

Beliefs about medication predict the misattribution of a common symptom as a medication side effect – evidence from an analogue online study

Running head: Misattribution of a common symptom as a medication side effect

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Abstract

Objective

Some perceived medication side effects may be 'normal' symptoms that patients misattribute to the medication. Using an analogue approach, we tested if medication beliefs predict whether participants misattribute a headache as a side effect and subsequently intend to stop medication.

Methods

We recruited 690 participants, 223 reporting a past asthma diagnosis. They received information about asthma and Molair, a fictitious asthma treatment modelled on a licensed treatment (montelukast). We varied the description of efficacy and side effects (which did not include headache). Pre-exposure to this information, participants completed the Beliefs about Medicine Questionnaire (BMQ)-General and the Perceived Sensitivity to Medicines Scale (PSM), post-exposure they completed the BMQ-Specific. Participants were asked to imagine they experienced a headache while taking Molair. Finally, they rated whether the headache was a side effect (misattribution) and if they would stop taking Molair (behavioural intention).

Results

Nearly a quarter (170) of participants misattributed the headache to Molair and 69 (10%) subsequently intended to stop Molair. Both outcomes were predicted by general and specific medication beliefs. Odds of misattribution (m) and behavioural intention (i) increased with higher General Harm (OR_m=1.90, OR_i=2.72), General Overuse (OR_m=1.74, OR_i=1.56) and Molair Concern beliefs (OR_m=1.52, OR_i=1.78, all $p < .01$), but decreased with General Benefit (OR_m=0.72, OR_i=0.53) and Molair Necessity beliefs (OR_m=0.72, OR_i=0.70, all $p < .05$).

Conclusion

Symptom misattribution and subsequent intentions to stop Molair were predicted by pre-exposure beliefs about medicines in general and post-exposure beliefs about Molair. Patients with negative medication beliefs may be prone to misattribute symptoms and subsequently stop medication.

Key words: adherence, asthma, attribution, beliefs about medicines, nocebo, side effects

Highlights:

- We tested if medication beliefs predict misattribution of symptoms as side effects
- Participants imagined they took a fictitious asthma medication and had a headache.
- General and specific medication beliefs predicted misattribution of the headache.
- Misattribution and negative beliefs increased intention to stop medication.

Introduction

The prescription of a medicine is one of the most common interventions in affluent healthcare systems. Appropriate medication use is crucial to the management of most long-term conditions that account for the majority of health spending (1). But, the capacity of medication to improve health is compromised by adverse effects and nonadherence (2, 3). People who experience (and sometimes merely anticipate) side effects are prone to nonadherence (4, 5), and consequently less likely to experience the full benefit from their treatment, with implications for morbidity, mortality and healthcare utilization. For patients who take their medication, side effects add to the burden of disease and treatment (6), increase anxiety and reduce quality of life (7, 8). Problems linked to medication side effects in ambulatory (e.g. treatment changes, additional doctor visits) and non-ambulatory settings (e.g. longer hospitalization) were estimated at over \$170 billion per year in the US alone (9).

Understanding determinants of side effects therefore has implications for patients and healthcare systems. Side effects are often caused by specific pharmacological effects of medication. For example, aspirin inhibits prostaglandin pathways in the stomach, which can lead to gastric erosion (10). Psychological factors such as expectations and conditioning (11) also contribute to side effects. Around 20-25% of chemotherapy patients experience nausea or vomiting *before* drug administration (12, 13), indicating the importance of non-pharmacological factors in side effect experiences.

The misattribution of symptoms arising due to disease, everyday activities or normal bodily variations, as side effects may be another psychological process contributing to side effect reports (14, 15). Symptoms like dizziness, headache and fatigue are frequently reported as “side effects” by patients receiving placebo in randomized controlled trials (16-19) and are common in healthy individuals not taking medication (20-22).

