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Predicting expectations of side-effects for those which are warned versus not warned about in patient information leaflets

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Abstract

Background: Research investigating predictors of side-effect expectations is disparate and largely based on hypothetical vignettes.

Purpose: Secondary analysis of a randomised controlled trial investigating predictors of side-effect expectations for side-effects that were, or were not, warned about.

Methods: 203 healthy adults completed measures concerning demographics, psychological factors, baseline symptoms and medication-related beliefs before reading one of two types of patient information leaflet (PIL) (standard or positively framed PIL) for a sham medication and asking them about their side-effect expectations. Associations between these measures and side-effect expectations whilst controlling for the PIL received were assessed using regression analyses.

Results: 82.8% of participants expected side-effects that were warned about in the PIL, and 29.1% expected side-effects that were not warned about. Participants who were younger, from White backgrounds, less optimistic, experienced increased anxiety and received the standard PIL were more likely to expect side-effects that were warned about. Those with higher beliefs about medicine overuse and lower trust in medicine development were more likely to expect side-effects that were not warned about. Higher somatisation, baseline symptoms, modern health worries scores and lower trust in pharmaceutical companies were associated with increased expectations for all side-effects

Conclusion: The results suggest we cannot only rely on altering side-effect risk communication to reduce side-effect expectations and therefore nocebo effects. We must also

consider patients' beliefs about trust in medicines. More work is needed to investigate this in a patient sample in which the medication is known to them.

Key words: side-effects, expectations, predictors, nocebo effect

Background

Around 50% of patients fail to take their medication as prescribed (1).This has been estimated to cost the National Health Service billions in additional healthcare costs (2), and more recently has been estimated to cost up to $52 000 per person annually worldwide (3). One of the reasons why people may choose not to take their medication or not take it as prescribed is a fear of side-effects (4, 5), which in turn is influenced by their side-effect expectations. Side-effect expectations have been associated with decreased intention to adhere to medications (6); and can contribute to the side-effects that patients experience through a psychological phenomenon known as the nocebo effect, whereby expectations that a medication will cause side-effects are self-fulfilling (7-10).

In order to identify factors to target in interventions to minimize side-effect expectations, and populations which may be particularly susceptible to heightened side-effect expectations, Smith, et al. (11) conducted an exploratory systematic review. They found some evidence that patients' clinical characteristics and the presentation format of how medication side-effects were communicated may impact expectations; but for the most part there was inconclusive evidence, particularly regarding the role of personal characteristics, psychological traits or states, and medication beliefs. This was likely due to the heterogeneity and poor quality of studies, and the lack of replication of the risk factors that were studied. In addition, most of the studies asked participants about specific side-effects that had been warned about, and they were based on hypothetical scenarios.

However, side-effect expectations may not be limited to those that are listed by clinicians or appear in patient information leaflets (PILs). When patients are faced with a

medication they are about to take, it is possible their side-effect expectations can extend beyond this list due to previous experience, knowledge of how their body reacts to medicines, and beliefs about the medication in question (12, 13). As such there may be different factors associated with side-effect expectations depending on whether they were warned about or not. Interventions altering side-effect communication to reduce expectations such as positively framing side-effect risk in PILs (14) might not extend to side-effects that patients' expect but which they are not warned about; whereas beliefs about and trust in medication may be more important in generating patients' expectations of side-effects that are not warned about.

This study builds on previous work by looking at the associations between personal characteristics, psychological factors, medication related beliefs and framing on expectations of side-effects that had been previously warned about and those that had not. This will help to build on the evidence base of factors that influence expectations of side-effects and provide avenues for interventions to target.

Method

This is a secondary analysis of the baseline components of a randomised controlled trial (RCT) which has been reported elsewhere, for full methods see: Webster, et al. (15). A brief summary of the methods is included below.

Design

An RCT which took place at the Wellcome Trust King's Clinical Research Facility and was approved by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee at King's College London (Reference number: PNM 14/15-62). In short, the RCT tested if changing how side effect information is framed in PILs reduces side-effect reporting. Participants completed baseline measures and were randomised to receive a PIL for "a well-known tablet available without prescription" that used standard side effect risk information (e.g.,

"Common, 1 in 10 people will be affected") or positively framed wording (e.g., "Uncommon, 90% of people will not be affected"). After reading their PIL, participants completed side-effect expectations measures and took the tablet (a placebo), completing side-effect reports one hour later.

