)

Some started questioning their thinking about medication side effects:

“I was thinking that if people are reporting things they were feeling, there is no way to determine whether or not these feelings are due to the medication or due to something else that has happened to them.” (female, white, US resident, 35-44 years)

“I am wondering how many symptoms are mental more than physical.” (female, white, US resident, 22-34 years)
One participant flipped the argument on the head and started reasoning about efficacy of medicines instead:

“It’s interesting to read about - the most pertinent point I can think of is that I have known for somebody in my family who is a bit stubborn, being told that paracetemol was flu medicine and they felt better that afternoon. I do not know a lot about statins, only what I learned from the prior notes. What went through my mind is more questions about whether medicines work or not? Whether there is a lot of point in using them.” (male, Chinese, US resident, 22-34 years)

Negative thoughts were rare, but one participant did not believe the veracity of the information, fearing that it was propaganda by the pharmaceutical industry:

“I am not sure that I believe these comments. Who funded that study--the drug companies?”(female, white, US resident, 45-54 years)

6.8 Discussion

6.8.1 Summary of findings

This feasibility study examined whether online interventions based on social cognitive models of attitude change are useful in changing individuals’ beliefs about harm and benefits of pharmaceutical medicines. Several putative consequences of the interventions were examined: I tested whether the interventions changed individuals’ perception of the fictitious anti-histamine drug Xymex after reading the patient information leaflet of this medication. In addition, using a scenario-approach, I examined whether the interventions reduced the likelihood that individuals attributed an unrelated symptom (nausea, which had not been listed in the patient leaflet) as a side effect and subsequently intended to stop taking Xymex.

Several interventions (Interventions 2, 4, 9) were successful in changing participants’ beliefs about the harmfulness of pharmaceuticals (both in within group and between-group comparisons). However, only Intervention 2 subsequently reduced participants’ concerns about the fictitious anti-histamine medication Xymex. The belief change interventions 1-9 failed to significantly affect the attribution of an unrelated symptom as a side effects and subsequent behavioural intentions to stop treatment. The debiasing intervention (Intervention 10), which did not explicitly target medication beliefs, but tried to forewarn individuals about a possible bias in symptom attribution, did however significantly reduce symptom misattribution.

Detailed findings from each set of interventions (grouped by underlying theoretical models) are outlined below.
Cognitive Dissonance (Interventions 1 and 2)

The cognitive dissonance intervention, where participants could freely choose to write a persuasive essay arguing that medicines are safe and not harmful (Intervention 2), was effective in reducing beliefs about the harmfulness of pharmaceutical medicines in general and concerns about the anti-histamine medication Xymex. Participants in this intervention group were marginally less likely to attribute the unrelated nausea symptoms as a side effect ($p=.06; \text{Cohen's } d=0.38$) and to subsequently intend to stop taking Xymex ($p=.08; \text{Cohen's } d=0.35$) than participants in the control group. The other cognitive dissonance essay task (Intervention 1) had no significant effect on medication beliefs. In this intervention participants could freely choose to write an essay arguing that the benefits of medicines outweigh the risks. Manipulation checks indicated that while there was no significant difference in psychological discomfort (a proxy for cognitive dissonance) between the two conditions, baseline medication beliefs were only significantly associated with discomfort in Intervention 2. It is plausible that even people who believe medicines to be generally harmful concede that there are instances were medicines are beneficial and potentially life-saving, resulting in low dissonance when arguing this position.

Elaboration Likelihood Model (Interventions 3 and 4)

An interesting finding emerged from the two ELM based interventions. The same two-sided persuasive arguments about the benefits and risks of medicines had different effects, depending on the message source. When individuals were told that the arguments were presented by a patient representative (Intervention 3), they rated medicines as less harmful after the intervention. When participants thought that a medical expert presented the identical arguments (Intervention 2), harm beliefs were not affected, but individuals believed pharmaceutical medicines as more beneficial. It is plausible, but purely speculative, that individuals believe medical experts to have a better grasp of the benefits of medicines (after all they interpret lab test results, are taught scientific evidence in medical school, etc.). On the other hand they may feel that they can trust patients more to understand the negative aspects of treatment: Patients (and not doctors) bear the burden of taking medication, while doctors are often perceived as “pill-pushers”(Horne, 1997)). It is interesting to note here that many patient forums are awash with patients discussing their experiences with side effects of specific drugs (Liu & Chen, 2013). Giving other patients who are taking the same treatment a (positive and reassuring) a voice
when discussing side effects, could thus be effective in reducing patients’ concerns about specific medications.

**Availability heuristic interventions (Interventions 5-7)**

Interventions based on the availability heuristic failed to change participants’ beliefs about pharmaceuticals. The tenet of this intervention was that it would feel difficult for participants to come up with a large number of harm arguments, thereby weakening individuals’ beliefs that there are many arguments to support this attitudinal position. But participants had no problem creating many harm arguments, using what could be called a sub-categorization strategy (Taylor, 1981): They simply listed different specific side effects (e.g. allergy, stomach problems) as possible harms. On a positive note, thinking about all these possible harms did not increase individuals’ harm beliefs or concerns about the anti-histamine medication. Yet, findings from the three interventions do not recommend them for inclusion in a future complex intervention.

**Social Identity Theory interventions (Interventions 8 and 9)**

In-group consensus information, stating that most people believe that the benefits of pharmaceutical medicines outweigh potential harms (Intervention 9), was successful in changing perceptions of harm. On the other hand in-group consensus information, stating that medicines are generally safe and not harmful (intervention 8) was not effective in changing individuals’ harm beliefs. Weighing up benefits and harms may have been more believable and balanced, thereby reducing resistance to persuasion (Knowles & Linn, 2004). Telling patients that patients with similar circumstances and demographic profile (versus simply referring to patients in general) benefit from and tolerate a specific drug well, may be another simple means to reduce the concerns patients may have about their medication in future intervention.

**De-biasing intervention (Intervention 10)**

Warning participants about the misattribution of symptoms as side effects did not change people’s perceptions about medicines in general or the specific anti-histamine medication, but was effective in reducing side effect attribution in the vignette. This is encouraging and replicates findings from a previous study using similar information about nocebo responding, albeit to environmental stimuli.
This type of intervention strategy is certainly promising for reducing symptom misattribution and nocebo-related side effects.

6.8.2 Qualitative insights

Using thought listing techniques as part of some interventions (Petty & Cacioppo, 1986) allowed me to gain qualitative insights into what motivates or deters individuals to change their beliefs. In particular issues around resistance to persuasion and trust were highlighted. People do not easily change their beliefs and persuasive information can all too easily be refuted as “propaganda” from untrustworthy sources which are biased by self-interest. Although resistance to persuasion was also apparent in the ELM based interventions, many participants appreciated the fact that both problems/challenges and positive aspects of treatment were acknowledged. Future complex interventions may want to take this possibly at first sight counterintuitive strategy on board. The debiasing intervention, where participants were informed about side effects to placebo and the risk of misattributing unrelated symptoms as side effects was very well received by participants. Participants were able to relate to the presented information and it was encouraging to see that some started to question their own thinking about side effects following the intervention.

6.8.3 Acceptability and transferability of interventions

General feedback from participants was very positive and drop-out rates were low, suggesting that the interventions were generally well accepted. But it rests to prove whether similar intervention techniques could be easily transferred to clinical samples. There are however indications that the cognitive dissonance intervention could be adapted to patient samples. Interventions using essay writing tasks (typically about stressful life events (Smyth, Stone, Hurewitz, & Kaell, 1999) and emotions (Petrie, Fontanilla, Thomas, Booth, & Pennebaker, 2004a)) have proved feasible and effective in influencing health outcomes (see meta-analysis (Smyth, 1998)) in the past.

