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What is the benefit of adding placebo side-effect information to positively framed patient leaflets? An online trial.

Abstract

Background: Positively framing side-effect risk in patient information leaflets (PILs) can reduce side-effect expectations and resulting nocebo effects (nonspecific medication side-effects unrelated to the drug's pharmacological action). There is scope to educate patients about nocebo effects in PILs to minimise their occurrence further.

Aims: To investigate if incorporating information on placebo reported side-effects reduces side-effect expectations compared to a positively framed only or standard PIL.

Methods: Participants (N=443) completed an online study and randomised to read one of three PILs for a hypothetical antibiotic: standard PIL (n=140), positively framed PIL (n=151), or positively framed PIL with placebo side-effect information (n=152). Participants' side-effect expectations, absolute risk perceptions, and intended adherence were recorded.

Results: The standard PIL resulted in significantly higher side-effect expectations compared to the positively framed + placebo side-effect information PIL. Including the placebo side-effect results had no effect on side-effect expectations compared to the positive framing only PIL, however there was a significant interaction between health literacy and PIL condition on side-effect expectations. Both positively framed PILs produced more accurate risk estimates for the more common side-effects. There was no difference in intended adherence between the three PILs.

Limitations: Our findings are limited by the highly educated sample and hypothetical context.

Conclusions: There was no benefit of adding placebo side-effect information, however alternative ways of explaining nocebo effects in PILs should be explored utilising clinical contexts and samples with a wider range of participant ages, and health literacy.

Key words: patient information leaflet, side-effect expectations, nocebo effect, positive framing, health literacy

Introduction

Medication prescriptions are the most commonly used clinical intervention (NICE, 2015), costing the UK £8.8 billion in 2018 (NHS, 2019b). However, as with all medicines, side-effects may occur. Side-effects are responses to medicines which are noxious and unintended (World Health Organisation, 1972). They can range from specific and observable events quite obviously linked to the pharmacological action of the medicine (e.g., vomiting, rashes, seizure), to more non-specific side-effects that may not always be due to the ingredients in the medicine, and misinterpretations of symptoms we experience as part of daily life (e.g., headaches, dizziness, nausea). Information about side-effects is contaminated by symptoms we experience in our everyday life, however healthcare professionals and patient information leaflets (PILs) that accompany medications are required to inform patients about the risks that may arise from a treatment to uphold informed consent (Dyer, 2015; MHRA, 2005). Informing and educating patients about side-effects enables them to better recognise symptoms that they experience as a side-effect, rather than as worsening of disease symptoms, or ignoring symptoms (Jose & AlHajri, 2018). However, at the same time it increases the likelihood of patients experiencing side-effects through the nocebo effect (Barsky et al., 2002).

The nocebo effect is defined as the experience of noxious symptoms in response to an inert exposure (Kennedy, 1961).More recently the term has been used to describe the non-specific side-effects that patients experience to their medication which cannot be linked to the pharmacological action of the drug (Wells & Kaptchuk, 2012). Evidence suggests that between 38-100% of reported side-effects consist of these non-specific symptoms which may not be caused by the drug itself (Mahr et al., 2017). Side-effects resulting from the nocebo effect can arise through negative expectations (Webster et al., 2016). These negative expectations can be generated from a variety of sources such as prior experience, PILs, the

media, friends, family and medical professionals. PILs have been receiving increased attention as a means of reducing these negative expectations. This is partly because a) they are an easy accessible cost-effective intervention that are required to accompany every medication; b) around 70% of patients prescribed a new medication read PILs, of which the side-effect section is the most commonly read (Raynor et al., 2007); and c) the way we currently communicate side-effect risk in PILs leads to overestimations of absolute risk and side-effect expectations (Webster et al., 2017a, 2017b) which may be contributing to nocebo effects (Benedetti et al., 2007) and have knock on implications for patient adherence (Kardas et al., 2013).

Non-adherence to any prescribed medication can have consequences for patients' health, however there is one medication in particular where this can also have consequences at the public health level, antibiotics. Antibiotics are one of the most commonly prescribed medications and are used to prevent or treat bacterial infections. An increase in inappropriate usage and lowered adherence has contributed to antibiotic resistance whereby antibiotics are becoming less effective, costing both the public in terms of their health and the NHS billions in added healthcare costs (Nunes et al., 2009). In 2019 a 20-year vision and 5-year plan was published by the UK government to ensure that resistance is contained and controlled (HM Government, 2019). NICE has also issued antibiotic prescribing guidelines to help slow the development of antimicrobial resistances (NICE, 2017).

As well as appropriate prescribing, it is also important for patients to adhere to the course of antibiotics as prescribed. However, it is estimated that 37.8% of patients prescribed antibiotics do not take the full course as prescribed (Kardas et al., 2005), with a more recent study showing that this can be as high as 87% (Tong et al., 2018). Common reasons for stopping antibiotics early include feeling better after a few days of treatment, as well as the experience of side-effects (Kardas et al., 2013; Zanichelli et al., 2019). However, common

side-effects of antibiotics affect the digestive system and are very similar to the non-specific symptoms that occur in everyday life and those that can be caused by anxiety, e.g. nausea, diarrhoea, bloating, loss of appetite (NHS, 2019a). It is therefore possible that antibiotics are subject to a high degree of nocebo-induced side-effects, supported by the fact that large scale clinical trials investigating antibiotics compared to placebo have shown that although up to 59% of participants experience side-effects to the active antibiotic, so to do 36% of placebo participants (Hansen et al., 2000; Lindbaek et al., 1996; Varonen et al., 2003). Finding ways to reduce these nocebo effects would be beneficial.