Participants

Participants were eligible for inclusion if they were healthy, aged 18 or over, fluent in English. They could not have a condition currently causing symptoms e.g. chronic/acute illness, pregnancy or taken anything that may interfere with symptoms reporting e.g. pain killers/alcohol. In addition, participants were asked if they were allergic to any medicines or inactive ingredients often found in them. Examples of inactive ingredients were given, covering those in the tablet (lactose, microcrystalline cellulose, magnesium stearate). Participants who listed allergies to any of the tablet ingredients were excluded.

Sample Size

The sample size was calculated for the original study (15),based on the assumption that 25% of participants in the standard condition would develop side-effects (10), and that in order to detect a reduction in 15 percentage points at $p < .05$ with 80% power, using a z-test for independent proportions, 200 participants were required (100 per group). The associations tested here are therefore exploratory.

Predictors

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

Psychological Factors. The following measures were included: State Anxiety Inventory – short version to assess anxiety level at the time of measurement (16); the Somatosensory Amplification Scale to assess participants' tendency to experience a somatic sensation as intense, noxious, or disturbing (17); the Patient Health Questionnaire Somatic

Symptom Severity Scale to assess somatisation by measuring the prevalence of the most common bodily symptom (18); and the Revised Life Orientation Test (19) which is used to assess dispositional optimism. All measures showed a high degree of internal consistency with Cronbach's alpha ranging from 0.74-0.77.

Baseline Symptoms. Participants' symptoms in the previous 24 hours was assessed using a modified Generic Assessment of Side Effects Scale (GASE) (20). Participants rated 23 listed symptoms on a four-point scale ranging from 0 "not present" to 3 "severe".

Medicine-Related Beliefs. These included: the overuse and harm subscales of the Beliefs about Medicines Questionnaire to assess participants general beliefs about medicines (21); the Modern Health Worries Scale to assess the extent to which participants are worried or concerned about different aspects of modern life (22); the Perceived Sensitivity to Medicines Scale to assess the extent to which participants felt that they were sensitive to different aspects of medication (23); trust in medicine and pharmaceutical companies was assessed using bespoke items. Participants rated three items assessing how much they trusted the current process in which medicines were developed, tested and approved for use, and two items assessing whether participants believed pharmaceutical companies acted in patients' best interests and if they are only interested in making money (reverse scored) on a five-point scale from 1 "strongly disagree" to 5 "strongly agree". Scores ranged from 3-15 for trust in medicine, and 2-10 for trust in pharmaceutical companies, with higher scores indicating greater trust. All measures showed a high degree of internal consistency with Cronbach's alpha ranging from 0.71-0.96, apart from trust in pharmacy which had a score of 0.45, which is likely due to the small number of items.

Side-effect framing. Participants were randomised to receive one of two PILs. Both contained the same information about the drug, how to take it and the potential side-effects, but the side-effects were either framed positively (e.g. "Uncommon, 90% of people will not

be affected") or using the standard 'negative' frame (e.g. "Common, 1 in 10 people will be affected"). Information regarding what the drug was used for and it's ingredients were withheld. For a copy of the PILs see supplementary material.

Outcome

Side-effect Expectations. Expectations of side-effects were also assessed using the modified GASE (20); but this time participants were asked to state how likely they thought they were to experience the side-effect in the hour after taking the tablet. Each side-effect was rated on a four-point scale from 0 "not at all" to 3 "very likely". The measure contained the 14 side-effects that were warned about in the PIL, and 9 side-effects that were not.

Procedure

Participants were recruited between Dec 1, 2015 to Dec 5, 2016 through university circular emails and posts on volunteering websites. Those interested were emailed an information sheet and completed a screening questionnaire to assess eligibility. The information sheet explained the aim of the study was to assess participants side effect experience to a well-known tablet. It explained they would not be told what the tablet is or what it is used for in order to not bias their views, but that it has been shown to have beneficial effects for people and that no prescription is needed to take it. Eligible participants arranged a time with the researcher to participate at the Clinical Research Facility. On the day of participation, the researcher re-checked participants' eligibility. After providing consent, participants completed the measures for demographics, psychological factors, baseline symptoms and medicine-related beliefs. After reading their assigned PIL, participants re-completed the anxiety measure and gave their expectations of side-effects. The trust variables were assessed after participants had taken the tablet in case assessing before may have increased participants' suspicions about the study. All participants received a monetary reward for taking part and were emailed a debrief after all participants had been tested.