In this paper we test whether cognitive representations of specific medications and pharmaceuticals in general (23-26) influence the attribution of symptoms as side effects. Specific medication beliefs are the salient beliefs influencing engagement with a specific treatment for a given condition. They are operationalised in the Necessity Concerns Framework (27, 28) which posits that evaluations of prescribed medicines are influenced by judgment of personal necessity for treatment relative to concerns about potential harm (29). These

evaluations are influenced by general 'social representations' of pharmaceuticals as a class of treatment (e.g. whether pharmaceuticals are fundamentally harmful, addictive chemicals that are over-prescribed by doctors (23, 26, 30)), representations of the health threat (e.g. illness representations) and somatic experiences and attributions (e.g. whether a symptom is attributed to illness or medication) (25, 31, 32). Symptom experiences and attributions are therefore a key determinant of how we think about and act upon illnesses (33-35). Medication beliefs have been linked to side effect reports in prospective clinical samples with rheumatoid arthritis (36), depression (37), and HIV/AIDS (38). A tendency for individuals with negative beliefs about medicine to attribute everyday 'normal' symptoms to their medication could contribute to these associations.

In this study, we asked participants to imagine taking a fictitious asthma medication and then experiencing a headache (not listed as a side effect of the medication). We probed whether participants attributed the headache as a side effect and subsequently intended to stop the medication. Although this was an analogue study, we wanted to make the scenario presented as concrete and believable to participants as possible. We therefore chose a common disease, asthma (39), so that we were able to recruit participants online who either had asthma or were familiar with it. Likewise, we chose headache, a common 'everyday' symptom and side effect **(22, 40, 41)** to probe symptom attribution. In addition, side effects and side effect-related discontinuation of asthma medication, and headaches to placebo have all been reported in asthma (42, 43). Our primary hypothesis was that participants with negative medication beliefs would be more likely to: (1) Misattribute the headache symptom as a side effect and (2) subsequently intend to stop the medication.

We systematically varied information about the fictitious medication, presenting it as highly or moderately effective and having either frequent or rare side effects. We expected the variation of the patient information to influence people's specific beliefs about the medication (e.g. increased concerns for participants randomized to high side effect frequency information). We also wanted to check whether any effect of beliefs on misattribution and intention were robust across this information variation. We 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. Because we were measuring beliefs about a fictitious medication, we also checked that the associations between general and specific beliefs were consistent with theoretical predictions (24) and previously reported associations (30).

Method

Data was collected in three consecutive waves. Within each wave, participants were randomised to different descriptions of the efficacy and safety of the fictitious medication. In all waves participants completed validated measures of medication beliefs and the symptom attribution vignette. Affect was assessed in wave three.

Participants and Recruitment

We included individuals over 18, with and without self-reported past asthma diagnosis. Only one response was allowed per participant (across the three waves). Participants were recruited on online job boards (e.g. Amazon MTurk, Crowd Guru, DailySurveyPanel) where subscribers complete surveys for small monetary rewards (around \$0.30 in this study), and an online research website (Psychological Research on the Net). This sampling approach has demonstrated reliability in studies of decision-making, personality and health (44-46).

Materials

Asthma and Molair information

Participants read information about asthma (see Appendix A) structured according to Leventhal's Common Sense Model of illness representations (47, 48). It described asthma causes (airway inflammation and sensitization), triggers (e.g. exercise, pollen), likely consequences, and asthma management (e.g. medicines and lifestyle changes) and asthma symptoms (e.g. difficulty breathing, wheezing) and their episodic nature.

Participants were randomized to one of four written patient information leaflets (PILs) of the fictitious asthma drug Molair (see Appendix B), modelled on the existing asthma medication, montelukast (49):

1) The "High Efficacy PIL" stated that Molair is highly effective '86.6% of patients reported 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 "*in less than 1 in 100 people*".

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

All four PILs contained the same list of 8 side effects, presented in randomized order. Headache was not listed as one of Molair’s side effects.