A potential solution whilst meeting informed consent requirements is using positive framing. Currently, side-effect information in PILs is presented in terms of how many people will be affected as a result of the medication (e.g., Very common, more than 1 in 10 people will be affected). Reframing this in a positive manner involves stating how many people are not affected by the side-effect (e.g., Uncommon, 8 in 10 people will not be affected). A review of 6 studies investigating the use of positive framing to diminish nocebo effects found all but one study showed a significant framing effect on at least one aspect of side-effects (experience, attribution or expectations) (Barnes et al., 2019). Therefore suggesting framing is a promising strategy for reducing nocebo effects.

Although positive framing may reduce the overestimation of side-effect risk caused by current PILs and reduce nocebo effects, it does not educate patients about the nocebo effect, which may provide further benefit. Studies have shown that informing participants about the nocebo effect can reduce side-effect reporting to wind turbines (Crichton & Petrie, 2015), and sham medication (MacKrill et al., 2021; Pan et al., 2019). Adding this information to PILs could reduce nocebo effects further without taking up time in consultations.

While altering side-effect communication in PILs could provide a cost-effective wide-scale intervention it is important to note it may not be a ‘one-size fits all’ approach. There are

certain characteristics which have been shown to be associated with side-effect expectations and nocebo side-effect experience such as negative medication related beliefs, prior side-effect experience and health literacy (Webster et al., 2017a, 2018a). As such people that score low on these may not be as influenced by altering the communication of side-effect risk in PILs.

We investigated the effect of adding placebo side-effect statistics to a positively framed PIL to illustrate the nocebo effect that not all side-effects are due to a medicines ingredients, and looked at the impact on side-effect expectations, absolute risk perceptions, and intended adherence for a hypothetical new antibiotic. We compared this to two other PILs, one which just contained positively framed side-effect risk, and a control PIL which followed current standards using negative framing. The interactions between medication beliefs, past antibiotic side-effect experience, health literacy and PIL type on side-effect expectations were also examined.

Method

The reporting of the study follows CONSORT guidelines (Schulz et al., 2010).

Design

This study was an online between-subjects RCT design with three conditions in which participants were randomised to read one of the following leaflets: control leaflet, positively framed leaflet or positively framed leaflet with placebo side-effect information.

Participants

Participants were recruited through adverts on the university's circular emails, the BSc psychology recruitment platform, social media platforms and Gumtree. In order to be eligible for the study, participants were required to be a minimum 16 years of age and fluent in English. To detect a small effect size (OR=1.68) at the 5% level (a=0.05) with 80% power,

we needed a sample size of 377 to carry out an ordinal regression with five categories with a likely skewed distribution (Taylor et al., 2006).

Materials and measures

Patient information leaflets

Three different PILs for a hypothetical new drug named 'Ormicillin' were developed. They were all based on a current PIL for penicillin but had different presentations of the side-effect section which were user tested with a group of 5 undergraduate students. Alongside the change to positive framing, statistical presentation and verbal descriptors were also altered between conditions. This has been previously acknowledged (Webster & Rubin, 2020) and the design reflects how positive framing is believed to be communicated in the most effective and understandable way to readers. See Table 1 for the differences between the three PILs.

Table 1. Differences in side-effect communication between the three PILs

Standard PIL	Positive framing PIL	Positive framing & placebo results PIL
Very common (more than 1 in 10 people are affected) **Common** (up to 1 in 10 people are affected) **Uncommon** (up to 1 in 100 people are affected) **Rare** (up to 1 in 1000 people are affected) **Very rare** (up to 1 in 10,000 people are affected)	**Uncommon** (80% of people are **not** affected) **Very uncommon** (90% of people are **not** affected) **Rare** (99% of people are **not** affected) **Very rare** (99.9% of people are **not** affected) **Extremely rare** (99.99% of people are **not** affected)	**Uncommon** (80% of people are **not** affected) **Very uncommon** (90% of people are **not** affected) **Rare** (99% of people are **not** affected) **Very rare** (99.9% of people are **not** affected) **Extremely rare** (99.99% of people are **not** affected) **Results from placebo-controlled trials** Several large experiments have given patients real ORMICILLIN or a fake 'placebo' without revealing which is which to test how effective ORMICILLIN is. In these experiments, 39% of patients given ORMICILLIN experienced side-effects but, importantly, so did 22% of patients given the placebo. This suggests that many of the side-effects that people think are caused by ORMICILLIN are not, in fact, caused by its active ingredients.

Primary outcomes

Intended adherence. One-item measuring intended adherence was created asking participants "If prescribed ormicillin, I would take all the tablets as directed by my doctor", measured on a 5-point scale from 1 "*strongly disagree*" to 5 "*strongly agree*".