Analysis

Ratings for each set of warned and non-warned side-effects were summed to give an overall expectation score. Multiple linear regressions were used to assess associations with expectations of side-effects that were warned about in the PIL. Associations with expectations of side-effects that were not warned about in the PIL were assessed using logistic regression. This was necessary because of the highly positively skewed data distribution, with the majority of participants not expecting these side-effects therefore not meeting the requirements for a linear regression. As such this variable was dichotomised into those that did expect side-effects (an overall expectation score of '1' or above) that were not warned about and those that did not (an overall expectation score of '0'). For both outcomes adjusted analyses were carried out whilst controlling for the experimental condition and any demographic characteristics that were significantly correlated with the outcomes.

As a post-hoc analysis we also investigated interaction effects using regression analyses to see if any individual difference variables moderated the effect of the side-effect framing.

All analyses were carried out using SPSS v26. To correct for multiple testing for each of the outcomes we used the Benjamini & Hochberg's False Discovery Rate correction (24). This is more powerful than the Bonferroni correction, as such addressing concerns that the Bonferroni correction may be overcautious. In addition it is more suited for our analyses involving testing many exploratory associations in a similar way.

Results

Participant Characteristics

The sample contained 65 men and 138 women (mean age = 27.15 years). The majority were of White ethnicity (59.6%), and in receipt of higher education qualifications (65%).

Side-effect expectations

Expectations of warned side-effects. The mean expectations score was 5.42 (SD=6.05). 82.8 % of participants (n=168) expected side-effects that were warned about.

Expectations of non-warned side-effects. The mean expectation score was 0.71 (SD=1.59). 29.1% (n=59) of participants expected side-effects that were not warned about.

Predictors

Table 1 shows the association between the measures and participants' side-effect expectations for side-effects that were warned about in the PIL and those that were not.

Demographics. There was no effect of gender, employment status or education level on side-effect expectations. Older participants, and ethnic minorities were less likely to expect side-effects which were warned about in the PIL, with each additional year resulting in a 0.13 decrease in expectations, and those from ethnic minorities having a 1.67 decrease in expectations scores compared to participants from white backgrounds. There was no effect of age or ethnicity on expectations of side-effects that were not warned about in the PIL.

Psychological factors. There was no association between somatosensory amplification and side-effect expectations. Those who experienced an increase in anxiety after reading the PIL, and had a higher somatisation score were more likely to expect side-effects that were warned about, with each point increase in anxiety and somatisation resulting in a 0.45 and 0.36 increase in expectation score respectively. Those who were more optimistic were less likely to expect side-effects that were warned about with each point increase in optimisms score resulting in a 0.22 decrease in expectation score. Only somatisation score was associated with expectation of side-effects that were not warned about with each point increase in somatisation score associated with a 15% increase in the odds of expecting these side-effects.

Symptoms. Baseline symptoms were associated with both types of side-effect expectations, each increase in participants' baseline symptom score was associated with a

0.50 increase in expectation score of side-effects warned about, and a 17% increase in the odds of expecting side-effects that were not warned about.

Medicine-related beliefs. There was no effect of participants beliefs about medicines, perceived sensitivity to medicines or trust in medicine development on expectations of side-effects that were warned about. Only modern health worries and trust in pharmaceutical companies were associated with these side-effect expectations, with each point increase in modern health worries associated with a 0.06 increase in expectation score, and each point increase in pharmaceutical trust associated with a 0.50 decrease in expectation score. These were also important in associations with expectations of side-effects that were not warned about, with each increase in modern health worries score associated with a 2% increase in the odds of expecting these side-effects, and each increase in pharmaceutical trust associated with a 26% decrease in the odds. Belief about the over use of medicines and trust in medicine development were significantly associated with expectations of side-effects not warned about with each point increase associated with a 13% increase, and 18% decrease in the odds of expecting these side-effects respectively.

Type of leaflet. Participants who received the standard PIL were more likely to expect side-effects that were warned about, with a 2.85 increase in expectation score compared to those who received the positively framed PIL. This effect did not extend to the expectation of side-effects that were not warned about with no significant difference in the odds of expecting these side-effects between the standard and positively framed PIL after correcting for multiple testing.