The information was in line with published montelukast efficacy data (50-52) and reported side effect rates to montelukast relative to placebo (53) (low frequency) and placebo in randomized controlled trials (54-56) (high frequency).

Measures

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.*” They were then asked 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 (stop taking Molair, speak to a doctor or pharmacist, take over the counter painkiller, rest, other, none of the above). Participants could select as many options as they wished and could specify additional actions. Behavioural intention was operationalised as selecting “stop taking Molair”.

Beliefs about Medicines Questionnaire (BMQ) (26)

Participants’ beliefs about Molair were assessed with the BMQ-Specific and general beliefs about pharmaceutical medicines as a class of treatment were assessed using 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 Molair”) and *concerns* about potential adverse consequences of taking it (6 items e.g. “Having to take Molair worries me”). The scales are validated (23, 26).

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.”). The General Benefit scale assesses beliefs about the degree to which medicines are fundamentally beneficial (e.g. “Medicines help many people live better lives.”).

All BMQ items were rated on 5-point Likert-type scales (1=strongly disagree to 5=strongly agree). Scale scores were computed by summing item scores within each scale and dividing it

by the number of scale items. Higher scores indicate stronger endorsement of scale constructs (range 1-5). The internal consistency of the BMQ-Specific (Cronbach's α : Molair Necessity=.88, Molair Concerns=.84) and BMQ-General was good (Cronbach's α : General Harm=.75, General Overuse=.77 and General Benefit=.91).

Perceived Sensitivity to Medicines Scale (PSM)

The PSM is a validated scale (57) which assesses beliefs about self in relation to medicines; specifically about personal sensitivity to medicines. The scale has 5 items (e.g. "My body overreacts to medicines."), which are rated on 5 point Likert-type scales (1=strongly disagree to 5=strongly agree). The PSM score was computed by dividing the total scale score by the number of scale items. Internal reliability was excellent (Cronbach's α =.91).

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

Visual analogue scales (VAS) were included to check whether PIL variations changed perceptions of Molair. Four VAS assessed side effect perceptions (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 measured 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 VAS sets (Cronbach's α s of .88 and .90 respectively)

Positive and Negative Affect Schedule (PANAS)

State Negative Affect was assessed with 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 (State NA_{PANAS}) scores were computed by averaging scores for all negative adjectives. Internal consistency was high (Cronbach's α =.95).

State and Trait Anxiety Inventory (STAI)

The STAI Form X (59) was used to measure State (State NA_{STAI} : 20-State Negative Affect items e.g. "I am tense.") and Trait Negative Affect (Trait NA_{STAI} : 20-items e.g. "I worry too much over something that doesn't matter."). Items were rated on 4-point Likert scales (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 α =.91).

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').