Side-effect expectations. The expectation of side-effects was assessed using a single item asking participants how likely they were to expect themselves to experience side-effects if they took Ormicillin, rated on a 5-point scale from 1 "*very unlikely*" to 5 "*very likely*".

Absolute risk perceptions. Similarly to Webster and Rubin (2020) participants were asked to provide a value out of 10,000 for how many people they would expect to experience five of the side-effects listed in the PIL from each of the different risk groups (diarrhoea, nausea, dizziness, anaemia, seizures), and any side-effect.

Potential moderators

Past antibiotic side-effect experience and adherence. Participants were asked about their experience with antibiotics, which consisted of the last time they took antibiotics, and which antibiotics they had been prescribed. They were also asked whether they had experienced antibiotic side-effects in the past– 'yes', 'no' or 'don't know', and how well they usually adhere to antibiotics measured using the item 'When taking antibiotics, I take all the tablets as directed by my doctor', rated on a 5-point scale from 1 "strongly disagree" to 5 "strongly agree" .

Perceived sensitivity to medicines. The Perceived Sensitivity to Medicines scale (Horne et al., 2013) was used to assess how sensitive participants thought they were to medicines. This provides a score from 5 to 25 with higher scores indicating higher sensitivity. Cronbach's alpha from our sample = 0.85.

Belief about medicines. We used the overuse and harm general subscales from the Beliefs about Medicines Questionnaire (BMQ) (Horne et al., 1999) to measure attitudes towards medicines in general. These subscales give scores from 4 to 20, with higher scores indicating higher perceived overuse or harm. Cronbach's alpha from our sample = 0.71 and 0.64 respectively.

Health literacy. A single item to assess health literacy was adapted from Morris et al. (2006) asking participants to state how often they needed help reading PILs, from 1 "always" to 5 "never". Higher scores indicated higher health literacy.

Demographics

Participants were asked their age, gender, ethnicity, qualifications, employment status and whether they or anyone in their household has a long-standing illness, disability or infirmity.

Attention checks

To ensure participants were paying attention we had a series of attention checks in place. Firstly participants who clicked forward from the PIL in less than 60 seconds were screened out of the survey and thanked for their participation. A cut off of 60 seconds was chosen as the fastest speed readers can read 1000 words in a minute (Just & Carpenter, 1987). Secondly they had to answer three multiple-choice questions based on the content of the leaflet. The questions included a) the name of the antibiotic, b) if the antibiotic affected ability to drive, c) the colour/shape of the antibiotic. If they got any of these questions wrong, they were screened out of the survey and thanked for their participation. Finally, there was a question asking participants to tick option 5, 'very likely' to certify that participants were still engaged and reading the questions. Those who did not tick option 5 were excluded from the analysis.

Procedure

The study was hosted on the survey programme, Qualtrics. Upon clicking the link in the adverts, participants were presented with the information sheet. To prevent the survey being hijacked by bots due to the prize draw, a CAPTCHA was added below the information sheet to confirm they were human. A consent form followed requiring participants to confirm their understanding of the information provided and wish to take part in the research. Participants confirmed their eligibility for the survey and those that were ineligible were screened out and

thanked for their interest. To anonymously record results, participants generated a user ID code allowing us to withdraw their data should they wish whilst maintaining anonymity.

The first part of the study collected data on participants' demographics, past antibiotic experience, perceived sensitivity to medicines, beliefs about medicines and health literacy. Participants were then randomly presented with one of three PILs using the inbuilt randomisation software provided by Qualtrics, allowing allocation concealment and masking of participants and researchers. They were instructed to read the PIL and told it was for a new antibiotic named Ormicillin. A warning was presented informing participants to read the PIL carefully and that they would be required to answer questions based on the content of the PIL. Those who read the PIL too quickly or answered any of the questions wrong were screened out. After passing the attention checks, participants answered questions regarding their intended adherence, side-effect expectations, and absolute risk perceptions. The order of items within each of the measures were randomised. Participants could then give a valid email address to enter a prize draw for £200, £100, or £50 worth of Amazon vouchers. This was considered a suitable prize given the length of the survey, and the attention checks that participants had to pass to complete the study. At the end of the study participants were presented with a debrief. The study received full ethical clearance and was approved by the University Ethics Committee (RESCM-19/20-13199).

Analysis

Ordinal regressions were used to assess differences in side-effect expectations and intended adherence between the three PIL conditions, whilst controlling for any baseline variables that correlated with the dependent variables. Interactions between PIL condition and previous side-effect experience, health literacy, perceived sensitivity to and belief about medicines were entered in to the analyses to test for any moderation effects on side-effect expectations.

For absolute risk perceptions participant responses were recoded as '0' if their answer was within the correct range and '1' if it was within the incorrect range for each side-effect. Correct range was defined as falling within the correct statistical risk bracket for that side-effect. Chi-squared tests were used to compare the number of correct absolute risk estimations across each of the PIL conditions and pairwise comparisons were carried out for significant results applying the Bonferroni correction to adjust for multiple testing.

All analyses were carried out using SPSS v26 and a cut off value of $p<.05$ was used for significance testing. All answers of 'don't know' or 'prefer not to say' were excluded from the analyses. We used listwise deletion to eliminate all observations that had one or more missing value across all variables specified in each analysis, e.g. 'Other' in the Gender category.