There have also been suggestions from nocebo researchers to educate patients about the nocebo effect in order to reduce side effects and to improve adherence (Bingel, 2014; Enck et al., 2013). Interventions following the logic of my debiasing intervention may prove feasible in clinical samples. Showing patients data about side effects to both placebo and their prescribed active medication may potentially reduce concerns and influence symptom attribution in clinical groups.
6.8.4 Strengths and limitations

The study had several strengths and weaknesses. Given the web-based sampling of participants and the online-delivery of interventions, there was no direct interaction with participants. This reduces potential acquiescence and social desirability response effects: Participants are less reluctant to express negative thoughts and are less inclined to give answers that please the researchers in an anonymous context (Gordon, 1987; Grimm, 2010). Yet even in this anonymous, low trust and somewhat commercial setting I found significant interventions effects. It will be important to examine whether effects are stronger if interventions are conducted in a more classical health research setting, with better established trust (Hall, Dugan, Zheng, & Mishra, 2001).

The online sampling allowed me to systematically pre-test a large number of possible intervention components. This came at the expense of relatively low number of participants per condition. The study was probably underpowered to detect significant differences in some of the secondary outcomes (e.g. side effect attribution), although some signs from effect size estimates are encouraging. Estimated effect sizes of even the effective beliefs change interventions were somewhat smaller than the one used to power the study, speaking to a lack of statistical power as a potential explanation.

Given the large number of interventions and possible comparisons and resulting risk of type-1 errors (or false positives), it is extremely important to not over-interpret the statistical significance of findings. A replication of the findings in an adequately powered study is therefore highly warranted. Future research will also need to establish how long-lived the intervention effects are (in this study only the immediate effect of the interventions was assessed) and whether these intervention approaches can be successfully applied to clinical samples.

Further studies are needed in order to confirm the ecological validity of this intervention development approach. Ecological validity in this study was of course compromised by the use of computer based intervention techniques, a predominantly healthy participant sample and the briefness of the interventions.

6.8.5 Conclusion

Taken together these findings provide interesting insights in how to design future complex interventions to change medication beliefs. The study clearly highlights the potential of analogue online pre-tests for intervention development. In
particular, the cognitive dissonance and debiasing interventions show potential for further development. An experimental placebo study is currently underway testing whether a complex intervention, combing some of the pre-tested components (e.g. cognitive dissonance essay, debiasing information) is effective in reducing side effect reporting to placebo.
Chapter 7: Conclusion

The principal aim of this thesis was to get a better understanding of the relationship between medication beliefs and side effects. Side effects are common and can be distressing for patients. It is thus understandable that patients who experience side effects consequently develop greater concerns about the specific medication and pharmaceutical medicines in general and believe that they are personally more sensitive to their effect. In this thesis I postulated that in addition to these known associations (Horne, 2003), medication beliefs may also influence whether patients report side effects in the first place. Several studies were conducted to provide empirical support for this hypothesis and answer the following specific research questions: 1) Do medication beliefs prospectively predict side effect reporting? 2) Why are medication beliefs associated with side effect reporting? 3) Can we change medication beliefs and thereby reduce non-specific side effects?

7.1 Summary of empirical findings

The first study (Chapter 2) tested whether the beliefs women had about pharmaceuticals in general and their perceived sensitivity to medicines before initiating bone loss treatment, as well as concerns about their newly prescribed bone loss treatment predicted side effect reporting over a 12 month follow-up period. The study showed that patients with more negative pharmaceutical schemas (i.e. those who perceived themselves as more sensitive to medicines, believed pharmaceuticals to be generally harmful at baseline) and with stronger concerns about their bone loss medications, reported significantly more side effects. The experience of side effects reduced persistence and self-reported adherence to medication, highlighting the clinical importance of the problem. The study replicated the well-established role of medication beliefs in medication taking behaviours (adherence, persistence), but went beyond existing studies by showing that medication beliefs also predict side effects, which may contribute to and perpetuate these behaviours. Findings from the study are in line with previously identified prospective associations between patients’ concerns about their antidepressant (Aikens & Klinkman, 2012) and arthritis medication (Nestoriuc et al., 2010) and the emergence of side effects. But this study made a distinct contribution by replicating these findings in a new patient group, with a larger sample and across more measurement points. In addition, it is the first study to show prospective association between pharmaceutical schemas and side effect reporting. A previous study
(Petrie et al., 2004b) that examined the effect of perceived sensitivity on side effects to travel vaccination did not find a significant effect at the one week follow-up.

The second study (Chapter 3) also demonstrated a prospective association between medication beliefs and side effect reporting, albeit in healthy individuals taking placebo (described as Modafinil). In addition, a non-treated natural history group and an open label placebo control group were included in this sham trial. The study was informed by recent research on the nocebo effect and examined several putative mechanisms linking medication beliefs to nocebo responding. In particular I examined whether individuals with more negative medication beliefs had more negative expectations and focused more on changes to bodily sensations, thereby increasing the likelihood of detecting symptoms. In addition to measuring the number of detected symptoms, I also assessed whether participants with more negative medication beliefs attributed more of these symptoms to the medication (i.e. reported side effects). Participants who were led to believe that they were taking active Modafinil reported significantly more symptoms and side effects than participants who were correctly informed that the administered pill was a placebo. The number of reported side effects to placebo-Modafinil was predicted by pharmaceutical schemas (beliefs about personal sensitivity to medicines, beliefs about the harmfulness of pharmaceuticals in general) and concerns about the study pill. I also found support for some of the postulated mechanisms: Participants who believed pharmaceutical medicines as generally harmful and less beneficial and who perceived themselves as more sensitive to the effects of medicines expected their bodies to feel worse when taking Modafinil. Participants who had stronger concerns and necessity beliefs reported paying closer attention to changes in bodily sensations after taking the study pill. Pharmaceutical schemas on the other hand were not significantly associated with self-reported attention to bodily sensations (but the direction of the relationship was in the predicted direction). Although the putative role of medication beliefs in nocebo responding has been previously discussed in the literature (Faasse & Petrie, 2013; Horne, 1999), this was the first study to empirically demonstrate the role of medication beliefs in nocebo responding and to elucidate putative underlying mechanisms.

The third study (Chapter 4) then examined the role of medication beliefs in the attribution of symptoms as side effects in more detail. This analogue online study used a scenario approach to test whether individuals with more negative medication beliefs were more likely to misattribute an unrelated common symptom (headache) as a medication side effect and subsequently intend to stop their
medication. I found that participants with more negative pharmaceutical schemas (i.e. who believed medicines to be more harmful and less beneficial) and stronger concerns about the medication were more likely to misattribute the headache symptom as a side effect. Misattributing the headache symptom as a side effect starkly increased behavioural intentions to stop treatment. Behavioural intentions were again predicted by medication beliefs: Participants with more negative pharmaceutical schemas and stronger concerns were more likely to intend to stop treatment. The importance of symptom misattribution in patient reported side effect has been repeatedly discussed in the literature (Barsky et al., 2002), but empirical evidence was very limited (Petrie et al., 2004b; Petrie & Weinman, 2003). Findings from the study are in line with theoretical predictions of models of illness and treatment representations (Horne, 2003). But while the role of illness representation in symptom appraisal has been well documented (Baumann et al., 1989; Leventhal et al., 1982), this was one of the first studies to show the importance of medication beliefs in the misattribution of symptoms as side effects.