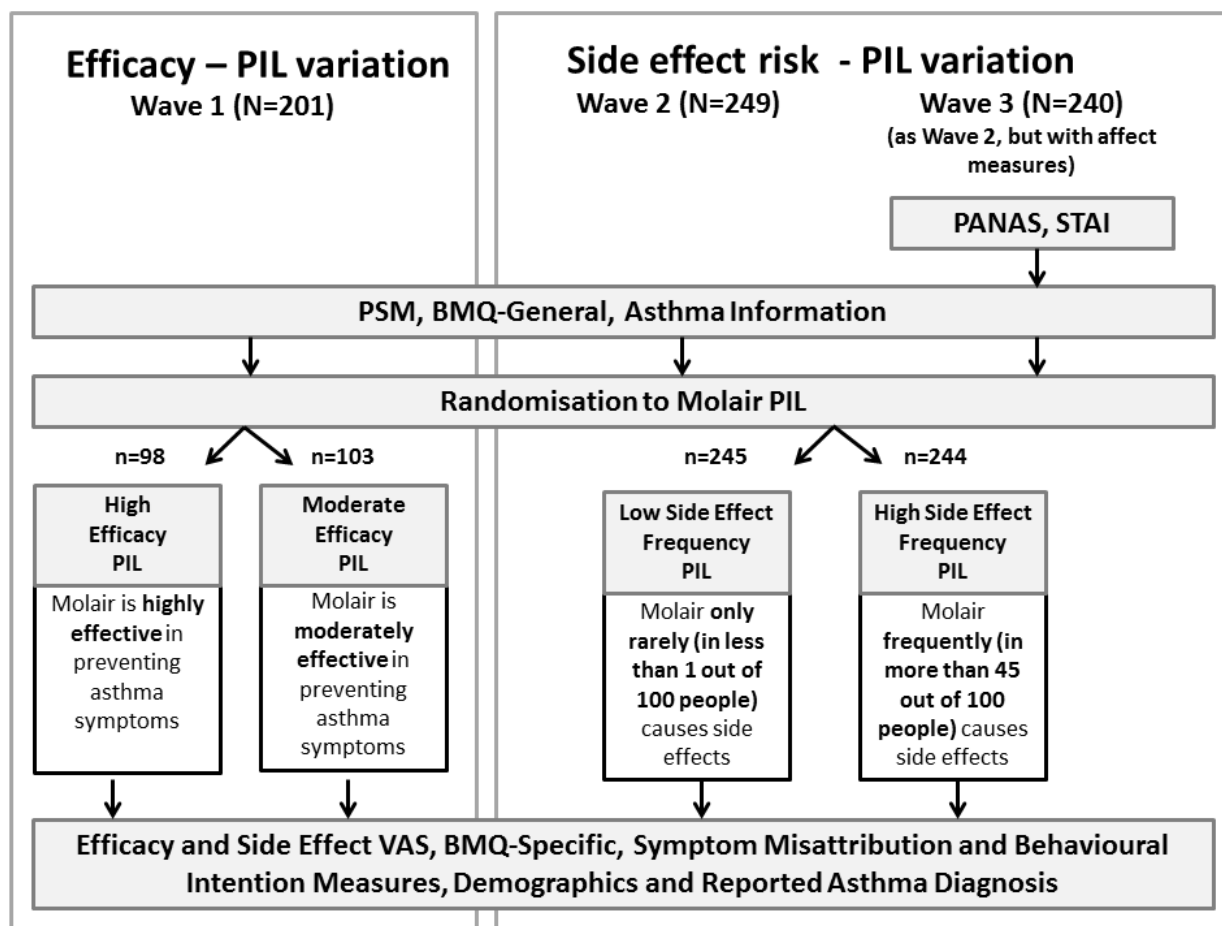
Procedures

The study was exempt from REC approval as confirmed by the UCL Research Ethics Committee.

Data was collected using Qualtrics online software (60). After giving informed consent, participants completed the PANAS and STAI (wave 3 only, see Figure 1), PSM and BMQ General. Next they received information about asthma and were randomised 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, participants completed the Efficacy and Side Effect VAS and BMQ-Specific, and brief memory tasks (reported elsewhere). 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 approximately 14 minutes to complete the study.

Figure 1: Overview of Procedures



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

Sample size and statistical analysis

The sample size needed to detect an association between medication beliefs and symptom misattribution was calculated using GPower v3.1. 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 (61) was used to ascertain that 251 participants were needed to detect this univariable association with 80% power and a two-tailed alpha error probability of .05.

Two checks were conducted to assess the validity of the model. Independent t-tests assessed whether PIL variations changed Side Effect /Efficacy VAS ratings and specific medication beliefs. Associations between general and specific medication beliefs and perceived sensitivity to medicines were examined with Pearson correlations.

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. We also used moderation analysis 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 the outcome is more likely, ORs below 1 indicate the outcome is less likely. An OR of 1.5 constitutes a small, 3.5 a medium, and 9 a large effect size (62). Classification tables and the Hosmer Lemeshow Test (HLT) assessed adequacy of model fit.