Moderation

After correcting for multiple testing there were no significant interactions between the individual difference variables and side-effect framing. Indicating the predictors studied here

did not moderate the effect of side-effect framing on expectations of warned or non-warned side-effects. See supplementary material for full results.

		Warned side-effects			Non-warned side-effects		
Variable	No (%) or Mean (SD)	Adjusted B* (95% CI)	p value	Cohen's d	Adjusted OR* (95% CI)	p value	Cohen's d
Demographics							
Gender							
Male	65 (32.0)	-0.79 (-2.17 to 0.60)	.265	-0.25	1.41 (0.74 to 2.69)	.292	0.19
Female	138 (68.0)	-			-		
Age	27.15 (8.63)	**-0.13 (-0.21 to -0.06)**	**.001**	**-0.59**	0.97 (0.93 to 1.01)	.126	-0.017
Ethnicity							
Other	82 (40.4)	**-1.67 (-2.99 to -0.36)**	**.013**	**-0.44**	0.80 (0.42 to 1.50)	.480	-0.12
White	121 (59.6)	-			-		
Employment							
Working	78 (38.4)	-0.53 (-2.02 to 0.97)	.488	-0.20	0.95 (0.51 to 1.79)	.877	-0.028
Not working	125 (61.6)	-			-		
Education							
School qualifications	71 (35.0)	0.37 (-0.97 to 1.72)	.546	0.17	1.39 (0.74 to 2.62)	.304	0.18
University degree	132 (65.0)	-			-		
Experimental condition							
Standard leaflet	101 (49.8)	**2.85 (1.57 to 4.13)**	**<.001**	**0.72**	1.90 (1.03 to 3.53)	.041	0.35
Positively framed	102 (50.2)	-			-		
Psychological factors							
Change in anxiety	-0.035 (1.68)	**0.45 (0.069 to 0.82)**	**.021**	**0.41**	1.12 (0.92 to 1.35)	.256	0.063
Optimism	14.80 (3.68)	**-0.22 (-0.39 to -0.05)**	**.011**	**-0.44**	0.94 (0.87 to 1.03)	.168	-0.034
Somatisation	4.18 (3.25)	**0.36 (0.17 to 0.55)**	**<.001**	**0.59**	**1.15 (1.04 to 1.26)**	**.004**	**0.077**
Somatosensory amplification	23.52 (6.16)	0.09 (-0.01 to 0.19)	.091	0.33	1.02 (0.98 to 1.08)	.306	0.011
Symptoms							
Symptoms in previous 24 hours	2.95 (3.29)	**0.50 (0.26 to 0.73)**	**<.001**	**0.67**	**1.17 (1.04 to 1.31)**	**.007**	**0.087**
Medicine-related beliefs							
MHW	25.82 (20.37)	**0.06 (0.02 to 0.09)**	**.001**	**0.57**	**1.02 (1.01 to 1.04)**	**.007**	**0.011**
BMQ overuse	10.91 (3.28)	0.06 (-0.15 to 0.26)	.578	0.18	**1.13 (1.02 to 1.24)**	**.015**	**0.067**
BMQ harm	7.94 (2.68)	0.06 (-0.19 to 0.31)	.631	0.17	1.07 (0.96 to 1.20)	.208	0.037
PSM	7.26 (2.81)	0.16 (-0.07 to 0.39)	.181	0.28	1.11 (0.99 to 1.23)	.063	0.058
Trust in medicine development	11.72 (2.10)	-0.19 (-0.49 to 0.12)	.231	-0.26	**0.82 (0.71 to 0.96)**	**.011**	**-0.11**
Trust in pharmaceutical companies	5.42 (1.63)	**-0.50 (-0.88 to -0.11)**	**.013**	**-0.43**	**0.74 (0.60 to 0.90)**	**.003**	**-0.17**

Table 1. Predictors of side-effect expectations: warned vs non-warned

Note:
*Controlling for age, ethnicity and experimental condition which significantly correlates with warned-side effects
**Controlling for experimental condition which significantly correlates with non-warned side-effects
- = Reference category
MHW = modern health worries, BMQ = beliefs about medicines, PSM = perceived sensitivity to medicine
Bold = remains significant after correcting for multiple testing using the Benjamini & Hochberg procedure

Discussion

Summary of main results

Patients' expectation of side-effects may extend beyond those which are warned about in communication from official sources such as clinicians or PILs. These expectations can affect

patients' engagement with and adherence to their treatment. It is important to identify predictors of patient side-effect expectations, however most previous research has used hypothetical scenarios and only asked participants about their expectations of side-effects which they have already been warned about (11). This study builds on this by replicating factors in a situation where participants are about to receive what they believe is an active medication and also asks participants about their expectation of side-effects which extended beyond the PIL they received.