Results

Sample Characteristics

A total of 443 individuals completed the study between 1st November 2019 and 30th December 2019 and were included in the sample analysis. Participants took an average of 27 minutes to complete the study. Rigorous checks were in place during the survey to ensure participants were paying attention to the content (see Figure 1 for exclusions). Sample characteristics illustrate that the sample was female dominated and in a younger age bracket (M_{age} = 25.47, age range: 16-77), further details are provided in Table 2.

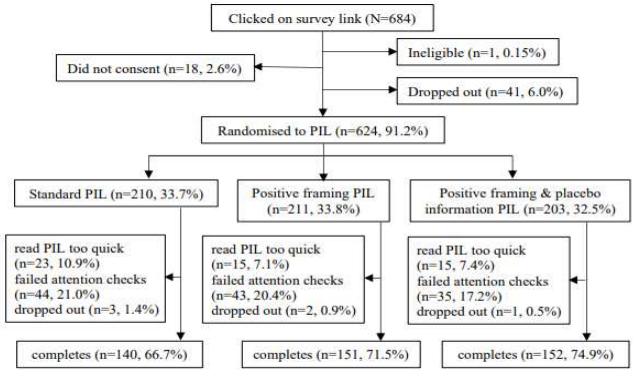

Figure 1. Participant flow through study

Table 2. Participant Characteristics

Characteristics	Standard PIL (n = 140)	Positive framing PIL (n = 151)	Positive framing & placebo results PIL (n = 152)	Total (N = 443)
Gender				
Male	25 (17.9%)	28 (18.5%)	28 (18.4%)	81 (18.3%)
Female	113 (80.7%)	122 (80.8%)	124 (81.6%)	359 (81.0%)
Other	2 (1.4%)	1 (0.7%)	-	3 (0.7%)
Age	25.1 (10.6)	26.0 (10.6)	25.2 (10.7)	25.5 (10.6)
Ethnicity				
White	80 (57.1%)	94 (62.3%)	92 (60.5%)	266 (60.0%)
Asian	42 (30.0%)	36 (23.8%)	44 (28.9%)	122 (27.5%)
Mixed	10 (7.1%)	11 (7.3%)	10 (6.6%)	31 (7.0%)
Black	3 (2.1%)	3 (2.0%)	2 (1.3%)	8 (1.8%)
Arab	3 (2.1%)	4 (2.6%)	1 (0.7%)	8 (1.8%)
Other	2 (1.4%)	2 (1.3%)	2 (1.3%)	6 (1.4%)
Prefer not to say	-	1 (0.7%)	1 (0.7%)	2 (0.5%)
Employment				
In full time education	83 (59.3%)	85 (56.3%)	86 (56.6%)	254 (57.3%)
Working	46 (32.9%)	53 (35.1%)	56 (36.8%)	155 (35.0%)
Unemployed	7 (5.0%)	11 (7.3%)	8 (5.3%)	26 (5.9%)
Retired	4(2.9%)	2 (1.3%)	2 (1.3%)	8 (1.8%)
Education qualification				
School/equivalent	55 (39.3%)	57 (37.7%)	62 (41.1%)	174 (39.4%)
Higher education	65 (46.4%)	72 (47.7%)	72 (47.4%)	208 (47.0%)
None	20 (14.3%)	21 (13.9%)	16 (10.5%)	57 (12.9%)
Prefer not to say	-	1 (0.7%)	2 (1.3%)	3 (0.7%)
Longstanding illness/disability				
Myself	7 (5.0%)	22 (14.6%)	12 (7.9%)	41 (9.3%)
Someone in household	18 (12.9%)	18 (11.9%)	20 (13.2%)	56 (12.6%)
No	110 (78.6%)	107 (70.9%)	116 (76.3%)	333 (75.2%)
Prefer not to say	5 (3.6%)	4 (2.6%)	4 (2.6%)	13 (2.9%)
Last time took antibiotics				
Currently taking	2 (1.4%)	7 (4.6%)	5 (3.3%)	14 (3.2%)
<1 year ago	57 (40.7%)	60 (39.7%%)	54 (35.5%)	171 (38.6%)
1-5 years ago	52 (37.1%)	55 (36.4%)	61(40.1%)	168 (37.9%)
> 5 years ago	18 (12.9%)	17 (11.3%)	15 (9.9%)	50 (11.3%)
Never	3 (2.1%)	6 (4.0%)	10(6.6%)	19 (4.3%)
Don't know	8 (5.7%)	6 (4.0%)	7 (4.6%)	21 (4.7%)
Experienced side-effect to antibiotics				
Yes	31 (24.0%)	36 (25.9%)	38 (28.1%)	105 (26.1%)
No	83 (64.3%)	93 (66.9%)	83 (61.5%)	259 (64.3%)
Don't know	15 (11.6%)	10 (7.2%	14 (10.4%)	39 (9.7%)
Past adherence to antibiotics				
Adherence, mean (SD)	4.27 (1.14)	4.58 (0.69)	4.33 (1.11)	4.40 (1.00)
Beliefs about medicines (overuse)	10.84 (3.09)	10.88 (2.89)	11.30 (3.07)	11.01 (3.01)
Beliefs about medicines (harm)	8.07 (2.52)	8.23 (2.60)	8.16 (2.66)	8.16 (2.59)
Perceived sensitivity to medicines	10.89 (3.82)	11.23 (3.92)	10.53 (3.38)	10.88 (3.72)
Health Literacy	4.48 (0.89)	4.54 (0.72)	4.53 (0.76)	4.52 (0.79)

Note:

Data are N (%) or Mean (SD).