Results

Survey completion rates and data exclusions

We obtained 782 responses. 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 noncompleters ($p>.05$). Responses from 690 participants (wave 1=201, wave 2=249, wave 3=240) were retained.

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 I).

Main outcomes: 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. We did find 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 II).

Between group comparisons of medication beliefs and Efficacy/Side Effect VAS

Molair Necessity was higher for participants who were randomized to the “High Efficacy” (M=3.06, SD=0.78) compared to the “Moderate Efficacy” PIL (M=2.78, SD=0.73, $t(199)=2.60$, $p<.01$). Molair Concerns were higher for participants who saw the “High Side Effect Frequency”

($M=3.10$, $SD=0.83$) compared to the “Low Side Effect Frequency” PIL ($M=2.90$, $SD=0.83$, $t(487)=2.59$, $p<.01$). 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 $t_s>6.2$, $p_s<.001$). Independent t-tests demonstrated no significant differences between participants with and without reported asthma diagnosis in general and specific medication beliefs ($p_s>.05$). Participants with a reported asthma diagnosis perceived themselves to be more sensitive to the effects of medicines ($M=2.72$, $SD=1.05$) than those without ($M=2.47$, $SD=0.97$; $t(685)= 3.05$, $p<.01$).

Inter-correlations medication belief scales

Concerns about Molair were significantly positively correlated with individuals’ perceptions of medicines as generally harmful ($r=.371$) and over-prescribed by doctors ($r=.382$). Participants with stronger benefit beliefs showed reduced Molair Concerns ($r=-.101$) and higher Molair Necessity beliefs ($r=.260$). Perceptions of higher personal sensitivity to medicines were significantly positively correlated with beliefs that medicines are fundamentally harmful ($r=.247$) and overprescribed ($r=.198$) as well as Molair Concerns ($r=.259$, all $p_s<.01$, two-tailed).

Table 1: Sample characteristics

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

Note. ^a 1 missing value; ^b 2 missing values; ^c 4 missing values; ^d self-reported past asthma diagnosis; SD=standard deviation; p-values refer to Chi-Square tests between waves (with the exception of age: Univariate ANOVA)

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

Univariable logistic regression was used to explore whether misattribution and behavioural intention were associated with general and specific medication beliefs. People who had more negative general and specific medication beliefs 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 with symptom misattribution and behavioural intentions (see Table II).

We then constructed two hierarchical logistic regression models to test whether negative general and specific medication beliefs predicted symptom misattribution and behavioural intention when entered jointly into the model (see Table III, Figure 2). We included demographics (age, gender), asthma diagnosis and PIL variations 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 HLTs.

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 ($X^2(3)=3.68$, $p=.30$), while step 2 (general and specific medication beliefs and PSM) improved the model considerably ($X^2(6)=13.51$, $p<.05$; full model $X^2(9)=17.20$, $p<.05$). 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 behavioural intention, the affect block ($X^2(3)=2.01$, $p=.57$) was not significant, while the medication belief block significantly improved prediction ($X^2(6)=18.92$, $p<.01$). Only General Harm (OR=3.79,

95%CI [1.62,8.90]) was a significant predictor. The full model ($X^2(9)=20.92$, $p<.05$) had adequate fit (HLT $p>.05$) and accounted for 90.0% correct classification of cases.

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 ($ps>.05$), 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 ($ps>.05$), indicating medication beliefs have similar effects for individuals with and without reported asthma.