Study 3 showed that pharmaceutical schemas can influence the attribution of unrelated common symptoms as side effects. Study 4 (Chapter 5) looked in more detail at the psychological processes linking pharmaceutical schemas to side effect attribution. The primary aim of the study was to investigate whether pharmaceutical schemas influence how individuals process and remember side effect information from a patient leaflet and whether this in turn affects side effect attribution. I hypothesized that the misattribution of a symptom to a medication side effect would be less likely if participants remember the information they have been given about known side effects of the medication more accurately. In line with findings from Study 3, I found that more negative pharmaceutical schemas increased side effect attribution. But this was the first study to show that medication beliefs also influenced recall and recognition of side effect information: Participants who perceived pharmaceuticals as more harmful recalled fewer listed side effects and were less able to discriminate between listed and new side effects (reduced Recognition Sensitivity). Participants who believed medicines to be more beneficial recalled more side effects correctly and showed better Recognition Sensitivity. Better memory for listed side effects decreased the likelihood that an unlisted symptom was attributed as a side effect. The relationship between pharmaceutical schemas and side effect attribution was partially mediated by memory for side effect information. Previous studies have shown poor memory for medical information (Barsky, 2002; Ley, 1979), but few have examined potentially modifiable
psychological factors related to memory (Watson & McKinstry, 2009) and linked memory for side effects to symptom attribution decisions. Although there was evidence for the role of illness schemas in the recall of illness symptoms (Baumann et al., 1989), this was the first study to demonstrate that pharmaceutical schemas, as assessed with the BMQ-General and PSM, are associated with memory for side effect information.

Finally, Study 5 (Chapter 6) examined whether social cognitive interventions could be effective in changing pharmaceutical schemas and whether this reduced individuals’ tendency to attribute an unrelated symptom as a medication side effect. Participants in this feasibility study were randomized to one of ten short active interventions or a control intervention. Participants who were asked to write an essay arguing that medicines are not harmful, who read two-sided persuasive arguments about the benefits and risk of medicines or who saw in group-consensus information, stating that the benefits of medicines outweigh the harms, had significantly reduced harm beliefs after the intervention compared to baseline. There was a non-significant trend for reduced side effect attribution and behavioural intentions to stop treatment for participants who wrote an essay arguing that pharmaceuticals are not harmful. Side effect attribution was significantly reduced for participants who were randomized to an intervention that informed about them about nocebo effects and symptom misattribution. Several studies have attempted to change patients' beliefs about medication using psychoeducational strategies (Chapman et al., 2015; Karamanidou et al., 2008; Zwikker et al., 2014), but this was the first study to apply more general theories of attitude change and persuasion to the intervention development. In addition this was the first study to focus on changing pharmaceutical schemas instead of beliefs about specific medications.

7.2 Evaluation of empirical evidence:

The aim of this section is to evaluate whether the evidence gathered across these studies supports the postulated role of medication beliefs in the reporting of side effects. I broadly follow the framework developed by Bradford Hill (Hill, 1965) to critically assess evidence for causal relationships. Please note that meeting these criteria (in isolation or in aggregated form) does not provide indisputable evidence for or against the hypothesis, but strengthens our confidence in the credibility of the hypothesis.
7.2.1 Temporal precedence

Logically a cause must precede an effect. It is impossible to draw firm inferences about cause and effect if both the putative cause and the effect are measured at the same time. Findings from prospective studies thus strengthen the credibility of a causal relationship between medication beliefs and side effect reporting. Two studies were conducted to test whether medication beliefs prospective predict side effect reporting (see Research question 1).

Findings from both studies corroborate findings from the literature review (see section 1.3.3). The studies show that individuals’ pre-existing beliefs prospectively predict side effect reporting in patients taking active medication (Study 1) and in healthy volunteers taking Modafinil placebo (Study 2). In both studies individuals who started out with more negative medication beliefs (e.g. stronger perceived sensitivity to medicines, greater concerns) reported more side effects.

Results from the cross-lagged structural equation model in Study 1 suggest a bi-directional relationship whereby the experience of side effects also increases subsequent concerns. It also plausible that individuals who experienced side effects (e.g. racing heart) after taking placebo Modafinil in Study 2 developed stronger concerns about Modafinil after experiencing these symptoms (although this wasn’t assessed in this study).

These findings point to the possible existence of a vicious circle, whereby negative medication beliefs increase side effects, the experience of side effects in turn strengthens negative beliefs, which then subsequently increase the likelihood that patients experience/report side effects (see also Figure 6 in the Introduction).

7.2.2 Strength of the association

Statistical associations between medication beliefs and side effect reporting/attribution were small to moderate in effect, yet very consistent across the different studies. For example Study 3 found that for a one unit increase on the BMQ-General Harm Scale, the predicted odds of side effect misattribution were increased by 90%. In a similar vein in Study 2, a one unit increase in BMQ-General Harm increased the expected number of reported side effects by 70% in participants receiving deceptive Modafinil placebo. Although some of the observed effect sizes would be classified as small (Cohen, 1988), Hill (1965) rightly pointed out that this does not mean one should readily dismiss a cause and effect relationship.
7.2.3 Consistency

Perhaps the strongest support for the postulated causal relationship comes from the consistency of the findings. Associations between medication beliefs and side effect reporting/attribution were replicated in studies in different settings (e.g. clinical setting in Study 1; lab setting in Study 2) and using different methods (e.g. experimental placebo paradigm in Study 2, vignette approach in Studies 3-5).

7.2.4 Plausibility

While Hill refers to biological plausibility, I follow other researchers' lead by enlarging this criterion to theoretical plausibility (Rychetnik, Frommer, Hawe, & Shiell, 2002). To the lay person it may seem surprising that factors other than the pharmacological action of the drug may influence side effects. But the growing body of research on the nocebo effect clearly demonstrates that psychological factors can contribute to side effects. There is thus a sound theoretical plausibility for the postulated association. This is further strengthened by the fact that I also showed how (i.e. through which nocebo mechanisms) medication beliefs may influence side effect perception and reporting. Several putative mechanisms were identified that could explain why medication beliefs are linked to side effect reporting (see Research Question 2). More negative medication beliefs were associated with increased side effect expectations (Studies 2-4), greater monitoring of bodily changes following deceptive placebo treatment (Study 2) and a tendency to attribute ambiguous sensations (Study 2) or a common unrelated symptom (Studies 3-4) as side effects.

7.2.5 Coherence

Somewhat related to theoretical plausibility is the criterion of coherence. The postulated association between medication beliefs and side effect is compatible with existing theories of illness and treatment representations (Horne, 1999) as well as general models of symptom perception (Cioffi, 1991) (see section 1.5.1 for an overview) and theories of medically unexplained symptoms (see also the analogy criterion below).

7.2.6 Experimental evidence

Random assignment to the exposure of interest is considered one of the most stringent tests of causality (Reiter, 2000). Medication beliefs are social cognitive constructs that are informed by previous experiences with medication (Horne, 1997), social learning (i.e. witnessing other people’s reactions and attitudes...
to medicines), official health communication and the media amongst others (Horne, 2003). Most people in the developed world will therefore have pre-existing beliefs about pharmaceutical medicines. What can therefore be manipulated is not the presence of the exposure, but the extent to which participants hold certain beliefs. Participants in Study 6 were randomly assigned to either a belief change or a control intervention and side effect attribution was measured using a vignette scenario. This study provided inconclusive but directional evidence that a reduction in harm beliefs could reduce side effect attribution. For example the cognitive dissonance intervention (Intervention 2) significantly reduced patients’ beliefs that pharmaceutical medicines are generally harmful, but the effect on side effect attribution was small (d=.38) and only marginally significant. Better powered studies are needed to provide definitive answers to whether changes in medication beliefs can reduce side effect reporting and the attribution of symptoms as side effects (Research Question 3). Some of the more effective intervention approaches (cognitive dissonance, ELM, SIT) show promise and should be considered for inclusion in future complex interventions.