Due to small cell sizes in some of our variable categories, we collapsed these as follows in our analyses:

Ethnicity: White vs Other (Asian, Mixed, Black, Arab and Other)

Employment: Working vs Not working (In full time education, unemployed, retired)

Longstanding illness/disability: Yes (myself, someone in household) vs No

Last time took antibiotics: In the past year (currently taking, <1 year) vs More than a year a go (1-5 years ago, >5 years ago) vs Never

There were no significant differences in participant characteristics between conditions ($p > .05$).

Side-effect expectations

Differences in side-effect expectation ratings between the three PIL conditions are shown in figure 2a. Participants who received the standard PIL had significantly higher odds of having higher side-effect expectations compared to participants who received the positive framing + placebo results PIL (OR = 21.43). There was no significant difference in side-effect expectations between the two positively framed PILs (see Table 3).

Intended adherence

Differences in intended adherence ratings between the three PIL conditions are shown in figure 2b. There was no significant difference in intended adherence ratings between the three conditions, whilst controlling for age, gender, ethnicity, past antibiotic adherence, health literacy and beliefs about medicines which were correlated with intended adherence (see Table 4).

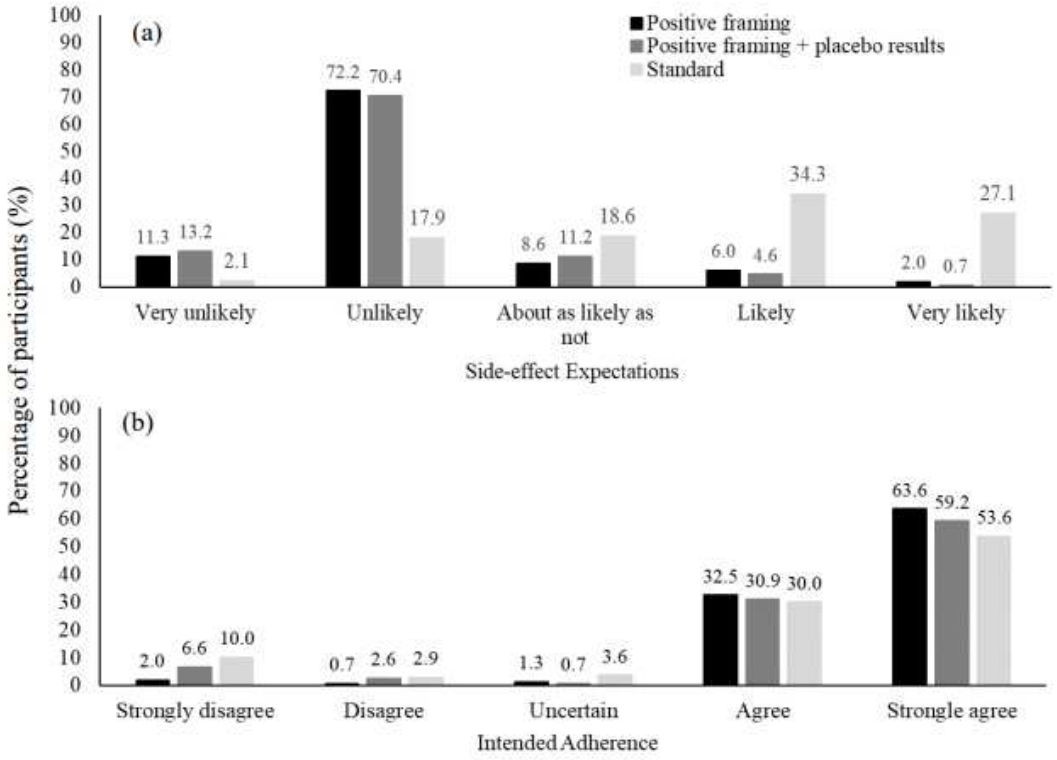

Figure 2. Summary of ratings of (a) side-effect expectations and (b) intended adherence between the three PIL conditions

Table 3. Differences in side-effect expectations between the three PIL conditions

PIL	Side-effect expectations, Odds ratios (95% CI)	p value
Standard	**21.43 (12.62 to 36.38)**	**<.001**
Positive framing	1.10 (0.68 to 1.79)	.688
Positive framing + placebo results	Reference	

Table 4. Differences in intended adherence between the three PIL conditions

PIL	Intended adherence, Adjusted* Odds ratios (95% CI)	p value
Standard	0.68 (0.41 to 1.13)	.141
Positive framing	0.92 (0.55 to 1.55)	.437
Positive framing + placebo results	Reference	

*Controlling for ethnicity, past antibiotic adherence, health literacy, beliefs about medicines overuse and harm which were associated with the DV.