Table II: Univariate logistic regression models predicting symptom misattribution and behavioural intention to stop treatment

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

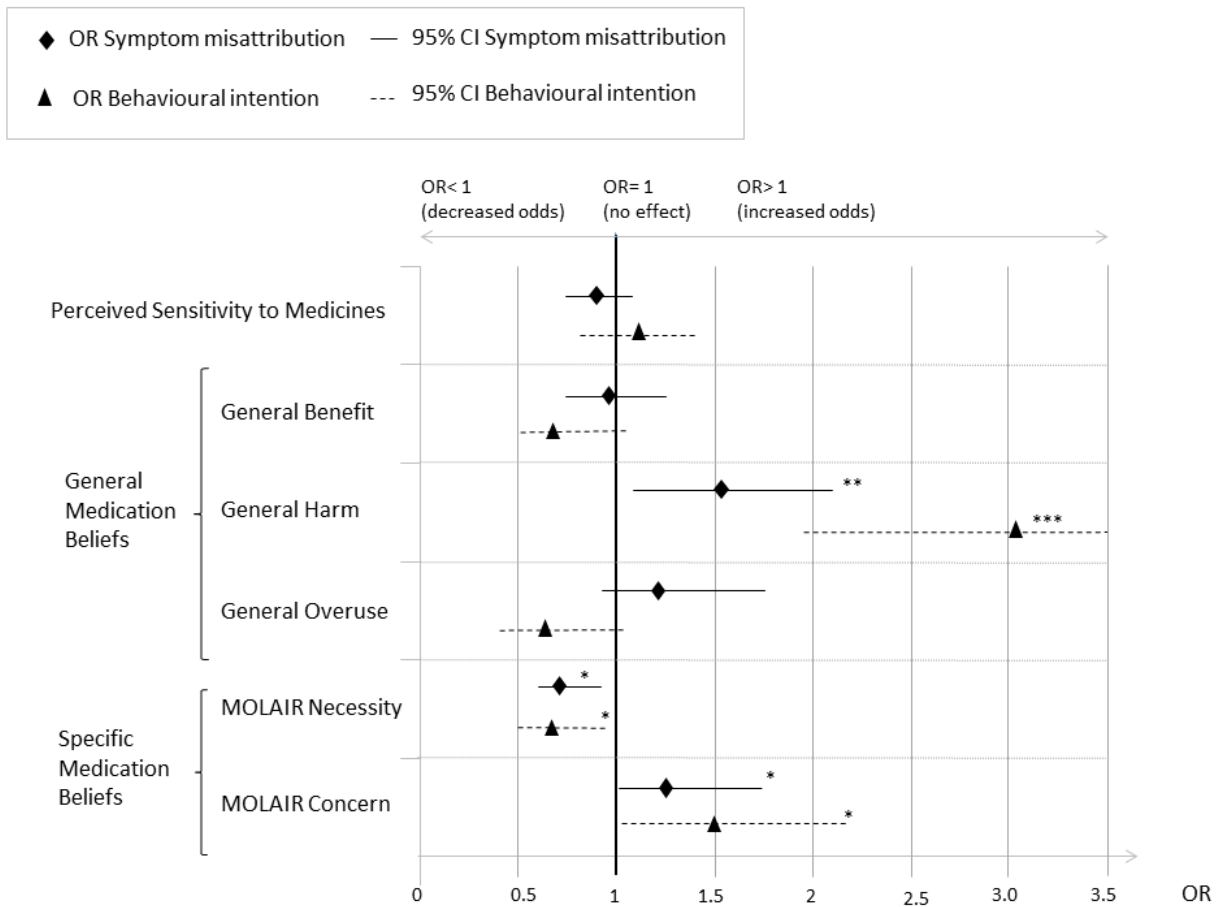
Note. OR=Odds ratio; CI=confidence interval; PSM=Perceived Sensitivity to Medicines; NA= negative affect; PANAS= Positive and Negative Affect Schedule, STAI = State Trait Anxiety Inventory, ^a N=690, ^b N=240 (data available for wave 3 only); ^creference category=male; * $p < .05$, ** $p < .01$, *** $p < .001$

Table IV: Multivariate hierarchical logistic regression models predicting symptom misattribution and behavioural intention to stop medication (N=690)