7.2.7 Consideration of alternative explanations

While I have tried to examine possible alternative explanations, it would be presumptuous to claim that I have managed to rule out all other potentially important factors. I showed for example that medication beliefs predicted side effect attribution when controlling for negative affect (Study 3). It was beyond the scope of this already ambitious and data intensive thesis to look at a variety of other variables that may have affected both medication beliefs and side effect experience (i.e. confound the detected relationship). This is certainly an important target for future investigations and will be discussed in more detail in section 7.6.2 below.

7.2.8 Specificity

Medication beliefs are certainly not the only factor determining side effect experience. For example findings from Study 1 speak to the importance of depression and anxiety. Study 2 clearly illustrates that negative affectivity and somatization are also important contributing factors. But absence of specificity does not negate a causal relationship. Indeed current reasoning on causality acknowledges that the world is a complex and messy place and that most phenomena are the result of multiple causal influences. One-to-one cause-effect relationships are the exception rather than the rule (Ward, 2009).
7.2.9 Analogy

I believe it is possible to draw an analogy between side effects and medically unexplained symptoms, i.e. physical symptoms which cannot be explained by any disease specific pathology (Kirmayer, Groleau, Looper, & Dominice, 2004). This was however not specifically examined in this thesis. At least some patient reported side effects could be described as pharmacologically unexplained symptoms. And just as psychological factors (e.g. negative affectivity (De Gucht, Fischler, & Heiser, 2004), somatization (Katon & Walker, 1998), somatosensory amplification (Barsky, Goodson, Lane, & Cleary, 1988)) have been shown to influence medically unexplained symptoms, it seems reasonable to assume that medication beliefs influence side effects.

7.2.10 Summary

There is considerable debate about how to quantify the degree to which each criterion is met or how to aggregate the results into a judgement of causality (Swaen & van Amelsvoort, 2009; Ward, 2009). Importantly, even adequate fulfilment of the criteria does not provide irrefutable evidence for a causal association. Despite these big caveats and the inherent limitations of the studies (see 7.4 below for a detailed discussion), I believe that the evidence gathered over the five empirical studies does lend credibility to the claim that medication beliefs (are one of many possible factors that) influence the perception and reporting of side effects.

7.3 Original contribution to knowledge

This thesis makes several important original contributions to the literature on medication beliefs and nocebo effects.

While there is extensive empirical evidence for the role of medication beliefs in medication taking behaviour (e.g. treatment uptake, adherence, persistence) (Horne et al., 2013a), our understanding of the role of medication beliefs in side effect perception/reporting was so far very limited. Yet understanding links between medication beliefs and side effects, may prove helpful in understanding how medication beliefs influence medication taking behaviours.

Many of the empirical findings in my thesis are novel. My experimental placebo study (Study 2) was the first study to provide empirical evidence for an association between medication beliefs and nocebo responding. Participants who started off with more negative pharmaceutical schemas were more likely to detect
symptoms and attribute these symptoms as side effects when taking Modafinil placebo. While the role of medication beliefs in side effect attribution has been previously discussed in the literature, I used a novel study approach (analogue online vignette) to provide empirical evidence for the role of medication beliefs in side effect attribution. In addition, my thesis provided important insights in the relevance of medication beliefs for information processing and memory. Study 4 was the first study to show that medication beliefs can influence memory for side effect information. Perhaps contrary to clinical intuition, I demonstrated that participants with more negative pharmaceutical schemas paid less attention to side effect information (as indicated by reduced reading times) and showed poorer recall and recognition of the listed side effects. Finally, although there have been previous attempts to modify medication beliefs, Study 6 was the first study explore whether more cognition focused intervention strategies based on social cognitive models of attitude change could be effective in reducing overly negative medication beliefs.

This thesis also makes an important contribution to research on the nocebo effect. The Modafinil placebo study (Study 2) was one of the first studies to examine both symptom detection and attribution of symptoms as side effects. Including a non-treated natural history group allowed me to compare the amount of symptoms that would occur in the absence of treatment to the amount of symptoms occurring when patients expected to be taking an active drug (i.e. quantify symptom increase caused by nocebo effect). In addition, I showed that in order to induce placebo effects without deception it is likely necessary to describe placebos in more positive terms than those commonly used in placebo descriptions in clinical trials.

This thesis did not only contribute to knowledge, but was also original from a methodological point of view in that it used innovative approaches to sampling (e.g. crowdsourcing) and data collection (e.g. using online experiment software).

This thesis also provided novel empirical support for the theoretical treatment belief model (Horne, 1997, 2003). The model states that peoples’ general beliefs about pharmaceutical medication or pharmaceutical schemas (as measured with the BMQ-General and PSM) influence how patients’ evaluate specific medicines (as measured with the BMQ-Specific). Although the postulated relationship is readily plausible, previous empirical support relied almost entirely on cross-sectional correlational evidence (see also section 1.3.1.3). My thesis added to the limited existing evidence by showing that womens’ beliefs about pharmaceuticals in general and perceptions of personal sensitivity to medicines at
baseline predicted subsequent perceptions of necessity and concerns about bone loss treatment follow-up (see section 2.5.1.3). In addition, the vignette studies (Studies 3-5) showed that individuals' evaluation of an unfamiliar medication (hypothetical drug presented in a patient information leaflet) is influenced by pre-existing beliefs or schemas. Finally, there is also experimental evidence from Study 5. Findings from this study suggest that modifying individuals' beliefs about the harmfulness of pharmaceutical medicines in general may be effective in reducing the concerns individuals have about specific treatment (see section 6.7.8).

Findings from my thesis also suggest that the important role of pharmaceutical schemas in shaping treatment outcomes may have previously been overlooked. Most existing empirical studies assessing the relationship between medication beliefs and adherence focus on specific necessity and concern beliefs (often operationalised within the necessity concerns framework). If mentioned at all, general beliefs about medicines are only referred to in their relation to specific beliefs. Yet my findings suggest that general beliefs about pharmaceuticals seem to play an important role in how patients evaluate and remember treatment information (see Study 4), appraise symptoms and side effects (all studies), and in predicting whether patients adhere to (Study 1) or intend to take their treatment as prescribed (Studies 3-5).

7.4 Limitations of thesis

Specific limitations of each study have been discussed in the relevant chapters. The aim of this section is therefore to look at limitations arising across the whole body of research.

7.4.1 Representativeness of samples and external validity

The external validity of the findings, i.e. the degree to which the results can be generalized to and across individuals, is closely linked to the representativeness of the samples studied. The prospective clinical study (Study 1) involved a large sample of women, recruited across many different primary care practices in different European countries. But due to the studied condition (post-menopausal osteoporosis) the sample was restricted to women. Although many studies have failed to find a significant effect of gender (Geers et al., 2011; Jensen & Karoly, 1991; Mazzoni et al., 2010; Witthöft & Rubin, 2013), others did report greater nocebo effects for women than men (Klosterhalfen et al., 2009; Liccardi et al., 2004; Ströhle, 2000). In addition, women agreeing to take part in such a long and cumbersome study (the questionnaire booklet of the original study spans over 100
pages), may not be very representative of women at risk for osteoporotic fractures in general.