Moderators

There were no significant interaction effects between PIL condition and previous antibiotic side-effect experience, perceived sensitivity to medicines or belief about medicines. However there was a significant interaction between PIL condition and health literacy. Each one point increase in health literacy score resulted in an increased odds of 1.82 of having higher side-effect expectations in the standard PIL condition compared to the positive framing + placebo results condition. There was no significant interaction with health literacy between the two positive framing conditions. For full moderation results see Electronic Supplementary Material 1.

Absolute risk perceptions

The number of correct and incorrect absolute risk perceptions was found to significantly differ between the conditions for diarrhoea, anaemia, seizures, and any side-effect, with no significant difference found for nausea and dizziness (see Table 5). Pairwise comparison revealed mixed results with the standard PIL resulting in more correct responses than both positively framed PILs for anaemia (ps < .01), and the positively framed PIL for seizure (p<.01), but resulting in fewer correct responses for diarrhoea and any side-effect compared

to both positively framed PILs (ps<.001). No differences were observed between the positive framing PIL and positive framing with placebo results PIL (ps>.05).

Table 2. Difference in absolute risk perceptions between the three conditions

Side effect	**Standard PIL** (n = 140)	**Positive framing PIL** (n = 151)	**Positive framing & placebo results PIL** (n = 152)	**Chi-square (χ^2)**
Diarrhoea (Very common)				
Correct (%)	58 (41.4%)	132 (87.4%)	131 (86.2%)	**98.83**
Incorrect/Underestimation (%)	82 (58.6%)	19 (12.6%)	21 (13.8%)	***p* < .001**
Nausea (Common)				
Correct (%)	123 (87.9%)	127 (84.1%)	124 (81.6%)	2.20
Incorrect (%)	17 (12.1%)	24 (15.9%)	28 (18.4%)	p = .333
Underestimation (%)	*7 (5.0%)*	*22 (14.6%)*	*24 (15.8%)*	
Overestimation (%)	*10 (7.1%)*	*2 (1.3%)*	*4 (2.6%)*	
Dizziness (Uncommon)				
Correct (%)	124 (88.6%)	123 (81.5%)	124 (81.6%)	3.50
Incorrect (%)	16 (11.4%)	28 (18.5%)	28 (18.4%)	p = .174
Underestimation (%)	*4 (2.9%)*	*20 (13.2%)*	*23 (15.1%)*	
Overestimation (%)	*12 (8.6%)*	*8 (5.3%)*	*5 (3.3%)*	
Anaemia (Rare)				
Correct (%)	123 (87.9%)	109 (72.2%)	112 (73.7%)	**12.38**
Incorrect (%)	17 (12.1%)	42 (27.8%)	40 (26.3%)	***p* = .002**
Underestimation (%)	*2 (1.4%)*	*25 (16.6%)*	*27 (17.8%)*	
Overestimation (%)	*15 (10.7%)*	*17 (11.3%)*	*13 (8.6%)*	
Seizures (Very rare)				
Correct (%)	118 (84.3%)	106 (70.2%)	114 (75.0%)	**8.19**
Incorrect/Overestimation (%)	22 (15.7%)	45 (29.8%)	38 (25.0%)	***p* = .017**
Any				
Correct (%)	46 (32.9%)	90 (59.6%)	88 (57.9%)	**25.76**
Incorrect/Underestimation (%)	94 (67.1%)	61 (40.4%)	64 (42.1%)	***p* < .001**

Note: Chi-square analyses were carried out to assess differences in the distribution of correct vs incorrect absolute risk perceptions. Where relevant we have broken the incorrect responses into under and overestimates. For Diarrhoea and Any side-effect it was only possible for incorrect responses to be underestimates. For Seizures it was only possible for incorrect responses to be overestimates.

Discussion

This research adds to growing literature on the development of strategies to reduce nocebo effects that do not withhold information or compromise informed consent, having positive implications for patients' quality of life, adherence and healthcare costs. Similar to previous research (Webster & Rubin, 2020), we found that positively framing side-effect risk in PILs significantly reduced side-effect expectations compared to the standard PIL, but while there

was no detriment in including placebo side-effect information to the positively framed PIL, there was no benefit either. There was also no difference in intended adherence to the hypothetical antibiotic between the three PIL conditions. This could have been due to a ceiling effect as adherence ratings were high across the sample.

Quite rightly there is concern that interventions such as altering the communication of side-effect risk in PILs may only be effective for certain groups of people, such as those that are more concerned about medications, have better health literacy and more negative previous experiences. We found no interaction effects with medication beliefs or previous antibiotic experience, demonstrating that positive framing was similarly effective in reducing side-effect expectations for those who scored higher or lower on these measures. However we did find that positive framing was more effective at lowering side-effect expectations for participants with higher health literacy scores. As such positively framing side-effect risk was not as effective in lowering side-effect expectations for those with lower health literacy scores. In a sample of highly educated participants this finding is concerning as even in a sample with high health literacy scores with little variation we found this interaction effect. However, we urge particular caution in the interpretation of these findings. It is possible that the significant interaction with health literacy could be due to a minority of the sample scoring low on this measure. Indeed, removing these participants from the moderation analyses, the interaction results become insignificant (see supplementary material 2). It is therefore imperative that before any conclusions can be drawn future research should investigate such interactions in samples that have greater variability in their health literacy scores.