We found that the majority of participants did expect side-effects that were warned about in the PIL, but almost 30% of participants also expected side-effects that were not warned about. Therefore, although PILs are an important source of side-effect expectations, there are other factors at play.

Participants' age, ethnicity, change in anxiety after reading the PIL, and optimism were significantly associated with expectations of side-effects that were warned about in the PIL. This supports the findings by Smith, et al. (11) showing no evidence of associations with gender, education or employment status, some evidence for associations with anxiety, and adds to the mixed findings regarding associations between age, ethnicity and side-effect expectations. It contradicts previous findings on optimism. Looking into this in more detail, the studies that showed no association with age or that older participants had higher side-effect expectations were of studies about hypothetical situations, whereas the non-hypothetical studies tended to show that younger participants had higher side-effect expectations (11). This may be because younger adults do not have much experience or knowledge about medications and are therefore more influenced by the PIL than older adults. We are unsure why people from ethnic minorities had lower side-effect expectations, however, a previous lack of association between optimism and side-effect expectations

maybe a result of the hypothetical nature of past studies (13, 25), in which optimism may not play as strong a role.

For expectation of side-effects which were not described in the PIL, demographics, anxiety and optimism had no effect, and instead participants' medication-related beliefs were important predictors. These have shown to be associated with side-effect expectations in the past (13, 25). Their particular influence on side-effects that are not discussed in the PIL may be precisely because there is little influence of the PIL, allowing more scope for a person's general beliefs about medication to play a role. In line with this, positive framing reduced side-effect expectations of those side-effects mentioned in the PIL, supporting previous findings (26), however this effect did not translate to expectations of side-effects that were not mentioned in the PIL. This may be why Faasse, et al. (27) did not find a framing effect on side-effect expectations, as they only framed four symptoms and asked for participants side-effect expectations as a whole, as such they may have expected more symptoms than the four just presented to them. Interestingly we found no significant interactions between the individual difference variables (demographics, symptoms, psychological factors or medication beliefs) and side-effect framing, demonstrating that positive framing was similarly effective in reducing expectations of warned side-effects regardless of participants' individual differences.

For all side-effect expectations (both warned in the PIL and not warned), participants' somatisation, baseline symptoms, modern health worries and trust in pharmaceutical companies were important predictors. This supports the findings from Smith, et al. (11) that people who are currently experiencing symptoms have increased side-effect expectations. To our knowledge, this is the first study to investigate an effect of somatisation, modern health worries and trust in pharmaceutical companies on side-effect expectations.

Limitations

One limitation inherent in our design is that those who took part in the study are likely to be more generally trusting of medications compared to the general population. As such participants' expectation of side-effects may be an underrepresentation. On the other hand as participants were directly asked to report on 23 possible side-effects after having read the PIL, it is possible that they would not have considered these side-effects independently under 'normal' circumstances and so this could have inflated side-effect expectations. Related to concerns about representativeness, the sample were particularly well-educated, with 65% having a higher education qualification, and young with a mean age of 27. This lack of representativeness may have introduced biased associations (28).

The sample size calculation for this study was based on the requirements of our linked RCT, rather than the ability to assess associations between baseline measures and side-effect expectations. As such the results reported here should be interpreted with caution, as we may have missed weak associations.

Another potential limitation is the fact we used percentages for the positive framing PIL rather than natural frequencies, and therefore the results of the framing effect may be due to this difference. Percentages were initially chosen to make the positively framed PIL as effective as possible since evidence has shown that percentages can elevate perceptions of likelihood compared to the corresponding natural frequencies (29). However, we have since tested this in a more recent study comparing positive framing using percentages and natural frequencies and found no difference in side-effect expectations between the two (30) as such we believe it is unlikely to have played a role in the findings.