The samples for the remaining studies involved non-patients or a mixture of healthy individuals and individuals with previous experience with the condition. For the placebo lab experiment (Study 2) a convenience sample of healthy students was recruited. The over-reliance on student samples in the behavioural sciences has long been criticised (Gordon, Slade, & Schmitt, 1986), but there are several reasons that speak to the acceptability of using student volunteers in this case: For one, it is ethically problematic to deceive patients with the purpose of inducing symptoms (Benedetti, 2010; Finnis, Kaptchuk, Miller, & Benedetti, 2010). Secondly, we selected a drug (the cognition enhancing drug Modafinil), that is relevant for the target population. Thirdly, there are many instances in which patients take pharmaceutical medicines not to treat an existing condition, but to prevent the condition (e.g. statins). However there is again a likely risk of self-selection bias, in that students who agree to take part in a study to assess the efficacy and safety of a prescription drug may be more likely to have fewer concerns about pharmaceuticals in general and the drug in question.

Three of the five studies presented in this thesis were conducted with convenience online samples. Although this sampling approach has been shown to be reliable (Gosling, Vazire, Srivastava, & John, 2004; Ritter et al., 2004; Whitehead, 2011), there are many ways in which online participants may differ from the general population. Participation is restricted to individuals with access to the internet and participants tend to be somewhat more technology savvy and younger (Paolacci et al., 2010) than the general population due to the still existing generational differences in internet use (V. Shah, 2001). As also witnessed in my samples, women tend to be more willing to participate in online studies than men (Gosling et al., 2004; Paolacci et al., 2010).

While the first two studies look at real medication taking behaviour and actual side effect experience, the last three studies relied on analogue scenario data: Patients were merely told that they were taking the medication and experiencing a common symptom. This does of course compromise the external validity of the findings. Taken together this clearly highlights the necessity to replicate these findings in more diverse and representative samples (if possible in patient groups) using different medications.
7.4.2 Method and response biases

In addition to the already outlined sampling bias, several other possible biases may affect the validity of findings. For instance, all key predictor and outcome variables were measured through self-report Likert type or visual analogue scales. It is thus not possible to distinguish between actual and reported levels of these variables. This also raises concerns about a potential common method bias, whereby some of the observed variance in the outcome is attributable to the measurement method rather than the construct in question (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). This type of systematic error variance can arise through several types of response biases (e.g. halo effects, social desirability effects, acquiescence bias, satisficing (Podsakoff, MacKenzie, & Podsakoff, 2012)). For example social norms of appearing agreeable and polite can make people more likely to agree rather than disagree with most survey questions. This acquiescence bias (or "yes–saying" tendency) (Ross & Mirowsky, 1984) could for example explain part of the association between medication beliefs and side effect attribution.

7.4.3 Experimenter bias

It is possible that predisposed notions or beliefs of the experimenter consciously or unconsciously influence outcomes in the expected direction (Rosenthal, 1966). Risk of experimenter bias was relatively low in all presented studies. For example all side effect outcome measures in the POSSIBLE EU study (Study 1) were assessed with mailed questionnaires, in the Modafinil placebo study (Study 2) with a computerized symptom check-list, reducing the effect of experimenter bias. Assignment to the two placebo conditions was blinded in the Modafinil placebo study (Study 2). It is however generally impossible to blind a natural history condition (Gøtzsche, 1994), implying that experimenter effects cannot be entirely ruled out. The risk of experimenter bias in Studies 3-5 was low as data was collected online, i.e. without direct experimenter interaction (Reips, 2000).

7.4.4 Reliability and validity of measures

The questionnaire measures used to assess medication beliefs (BMQ, PSM) have been well validated and showed acceptable to good internal consistency in the presented studies. Limitations of these instruments have been already discussed in the Introduction (see 1.3.2). Side effects were assessed with self-report scales, as common in studies assessing side effect burden. There is a general dearth of validated side effect measurement instruments (Rief et al., 2011) and neither of the side effect scales used for Study 1 or Study 2 has been previously validated. But
side effects outcomes derived from the scale in Study 1 correlated well with the previously validated side effect scale of the TSQM (Atkinson et al., 2004). Moreover the side effect scale used in Study 2 was adapted from the illness identity scale of the IPQ (Moss-Morris et al., 2002), which has been validated across a large number of different patient groups (Ashley et al., 2013; Broadbent, Petrie, Main, & Weinman, 2006).

7.4.5 Personal blind spots
Looking back at some of the studies, I would certainly change some aspects of their design if I was to run them again. But hindsight is certainly easier than foresight (Fischhoff, 1975) and “a person who never made a mistake never tried anything new” (Einstein). It was probably over-ambitious to include the various information manipulations in Studies 3 and 4. In hindsight, I now acknowledge that this may have unnecessarily overcomplicated matters. Also looking back at the intervention development study, it would have been wiser to pre-test fewer intervention components, yet to increase the number of participants per intervention in order to increase power. In hindsight it is also not very surprising that the symptom induction tasks in Study 2 were not particularly successful in inducing specific symptoms, given that they had to be fairly ambiguous to allow for symptom misattribution.

7.5 Clinical implications of the research
Given that most of my research relied on non-clinical samples (see 7.4.1) it is certainly premature to make any explicit claims about the clinical significance of this research. Yet there are several ways how my findings (if replicated in clinical populations, see also 7.6.1) could be applied to clinical practice.

7.5.1 Informing consultations about new treatment
Findings from my studies suggest that clinicians should pay greater attention to patients’ background beliefs about medicines when prescribing new treatment. Pharmaceutical schemas play an important role in how patients process information about new treatments, remember this information, evaluate specific treatments, and appraise symptoms arising during the course of treatment. The BMQ and PSM may be helpful in guiding clinicians in their exploration of unhelpful pre-existing beliefs during consultations. Clinicians should take any identified concerns and worries seriously and try to empathetically address these. Simply dismissing concerns as unfounded may jeopardize the doctor-patient relationship. Invalidating doctor-patient interactions (i.e. interactions that fail to communicate acceptance and
understanding) may actually facilitate the nocebo effect (Greville-Harris & Dieppe, 2015).

An interesting finding emerged from Study 4. Individuals with more negative pharmaceutical schemas remembered factual side effect information less accurately, biasing later symptom attribution decisions. Perhaps contrary to clinical intuition, this suggests that doctors should go over side effect information in more detail with patients who have stronger underlying concerns about medicines. Some clinicians have been reluctant to give out too much information about side effects (Berry, Gillie, & Banbury, 1995), fearing the nocebo effect of informed consent (see also section 1.5.1). If replicated, my studies do however suggest that information about known side effects may reduce the likelihood that unrelated symptoms are labelled as side effects.

7.5.2 Side effect complaints and treatment changes

Given the frequency of side effect reports in patients receiving mere placebo (see Chapter 1), it is reasonable to assume that nocebo effects contribute to the side effect burden in clinical practice. What my research suggests is that changing a patient to a different medication (with a different pharmacological mechanism) in order to reduce the side effect burden will not necessarily reduce side effects if the patients’ beliefs about medicines remain negative. What is therefore needed is not necessarily always a change in drug regimen, but an effective strategy to address patients’ concerns about treatment.

7.5.3 Applying persuasion literature to intervention development

My feasibility intervention study points to some potentially effective intervention techniques to modify medication beliefs. But it also clearly highlights the danger that interventions (be they to modify beliefs, increase adherence, increase vaccination uptake) could backfire. Ingrained beliefs are difficult to change and patients who resist persuasive attempts may actually strengthen their initial beliefs. Potentially, being more mindful of the literature on persuasion and applying its findings to intervention development may improve intervention success in clinical settings.