	Symptom misattribution		Behavioural intention	
	OR	95% CI	OR	95% CI
Step 1: PIL variation, demographics and asthma diagnosis				
X^2 Block:	$X^2(4)=8.20, p=.09$		$X^2(4)=14.76, p<.01$	
PIL variation	1.04	[0.94, 1.16]	1.04	[0.90, 1.21]
Gender ^b	0.84	[0.59, 1.22]	0.70	[0.41, 1.17]
Age	0.98*	[0.97, 1.00]	0.96**	[0.94, 0.99]
Reported asthma diagnosis ^c	0.94	[0.65, 1.36]	0.90	[0.53, 1.53]
Step 2: General Medication Beliefs and PSM				
X^2 Block:	$X^2(4)=40.30, p<.001$		$X^2(4)=50.22, p<.001$	
PIL variation	1.01	[0.91, 1.13]	1.00	[0.85, 1.17]
Gender ^b	0.86	[0.59, 1.27]	0.81	[0.47, 1.41]
Age	0.98*	[0.97, 1.00]	0.96**	[0.94, 0.99]
Reported asthma diagnosis ^c	0.99	[0.67, 1.46]	1.09	[0.62, 1.92]
General Harm	1.57**	[1.16, 2.12]	3.09***	[1.98, 4.80]
General Benefit	0.88	[0.67, 1.14]	0.61**	[0.43, 0.88]
General Overuse	1.40*	[1.05, 1.89]	0.79	[0.51, 1.22]
PSM	0.90	[0.74, 1.09]	1.08	[0.82, 1.43]
Step 3: Specific Medication Beliefs				
X^2 Block:	$X^2(2)=8.81, p<.05$		$X^2(2)=6.92, p<.05$	
PIL variation	1.02	[0.91, 1.14]	1.01	[0.86, 1.19]
Gender ^b	0.86	[0.58, 1.26]	0.80	[0.46, 1.40]
Age	0.98*	[0.97, 1.00]	0.96**	[0.94, 0.99]
Reported asthma diagnosis ^c	1.00	[0.67, 1.48]	1.12	[0.63, 1.98]
General Harm	1.55**	[1.14, 2.11]	3.07***	[1.95, 4.82]
General Benefit	0.98	[0.74, 1.30]	0.71	[0.49, 1.04]
General Overuse	1.28	[0.95, 1.73]	0.66	[0.42, 1.05]
PSM	0.90	[0.74, 1.09]	1.08	[0.81, 1.43]
Molair Necessity	0.74*	[0.58, 0.94]	0.69*	[0.49, 0.97]
Molair Concern	1.30*	[1.00, 1.68]	1.50*	[1.02, 2.20]
X^2 Total model:	$X^2(10)=55.88, p<.001$		$X^2(10)=71.90, p<.001$	
Hosmer Lemeshow Test:	$X^2(8)=10.22, p=.25$		$X^2(8)=6.44, p=.60$	
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; * $p<.05$, ** $p<.01$, *** $p<.001$

Figure 2: Hierarchical logistic regression models¹ predicting symptom misattribution and behavioural intention to stop medication (N=690)



Note. ¹ adjusted for PIL variation, gender, age and self-reported past asthma diagnosis;
OR=Odds Ratio, CI=95% Confidence Interval; * $p < .05$, ** $p < .01$, *** $p < .001$;

Discussion

Using an analogue approach, we have demonstrated that misattribution of symptoms as side effects may be common (about a quarter of participants misattributed headache, not listed in the PIL, as a medication side effect) and that general and specific medication beliefs predicted symptom misattribution. Participants were more likely to misattribute headache as a side effect and intend to stop treatment if they initially believed pharmaceutical medication to be generally harmful, over-prescribed by doctors, less beneficial, and if they had stronger concerns and more doubts about need for Molair. Perceived sensitivity to medicines (PSM) was unrelated to misattribution and behavioural intention. However, correlations between PSM and both general and specific medication beliefs were consistent with our theoretical model (63). As expected from an analogue approach with a hypothetical medication, correlations between the medication belief scales were small to moderate in scale (64), yet statistically significant and in the predicted direction. 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 and was similar for participants with and without self-reported past asthma diagnosis. We further demonstrated that medication beliefs predicted symptom misattribution when controlling for negative affect as a potential confounder.