Finally, in our study we chose to minimise the amount of deception required by informing participants that we would not tell them the identity of the tablet until after the study was completed, rather than providing them with a false cover story (31). One positive feature of this procedure is that our results were not influenced by participants' idiosyncratic

preconceived perceptions about the side-effects of any one specific medicine. However, we recognise that these preconceptions may be important to consider in real-world healthcare scenarios when participants have a specific ailment and drug action in mind when taking medication. This divergence from a real-world scenario may have contributed to the low rate of side-effect expectations, especially for those not warned about, as such contributing to the potential for missing weak associations in the data.

Implications for clinical practice

The benefits of positively framing side-effect risk do not seem to extend to the expectations participants have of side-effects that have not been warned about. This suggests we cannot only rely on altering how we communicate side-effect risk to reduce side-effect expectations and therefore nocebo effects. Clinicians should also consider patients' medication beliefs so these can be addressed and unnecessary expectation of side-effects reduced. It may be particularly effective for clinicians to address patients' somatisation, baseline symptoms, modern health worries and trust in pharmaceutical companies as these seem to affect side-effect expectations across the board. For example helping patients to think about the symptoms they experience (e.g. do they disappear when you are distracted, are there other possible explanations) may help patients reassess what is a side-effect and what isn't and therefore their expectations. In addition addressing any concerns they have about pharmaceutical companies can provide reassurance and reduce expectations. We recognise that trying to address these factors in time-limited consultations is a difficult ask and therefore innovative ways to tackle these unhelpful beliefs are needed.

Future research

Given the limitations of the exploratory nature of this study it is important to replicate this investigation in a patient sample about to take a known medication in order to build on the results presented here and the evidence base previously reviewed (11). This will help to

confirm if the significant associations found here translate to a clinical setting where the medication is known to patients, and identify if there are any other factors that could be important. For example the effect of information from media sources (32) on side-effect expectations could be important especially in terms of generating expectations of side-effects that go beyond those that are communicated to patients by a clinician or in patient information leaflets as they tend to focus on the more unusual or extreme cases. In addition future work could look at interventions which focus on increasing the positivity of patients (e.g. (33)) rather than the positivity of the communication of side-effects which might be more beneficial in reducing expectations of side-effects across the board and therefore nocebo effects.

Conclusions

The results presented here suggest it is important that we do not only rely on altering how we communicate side-effect risk to reduce side-effect expectations and therefore nocebo effects. We must also consider patients' beliefs about medicines and their trust in medicines, and develop feasible interventions to address these so that unnecessary expectation of side-effects are reduced. More work is needed in patient samples where the medication is known to them to verify the associations presented here and to investigate other potential influences on side-effect expectations such as information sources, e.g. social media, google.

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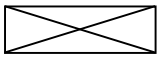
Supplementary material 1

Standard worded patient information leaflet

Package Leaflet: Information for the user

XXXXXXX hard tablets

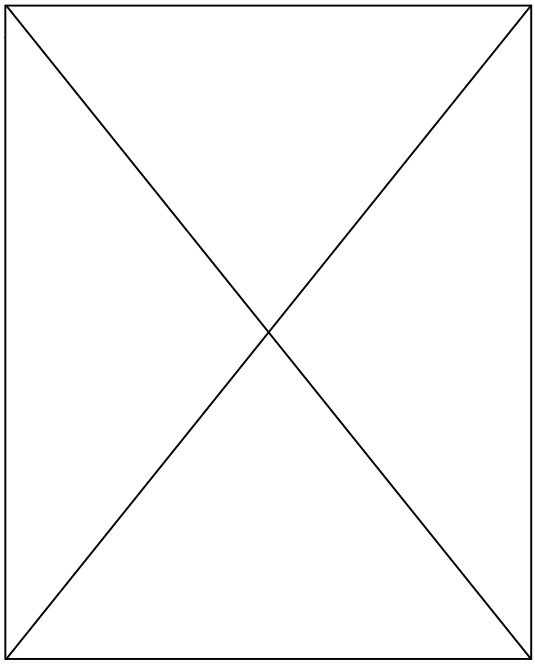


Read this leaflet carefully because it contains important information for you.

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

What is in this leaflet

1. What XXXXXXX is and what it is used for



2. What you need to know before you take XXXXXXX

Do not take XXXXXXX:

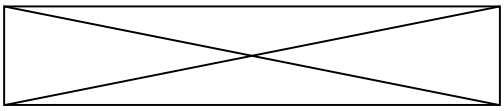
- **if you are allergic** to any of the ingredients of XXXXXXX listed in section 6.