7.5.4 Improving adherence by reducing nocebo related side effects

The experience of side effects is likely to reduce adherence. For example women who experienced side effects from their bone loss medication (Study 1) were more likely to show reduced persistence and adherence. My analogue studies
further showed that the misattribution of an unrelated symptom as a side effect starkly increased the odds of behaviour intentions to stop treatment. There is however hope that interventions that manage to reduce nocebo effects (e.g. debiasing intervention in Study 5) may improve adherence to treatment. Clinicians may want to discuss the nocebo effect with patients if they suspect nocebo-related side effects, particularly in patients with unhelpful medication beliefs.

7.6 Direction and areas for future research

7.6.1 Replication of findings in clinical samples

As outlined above (see section 7.4) there is a clear need to replicate findings from my vignette studies and the online intervention feasibility study in patient samples. Research applying the Common Sense Model of self-regulation shows how closely illness and treatment representations are interlinked (Horne, 2003). It is thus not clear whether the findings would be similar in patients with established (versus hypothetical) illness representations. A replication of the findings in a patient only sample would thus strengthen the external validity of findings. It is however encouraging to note here that I did not find differences in the relationship between medication beliefs and symptom misattribution between patients with or without asthma in my online vignette studies (no interaction effects, see section 4.5.10).

An even more valid test would be to probe the misattribution of real symptoms. I previously argued that it is difficult to unambiguously examine symptom misattribution in patients experiencing symptoms from real medication. One could however envisage a study in which a panel of experts assesses which proportion of patient reported side effects have a specific pharmacological mechanism or a lack thereof and test whether medication beliefs predict the number of non-specific side effects reported by patients.

Alternatively, I see clear scope in improving the existing vignette approach. This could be achieved developing a side effect attribution questionnaire, similar to the symptom attribution questionnaire (Robbins & Kirmayer, 1991) which has been developed to assess attribution of symptoms in patients with MUS (see also section 1.5.1).

A replication of findings from the Modafinil Placebo Study (Study 2) is also highly warranted. Placebo and nocebo effects are extremely context dependent (Benedetti, 2010) and it will be very informative to see whether the association between medication beliefs and nocebo responding can be replicated in a different
sample, using a different drug and experimental setting. Although care was taken to blind assignment to placebo conditions, rerunning the study with a different experimenter (if possible naïve to research on the nocebo effect) would further strengthen the validity of findings.

7.6.2 Examining possible interaction effects with other psychological patient characteristics

As outlined above, medication beliefs are only one of many putative psychological patient characteristics contributing to side effect perception/reporting and interaction effects are likely. But our understanding of how for example personality characteristics influence side effect reporting through nocebo mechanisms is still in its infancy (see Webster et al., 2016). In addition, there is as yet no clear understanding of the extent to which other psychological characteristics are related to medication beliefs. To my knowledge only one previous study explored the relationship between medication beliefs and personality traits (Emilsson et al., 2011). This small study (N=35) in patients with asthma examined whether the Big Five personality factors (Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness) were associated with specific medication beliefs. Significant positive correlations were found between necessity beliefs and conscientiousness and between neuroticism and specific medication concerns. There is evidence that neuroticism may influence nocebo-related side effects in patients taking antidepressant medication (Davis et al., 1995) and side effect reporting in response to antiretroviral treatment in a sample of HIV infected men and women (Johnson & Neilands, 2007). My own studies have shown that medication beliefs (in particular perceived sensitivity to medicines) are often positively correlated with negative affectivity (closely related to neuroticism) and there are indications that negative affectivity can lead to increased nocebo responding and side effect reporting in general (see also section 1.4.3). There is an abundance of other psychological traits and personality characteristics that could be associated with both medication beliefs and side effects. It is for example plausible that people with a more pessimistic disposition have more concerns about what could go wrong when taking medication. There is again emerging evidence that pessimism is related to increased symptom reporting in individuals receiving deceptive placebo (Geers, Helfer, Kosbab, Weiland, & Landry, 2005).

7.6.3 Refining belief change interventions

Given the documented role of medication beliefs in engagement with treatment (treatment uptake, adherence, persistence) and side effect
perception/reporting, there is a clear need to refine intervention strategies to modify unhelpful medication beliefs. My humble feasibility study may have shown some possible avenues for future more complex intervention. Yet instead of merely testing the immediate effect of these intervention components on medication beliefs and hypothetical symptom attribution, clear next steps would be to test whether these interventions have a longer lasting effect on medication beliefs and actual symptom attribution behaviour. A possible way to test this would be to look at whether an online belief change intervention could reduce side effect reporting in participants receiving a deceptive placebo. Longitudinal studies are needed to examine whether belief change interventions are effective in modifying beliefs not only in the short term, but over a longer period of time.

7.7 Conclusion of the conclusion

Taken together we can make a reasonably confident claim that medication beliefs do indeed play an important role in the emergence of side effects by influencing several cognitive-perceptual processes (e.g. processing of information about side effects, monitoring of bodily sensations, expectations and symptom attribution). Preliminary evidence suggests that strategies to modify medication beliefs may be effective in reducing side effect attribution, with the hope that this will improve quality of life and treatment outcomes for patients.
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Appendices

Appendix A: Assessment of comorbid conditions (Study 1)

Has the subject (currently or previously) experienced any of the following conditions during adulthood (≥18 years of age)? □ No □ Yes - if yes, specify below.

<table>
<thead>
<tr>
<th>Code</th>
<th>Condition</th>
<th>Currently or previously experienced condition?</th>
<th>If yes, is condition ongoing?</th>
<th>Currently receiving medication for this condition?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>01</td>
<td>Angina</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>Heart Valve Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>04</td>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>05</td>
<td>Thromboembolic Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>Coagulopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>07</td>
<td>Congestive Heart Failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08</td>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>09</td>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Upper GI (GERD, Reflux, Dyspepsia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Ulcers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Lower GI (IBS, Crohn’s Disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Chronic Liver Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Renal Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Pagets Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Hyperparathyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Hyperthyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Vision Impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Seizure Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Neuromuscular Dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Rheumatoid Arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Osteoarthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Vitamin D deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Other Inflammatory Disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Back Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix B: Side effect questionnaire (Study 1)

Please mark [x] whether you experienced each side effect below. For those you did experience, please indicate how severe each side effect is or has been, and how bothered you were by the side effect.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Did not have</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating/fluid retention</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Constipation</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Depression</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Dizziness</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Fatigue/tiredness</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Generalized aching</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Headache</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Heartburn</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Kidney problems</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Leg cramps</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Liver problems</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Menstrual bleeding</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Mood swings</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Nausea</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Pain swallowing</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Trouble thinking/remembering</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Vomiting</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Weight gain</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Weight loss</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
Appendix C: Screening questionnaire (Study 2)

Thank you for your interest in participating in my PhD research project titled “A placebo controlled trial to study the efficacy and safety of Modafinil”. The aim of the study is to test the efficacy and safety of the concentration enhancing drug Modafinil. Any medication you are currently taking and any health conditions you may have may therefore affect the results. Consequently we would like to ask you a few questions about you and any medication you might be taking before you take part.

This study is conducted by Monika Heller (monika.heller.12@ucl.ac.uk) as part of her PhD at the School of Pharmacy, UCL, supervised by Dr. Sarah Chapman (s.chapman@ucl.ac.uk). The study has been approved by the UCL research ethics committee, project ID Number: 4716/002. All data will be collected and stored in accordance with the Data Protection Act 1998.

DEMOGRAPHICS

Age (in years): _____________________

Gender:

☒ Male
☒ Female

What subject are you studying?

_______________________________________________

Year of study:

_______________________________________________

Are you currently taking any medication?

☒ Yes
☒ No
Are you taking any of the following medications?