Both positively framed PILs led to similar and in some cases more accurate risk perceptions for the more common side-effects compared to the standard PIL, but did not perform as well for the more rare side-effects. This supports the suggestions in the literature

that perhaps interventions to reduce nocebo effects should target the more common/minor side-effects, but the communication of rare (and often by association more severe) side-effects should remain unaltered (Colloca, 2017). However previous research has shown that positive framing using natural frequencies could be the answer to this as it performs equally to the standard PIL in terms of generating accurate risk perceptions, thus maintaining informed consent (Webster & Rubin, 2020). Again however, whether this holds for participants with lower health literacy scores needs to be further investigated.

In sum, incorporating information on placebo side-effect statistics had no significant additional impact across side-effect expectations, risk perceptions, or intended adherence compared to positive framing alone. This could be due to a variety of reasons. Firstly, participants may have paid more attention to the actual side-effects mentioned, as do many individuals when reading PILs (Raynor et al., 2007), and thought of the supplementary placebo side-effect information as insignificant. Secondly, it could be due to the fact that we attempted to explain the nocebo effect in a succinct way so that it could be easily incorporated in PILs. Previous successful attempts to explain nocebo effects have used educational workshops or dialogues with patients, and given more extensive written communication (Crichton & Petrie, 2015; Pan et al., 2019; Quidde et al., 2018). As such only giving information about placebo side-effect reporting statistics without much further elaboration, might not have been as sufficient. Thirdly, it could be that the effect of positive framing and information on the nocebo effect have different underlying mechanisms, e.g., framing primarily targets cognitions, yet education about the nocebo effect might affect symptom attribution later, when symptoms arise, and therefore not affect side-effect expectations (Michnevich et al., Under review; Pan et al., 2019)

We also acknowledge that the description of the results from placebo-controlled trials could have been more appropriately described. This was user tested with 5 undergraduate

students, but some of the terms could have been more appropriately described for lay people and those with lower health literacy.

Positive framing however, has only been shown to reduce expectations and side-effect experience of those side-effects specifically mentioned in the PIL (Webster & Rubin, 2021; Webster et al., 2018b). As suchattempting to explain the nocebo effect in PILs in addition to positive framing could help to reduce expectations and nocebo-induced side-effects across the board (i.e. not just limited to those mentioned in PILs). Therefore, we still recommend research looks into the potential benefit of educating patients about nocebo effects in PILs in addition to the use of positive framing.

Strengths and limitations

As far as we are aware this is the first study to investigate the effect of combining positive framing with nocebo education as a potential intervention to reduce nocebo effects in the context of medications. This study adopted an RCT design which reduces the risk of potential confounding factors influencing the results (Sibbald & Roland, 1998). The design ensures that individual differences between participants in the conditions are minimised, and in addition to this we controlled for any baseline characteristics that were associated with our dependent variables. Further, a number of attention checks were put in place to ensure that the analysis was solely based on valid data. It is true that incorrect responses to the attention check could have been due to the PIL not being clear enough, however all attention check questions were based on the wording used in a currently approved antibiotic PIL and were not in relation to any of the risk information altered as part of the study. In addition the time cut off was short enough to allow participants to scan the PIL as they might do in a real-world setting, however the fact that participants knew they had to pay attention to the PIL could have influenced the results. For example participants' absolute risk perceptions were likely

more accurate than they would have been if participants did not know they were going to be 'tested'.

The demographics of the sample also limits the generalisability of the findings. Not only was the sample highly educated, it also overly represented females who made up 81% of the completed responses. Research identifies that sex and gender influence medication use (Manteuffel et al., 2014; Thunander Sundbom & Bingefors, 2012), and drug experiences due to physiological differences (Whitley & Lindsey, 2009), which can impact side-effect expectations. In addition our sample was relatively young (mean age = 25.5), compared to the average patient that is prescribed antibiotics (Dolk et al., 2018). However, approximately half of all antibiotics are prescribed to adults aged 19–64, and our sample ranged from 16-77 years old. Still, the representativeness of the data can be questioned as effects found may not translate to males, those with lower education levels or more variable health literacy skills . Additional research is encouraged to establish effects and heighten generalisability.

A constraint inherent in the study design is that alongside the change to positive framing, statistical presentation and verbal descriptors were also altered between conditions. This is problematic for identifying whether the change in statistical presentations contributed to the results, the change in verbal descriptors, or a combination of both. This has been previously acknowledged (Webster & Rubin, 2020) and the design reflects how positive framing is believed to be communicated in the most effective and understandable way to readers. Future research could focus on teasing out the effects to determine causation and any cumulative effects.

The hypothetical nature of the study is an added limitation. Side-effect expectations and intended adherence were measured, as opposed to the actual experience of side-effects and adherence. Not all side-effect expectations will result in the experience of side-effects and intentions do not necessarily translate into behaviour (Sheeran & Webb, 2016).

Consequently, there is a recommendation for an increase in clinical based studies to test the effect of altering the side-effect communication in PILs on actual side-effects experienced and medication adherence.