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 (29). Previous studies also show that patients with stronger concerns about their medication (36, 37, 61) and more negative beliefs about medicines in general (65) report more side effects. 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 symptoms and sensations from normal bodily function (14, 66). 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. The size of the associations between medication beliefs and symptom misattribution/behavioural intentions in this study

were small to moderate (64), 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%).

Symptom misattribution is one of several (not mutually exclusive) processes that might explain the association between negative medication beliefs and side effect reporting in clinical groups. Patients with negative beliefs about medication may monitor their body more intensively during pharmacological treatment, leading to increased side effect reporting. Several experimental studies have shown that merely attending to bodily sensations may increase the perceived intensity (67) and frequency (68) of symptoms. Medication beliefs may also influence other known placebo mechanisms (69): patients with negative medication beliefs may form negative treatment expectations (70) and be predisposed to develop conditioned placebo responses. Manipulations that are likely to increase concerns about other substances, e.g. warnings about chemical pollution, have been found to increase conditioned learning of somatic symptoms (71). Patients with high concerns may be more likely to learn the association between medication cues and side effect responses,

Medication beliefs are part of a complex of psychological factors that may affect side effect reporting. Individuals with high negative affect report more symptoms (72-74) and side effects (75, 76). Concerns about medication have also been associated with negative affect (77). Negative affect may confound the relationship between medication beliefs and side effect attributions. This was not confirmed by our analysis, where the relationship between negative medication beliefs and concerns and side-effect misattribution was independent of negative affect. Other psychological factors such as Type A personality (78), somatization, depression (79), somatosensory amplification (75), pessimism (17) and alexithymia (80) (inability to identify and describe emotions) have been linked to side effect reporting to both active medication and placebo and could plausibly be associated with misattribution processes and concerns. These factors merit investigation in future studies.

There are several limitations of this analogue study using online recruitment. Our findings may not generalize to clinical settings, where patients have a medically confirmed diagnosis, comorbid conditions, take active medication and experience illness symptoms (81)). Due to the

nature of the online sampling procedure (82) relatively few participants in the older age segment (e.g.>65) and thus less likely to have been pre-exposed to medical conditions and medication use. Participants also may not have fully understood the information they received about the hypothetical drug. Research on health literacy suggests that patients' understanding of health information is also far from perfect in general practice (83). It will however be interesting to explore 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. Our confidence in the external validity of the analogue approach is strengthened by findings from research in patients with medically unexplained symptoms using a similar approach to study symptom attribution (84). In the extensively used Symptom Interpretation Questionnaire (85), 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 (85).

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. Medication beliefs are modifiable through cognitive-behavioural interventions (86). Potentially interventions to modify beliefs about medicines could therefore reduce non-specific side effects and related nonadherence.

Competing Interest Statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare that (1) RH has undertaken speaker engagements with honoraria with the following companies: Abbvie, Amgen, Biogen Idec, Gilead Sciences, GlaxoSmithKline, Janssen, Pfizer, Roche and Shire Pharmaceuticals. RH is a founder and share-holder of a UCL Business spin out company providing consultancy on medication-related behaviours to healthcare policy makers, providers and industry. (2) SC has undertaken speaker engagements with honoraria for Novartis and received consultancy fees from the UCL-business spin out company mentioned above (3) MH has no competing interests to report.

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Appendix A: Asthma background information

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.

High Efficacy/ Moderate Efficacy
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 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

Low Side Effect Frequency / High Side Effect Frequency
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 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

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