<table>
<thead>
<tr>
<th>Medications</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole (for indigestion, acid reflux or ulcers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclosporin (to prevent organ transplant rejection, or for arthritis or psoriasis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines for epilepsy (e.g. carbamazepine, phenobarbutal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines for depression (e.g. citalopram, fluoxetine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines for anxiety (e.g. diazepam)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers or beta-blockers for high blood pressure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please list any other medications you are currently taking.
Do you have a history of the following conditions?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of fainting/seizures</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>History of depression</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>History of anxiety/panic attacks</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

Thank you for completing this screening questionnaire. Please leave an e-mail address to confirm your interest in taking part in the study. Monika Heller, the PhD student responsible for this study will contact you regarding study appointments. Please do not hesitate to e-mail her in case you have any questions relation to the study (monika.heller.12@ucl.ac.uk).

Your e-mail address:
Appendix D: Adapted BMQ-Specific (Study 2)
Appendix E: IAT stimuli (Study 2)

**Flowers**

No itch association

![Flower images](image1.jpg)

Itch association

![Flower images](image2.jpg)

**Insects**

Itch association

![Insect images](image3.jpg)

No itch association

![Insect images](image4.jpg)
Appendix F: Modafinil patient information leaflet (Study 2)

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Modafinil** 200 mg tablets

Modafinil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Ask the researcher if you need more information or advice.
- If you get any side effects, or if you notice any side effects not listed in this leaflet, please tell the researcher immediately.

1. What Modafinil is and what it is used for

The active ingredient in the tablets is modafinil. Modafinil can be taken by adults who suffer from narcolepsy to help them stay awake. Narcolepsy is a condition that causes excessive daytime sleepiness and a tendency to fall asleep suddenly (sleep attacks).

Modafinil is increasingly used “off-label”: 70% of Modafinil use in the US is for other uses than the FDA approved narcolepsy indication. One in five UK university students have purportedly taken Modafinil to prevent sleepiness and increase concentration.

“Off-label” or lifestyle uses also include age-related memory decline, attention deficit disorder, depression, fatigue caused by high pressure jobs, memory problems associated with Alzheimer’s disease and jet lag.
2. What you need to know before you take Modafinil

❌ Do not take Modafinil and inform the researcher immediately if you:
   ✓ Are allergic to Modafinil or any of the other ingredients (lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate).
   ✓ Have an irregular heartbeat.
   ✓ Have uncontrolled, moderate to severe high blood pressure.

❗ Warnings and precautions:
   Please inform the researcher if you:
   △ Have ever had depression, low mood, anxiety, psychosis (loss of contact with reality) or mania (over-excitement or feelings of extreme happiness) or bipolar disorder because Modafinil may make your condition worse.
   △ Have kidney or liver problems
   △ Are aged less than 18 years old.
   △ If you are pregnant (or think that you may be) or breast-feeding.

❗ Other medicines and Modafinil:
   Tell the researcher if you are taking, have recently taken or might take other medicines. It is especially important if you are taking any of the following medicines:
   △ Omeprazole (for indigestion, acid reflux or ulcers)
   △ Ciclosporin (used to prevent organ transplant rejection, or for arthritis or psoriasis)
   △ Medicines for epilepsy (e.g. carbamazepine, phenobarbital)
   △ Medicines for depression (e.g. citalopram, fluoxetine)
   △ Medicines for anxiety (e.g. diazepam)
   △ Calcium channel blockers or beta-blockers for high blood pressure.
3. Possible side effects

Like all medicines, Modafinil can cause side effects, although not everybody gets them.

Tell the researcher straight away if:
- You have sudden difficulty breathing or wheeziness or if your face, mouth or throat begins to swell.
- You notice a skin rash or itching (especially if it affects your whole body). Severe rashes may cause blistering or peeling of the skin and ulcers in your mouth or eyes.
- You feel any changes to your mental health or wellbeing. The signs may include:
  - Mood swings
  - Confusion
  - Anxiety
  - Nervousness

Very common side effects (affecting more than 1 in 10 people):
- Headache
- Itch
- Dizziness
- Dry mouth

Common side effects (affecting fewer than 1 in 10 people):
- Awareness of your heart beat
- Chest pain
- Numbness or tingling of the hands or feet
- Blurred vision

Uncommon side effects (affecting fewer than 1 in 100 people):
- Vomiting
- Abnormal urine
### Appendix G: Systematic assessment of symptoms (Study 2)

Have you experienced any of the following bodily sensations during the study period?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>dizziness</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>nervousness</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>numbness or tingling of hands/feet</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>vomiting</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>rash</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>headache</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>sweating</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>difficulty breathing</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>blurred vision</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>drowsiness</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>vertigo</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>anxiety</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>confusion</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>upset stomach</td>
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<td>○</td>
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<tr>
<td>abnormal urine</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>itch</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>weakness</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>racing heart</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>slowing heart</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>dry mouth</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>swollen hands or feet</td>
<td>○</td>
<td>○</td>
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<tr>
<td>changes in mood</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>sleepiness or extreme tiredness</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>nausea</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>chest pain</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>other [please specify]</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

**Note:**

- ○ indicates yes
- □ indicates no
Appendix H: Asthma background information (Studies 3 and 4)

What is asthma?

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

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

- difficulty breathing
- wheezing and coughing
- a tight chest

Asthma symptoms flare up from time to time and there may be no apparent reason why. However, some people find that symptoms are made worse by triggers such as exercise, fumes, and pollen. These things cause your body to produce chemical substances called leukotrienes, which cause inflammation.

1 in 12 people in the United States suffer from asthma.

Treating asthma

While there is no cure for asthma, there are a number of treatments that can help control the condition. Treatment is based on two important goals:

- relieving symptoms
- preventing future symptoms and attacks from developing

Treatment and prevention involves a combination of medicines, lifestyle advice and identifying and then avoiding potential asthma triggers.
Appendix I: Molair patient information leaflets (Study 3)

Molair®

Molair belongs to a class of drugs called leukotriene modifiers (or leukotriene receptor antagonists). These medicines are used for the long-term control and prevention of asthma symptoms. Leukotrienes are substances made by your body that act as a trigger for an asthma attack. Blocking the action of leukotrienes helps prevent these attacks from occurring. Molair is taken in pill form.

Efficacy and Side effects
A recent large clinical trial (with 5855 asthma patients) has shown the effectiveness of Molair in adults. Following a 4-6 week treatment with Molair 86.6%/53.2% percent of patients reported a strong/small improvement in day-time asthma symptoms and 88.7%/56.7% a strong/small improvement in night-time asthma symptoms.

Molair can be highly/moderately effective in preventing asthma symptoms, but like all medicines it may cause side effects. Please speak to your doctor if you experience any side effects while taking Molair:

- Rash
- Dizziness
- Itching
- Muscle or joint pain
- Abdominal pain
- Yellowing of the skin
- Fatigue
- Flu like symptoms
Molair®

Molair belongs to a class of drugs called leukotriene modifiers (or leukotriene receptor antagonists). These medicines are used for the long-term control and prevention of asthma symptoms. Leukotrienes are substances made by your body that act as a trigger for an asthma attack. Blocking the action of leukotrienes helps prevent these attacks from occurring. Molair is taken in pill form.

**Efficacy and Side effects**
Clinical studies have shown that Molair can be effective in preventing asthma symptoms, but like all medicines it may cause side effects.