Conclusion

Positively framing side-effect risk in PILs significantly reduced side-effect expectations and improved risk comprehension for the more common side-effects, however there was no additional benefit of adding placebo side-effect information as a method of explaining nocebo effects. Future research should look at alternative ways of explaining nocebo effects in PILs as this may provide added benefit to positive framing by reducing side-effect expectations and experiences of side-effects which may not necessarily be listed in PILs. In addition, studies altering side-effect communication in PILs as a means to reduce nocebo effects should make efforts to use real world clinical settings and recruit samples with a wider range of participant ages, and levels of health literacy to improve the generalisability of future findings.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available as participants did not consent to this.

Electronic Supplementary Material

ESM1. Interactions* between perceived sensitivity to medicines, belief about medicines, health literacy, past antibiotic side-effect experience and leaflet condition on side-effect expectations (.doc)

ESM2. Sensitivity analysis examining the interaction* between health literacy and leaflet condition on side-effect expectations in the restricted sample (removing 13 participants scoring low (1 or 2) on the health literacy measure)

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ESM1

Interactions* between perceived sensitivity to medicines, belief about medicines, health literacy, past antibiotic side-effect experience and leaflet condition on side-effect expectations

Effects	Estimate	SE	Wald	df	p	95% CI
Standard	3.087	.271	129.705	1	.000	2.556 to 3.618
Positive	.101	.247	.166	1	.684	-.384 to .585
Positive + Placebo	Reference					
BMQ Harm	.082	.065	1.580	1	.209	-.046 to .210
Standard * BMQ Harm	-.023	.089	.066	1	.797	-.198 to .152
Positive * BMQ Harm	-.135	.094	2.049	1	.152	-.320 to .050
Positive + placebo * BMQ Harm	Reference					

Effects	Estimate	SE	Wald	df	p	95% CI
Standard	3.111	.272	130.379	1	.000	2.577 to 3.645
Positive	.115	.248	.214	1	.644	-.371 to .601
Positive + Placebo	Reference					
BMQ Overuse	.062	.057	1.172	1	.279	-.050 to .174
Standard * BMQ Overuse	-.014	.076	.035	1	.852	-.162 to .134
Positive * BMQ Overuse	-.117	.084	1.946	1	.163	-.280 to .047
Positive + placebo * BMQ Overuse	Reference					

Effects	Estimate	SE	Wald	df	p	95% CI
Standard	3.068	.271	128.061	1	.000	2.537 to 3.600
Positive	.090	.248	.132	1	.717	-.396 to .577
Positive + Placebo	Reference					
PSM	.006	.052	.015	1	.901	-.095 to .108
Standard * PSM	.069	.066	1.109	1	.292	-.060 to .198
Positive * PSM	.011	.068	.025	1	.874	-.123 to .145
Positive + placebo * PSM	Reference					

Effects	Estimate	SE	Wald	df	p	95% CI
Standard	3.979	.518	58.918	1	.000	2.963 to 4.995
Positive	.614	.546	1.264	1	.261	-.456 to 1.84
Positive + Placebo	Reference					
Health literacy	-.479	.223	4.602	1	.032	-.916 to -.041
Standard * Health literacy	.598	.282	4.500	1	.034	.046 to 1.151
Positive * Health literacy	.349	.328	1.135	1	.287	-.293 to .992
Positive + placebo * Health literacy	Reference					

Effects	Estimate	SE	Wald	df	p	95% CI
Standard	3.112	.496	39.323	1	.000	2.139 to 4.085
Positive	.013	.489	.001	1	.979	-.945 to .971
Positive + Placebo	Reference					
Past side-effects = No	-.264	.413	.408	1	.523	-1.074 to .546
Past side-effects = Yes	Reference					
Standard * Past side-effects = No	-.036	.562	.004	1	.949	-1.137 to 1.066
Standard * Past side-effects = Yes	Reference					
Positive * Past side-effects = No	.071	.584	.015	1	.903	-1.074 to 1.216
Positive * Past side-effects = Yes	Reference					
Positive + placebo * Past side-effects = No	Reference					
Positive + placebo * Past side-effects = Yes	Reference					

Note:
* Controlling for each term in the interaction
BMQ = beliefs about medicines, PSM = perceived sensitivity to medicine
Continuous predictors have been mean centred

ESM 2

Sensitivity analysis examining the interaction* between health literacy and leaflet condition on side-effect expectations in the restricted sample (removing 13 participants scoring low (1 or 2) on the health literacy measure)

Effects	Estimate	SE	Wald	df	p	95% CI
Standard	3.128	.279	125.828	1	.000	2.581 to 3.674
Positive	.137	.250	2.497	1	.582	-.352 to .627
Positive + Placebo	Reference					
Health literacy	-.387	.245	2.497	1	.114	-.867 to .093
Standard * Health literacy	.491	.365	1.810	1	.178	-.224 to 1.207
Positive * Health literacy	.146	.383	.145	1	.703	-.604 to .896
Positive + placebo * Health literacy	Reference					

Note:
N=430 (removing 13 participants scoring low on health literacy)
* Controlling for each term in the interaction
Continuous predictors have been mean centred