Please speak to your doctor if you experience any side effects while taking Molair:

Molair *only rarely (in less than 1 in 100 people) / frequently (in more than 45 out of 100 people)* causes the following side effects:

- Rash
- Dizziness
- Itching
- Muscle or joint pain
- Abdominal pain
- Yellowing of the skin
- Fatigue
- Flu like symptoms
Appendix J: Efficacy and Side Effect Visual Analogue Scales (Studies 3 and 4)

**Efficacy Visual Analogue Scale**

1. How effective do you think MOLAIR is in general for the prevention of asthma symptoms? (0=not effective at all to 100=extremely effective)
2. To what extent do you think MOLAIR prevents the symptoms of asthma in general? (0=no effect on symptoms to 100=completely prevents symptoms)
3. Imagine you personally had asthma and took MOLAIR for the prevention of asthma symptoms. How effective do you think MOLAIR would be in preventing your asthma symptoms? (0=not effective at all to 100=extremely effective)

**Side effect Visual Analogue Scale**

1. How frequently do you think people in general develop side effects when taking MOLAIR? (0=never to 100=always)
2. Imagine you personally had asthma and took MOLAIR for the prevention of asthma symptoms. What do you think is the likelihood that you would suffer from side effects? (0=not likely at all to 100=extremely likely)
3. Imagine you personally had asthma and took MOLAIR for the prevention of asthma symptoms. How bothersome do you think the side effects would be? (0=not bothersome at all to 100=extremely bothersome)
4. Imagine you personally had asthma and took MOLAIR for the prevention of asthma symptoms. How much of an issue do you think the side effects would be? (0=no issue at all to 100=extremely important issue).
Appendix K: Molair patient information leaflets (Study 4)

Patient Information Leaflet

Molair®

Molair belongs to a class of drugs called leukotriene modifiers (or leukotriene receptor antagonists). These medicines are used for the long-term control and prevention of asthma symptoms. Leukotrienes are substances made by your body that act as a trigger for an asthma attack. Blocking the action of leukotrienes helps prevent these attacks from occurring. Molair is taken in pill form.

Efficacy
A recent large clinical trial (with 5855 asthma patients) has shown the effectiveness of Molair in adults. Following a 4-6 week treatment with Molair 86.6% percent of patients reported a strong improvement in day-time asthma symptoms and 88.7% a strong improvement in night-time asthma symptoms.

Side Effects
Molair can be effective in preventing asthma symptoms, but like all medicines it may cause side effects. Please speak to your doctor if you experience any side effects while taking Molair:

- Fatigue
- Abdominal pain
- Itching
- Rash
- Muscle pain
- Dizziness
- Yellowing of the skin
- Joint pain
Appendix L: Adapted BMQ-Specific (Studies 3 and 4)

Imagine you personally had asthma and had been prescribed MOLAIR for the prevention of asthma symptoms.

Below are statements other people have made about MOLAIR. Please show how much you think you would agree or disagree with them by ticking the appropriate box.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Uncertain</th>
<th>Agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My health, at present, depends on MOLAIR.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Having to take MOLAIR worries me.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>My life would be impossible without MOLAIR.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>I sometimes worry about long-term effects of MOLAIR.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Without MOLAIR I would be very ill.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>MOLAIR is a mystery to me.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>My health in the future will depend on MOLAIR.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>MOLAIR disrupts my life.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>I sometimes worry about becoming dependent on MOLAIR.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>MOLAIR protects me from becoming worse.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>MOLAIR gives me unpleasant side effects.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
Appendix M: Xymex patient information leaflet (Study 5)

PACKAGE LEAFLET: INFORMATION FOR THE USER

XYMEX® 25mg
Promethazine hydrochloride

This medicine is available without prescription. However, you still need to take XYMEX tablets carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after 7 days.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. What XYMEX tablets are and what they are used for

XYMEX tablets contain a medicine called promethazine hydrochloride. This belongs to a group of medicines called phenothiazines. It works by blocking a natural substance (histamine) that your body makes during an allergic reaction. It also works directly on the brain to help you feel more relaxed.

XYMEX tablets can used in the following situations:

- To treat allergic conditions such as hay fever or rashes (like nettle rash or hives).
- To treat adults with difficulty sleeping (insomnia).
- To treat or stop you feeling sick (nausea) or being sick (vomiting) such as travel sickness.
2. Before you take XYMEX tablets

Do not take this medicine and tell your doctor if:
- The person taking this medicine is under 2 years of age.
- You are allergic to promethazine hydrochloride.
- You are taking a medicine for depression called a monoamine oxidase inhibitor (MAOI).

Check with your doctor or pharmacist before taking XYMEX if:
- You have asthma or bronchitis.
- You have epilepsy.
- You have liver or kidney problems.
- You have increased pressure in the eye (narrow angle glaucoma).
- You have any serious heart problems.

Talk to your doctor before taking this medicine if you are pregnant, might become pregnant, or think you may be pregnant. XYMEX tablets should not be taken 2 weeks before birth.

3. How to take XYMEX tablets

- Take this medicine by mouth.
- Do not take for longer than 7 days.

For allergies (such as hay fever, rashes and hives) the usual dose is:
- CHILDREN (5-10): A single tablet (25 mg) given at night. DO NOT give more than 25 mg a day.
- CHILDREN >10 and ADULTS: Start with a single tablet (25 mg) taken at night. This may be increased to a maximum of one tablet (25 mg) twice a day if necessary.
4. Possible side effects

Like all medicines, XYMEX tablets can cause side effects, although not everybody gets them.

**Stop taking XYMEX tablets and see a doctor or go to hospital straight away if you notice any of the following side effects:**
- An allergic reaction. The signs may include: a rash, swallowing or breathing problems.
- Liver problems that may cause the eyes or the skin to go yellow (jaundice).
- Muscle stiffness or shaking.
- Being unable to control some muscles in your head or face.
- You notice unusual movements of the tongue, facial muscle spasms, rolling eyes and trembling.
- Very fast, uneven or forceful heartbeat (palpitations).
- Tiredness which lasts for a long time.

**Tell your doctor or pharmacist if any of the following side effects get serious or last longer than a few days.**
- Dry mouth, blurred vision or you cannot pass water (urine).
- Feeling drowsy or sleepy, tiredness, disorientation, feeling restless.
- Feeling dizzy, lightheaded, faint (hypotension).
- Feeling confused, especially in elderly people.
Appendix N: Example arguments ELM interventions (Study 5)

What are the benefits (pros) and risks (cons) of pharmaceutical medicine?

![PROS CONS](image)

Medicines reduce disability and improve quality of life:

"Medicines reduce disability and improve the quality of life of millions of people. Disabilities are physical or mental conditions that prevent people from completing their normal daily activities (e.g. getting dressed, shopping for groceries, etc.). In the US, the share of the elderly population (>65 years) reporting difficulties with activities of daily living fell from 25% in 1984 to 20% in 1999. Better treatment plays an important role in this reduction. For example the probability of being disabled as a result of heart disease fell about 4% from 1989-1999. This explains between 14-22% of the total reduction in disability during this period. Ill health and disability are of course not limited to the elderly. In 2005 more than 133 million Americans, or 45% of the population, had at least one chronic condition and 26% had multiple chronic conditions. Medicines are crucial in minimizing the poor quality of life and disability associated with these chronic conditions. It is estimated that medicines add about 5 years of improved physical and mental functioning or reduced pain and suffering per individual."

What are the benefits (pros) and risks (cons) of pharmaceutical medicine?

![PROS CONS](image)

Medicines are unspecific and have general effects on the body:

"Many medicines have effects on parts of the body other than the parts involved in the illness which they treat. For example, some antidepressants can have effects on the digestive system. It would be comforting to think of medications as magic bullets that somehow know just where in the body to go, exert their healing action and then move along. But, often the action of a drug can have negative as well as positive effects for a patient. As medicines evolve we have gotten closer to the "magic bullet" ideal, but not nearly as close as we would like."