Warnings and precautions:

Before you take XXXXXXX, talk to your doctor

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

Other tablets and XXXXXXX



Pregnancy and breast-feeding

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

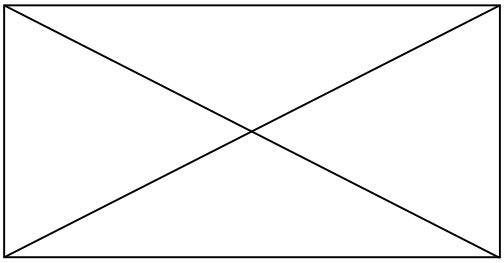
Driving and using machines

XXXXXXX has been known to have an effect on your ability to drive or use machines due to the occurrence of possible side effects. If you are affected do not drive or use machines until the side effects wear off.

3. How to take XXXXXXX

Take this tablet exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses



Method of administration
Swallow the tablet with water. The tablet can be divided into two equal halves.
Do not chew the tablet.
XXXXXXX can be taken with or without food. But it is recommended to be taken without food to achieve the greatest effect.

If you take more XXXXXXX than you should
Stop taking XXXXXXX.
In most cases of overdose, people have reported an increased number and severity of side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.

If you forget to take XXXXXXX
Take the next tablet as soon as you remember.

4. Possible side effects

Like all tablets, this tablet can cause side effects, although not everybody gets them. These side effects mostly occur within one hour after taking the first tablet and will usually stop as you continue to take them.

Very common side effects
(More than 1 in 10 people will be affected)
- Headache
- Nausea

Common side effects
(1 in 10 people will be affected)
- Cough
- Dizziness
- Pain in limb
- Runny nose
- Sore throat
- Stomach ache
- Tiredness
- Bloating

Uncommon side effects
(1 in 100 people will be affected)
- Itchy skin

Rare side effects
(1 in 1,000 people will be affected)
- Confusion
- Agitation
- Anxiety

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

5. How to store XXXXXXX

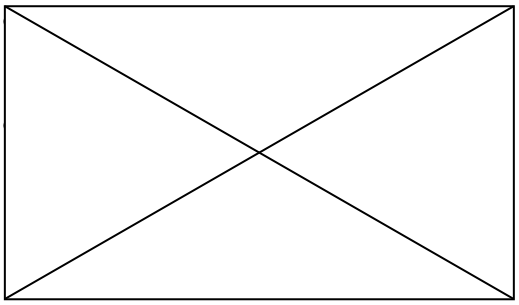
Keep out of the sight and reach of children.
Do not use this tablet after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25 ° C.

Do not throw away any tablets via wastewater or household waste. Ask your pharmacist how to throw away tablets you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What XXXXXXX contains



What XXXXXXX looks like
The tablets have a round white opaque body with a breakline.

This leaflet was last revised in 08/2015

Positively worded patient information leaflet

The only difference in the positively framed leaflet was the information which occurred in Section 4 as follows:

4. Possible side effects

Like all tablets, this tablet can cause side effects, although not everybody gets them. These side effects mostly occur within one hour after taking the first tablet and will usually stop as you continue to take them.

Uncommon side effects
(80% of people will not be affected)
- Headache
- Nausea

Very uncommon side effects
(90% of people will not be affected)
- Cough
- Dizziness
- Pain in limb
- Runny nose
- Sore throat
- Stomach ache
- Tiredness
- Bloating

Rare side effects
(99% of people will not be affected)
- Itchy skin

Very rare side effects
(99.9% of people will not be affected)

Supplementary material 2: Moderation analyses

Interactions* between each predictor variable and leaflet condition on warned side-effect expectations

Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.180	8.627	5	197	<.001
Condition	3.665	0.777	4.714	<.001					
Gender	0.508	0.980	0.518	.605					
Condition x Gender	-2.594	1.378	-1.883	.061					
Age	-0.127	0.038	-3.331	.001					
Ethnicity	-1.742	0.665	-2.621	.009					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.161	9.484	4	198	<.001
Condition	2.850	0.649	4.390	<.001					
Age	-0.113	0.054	-2.093	.038					
Condition x Age	-0.040	0.075	-0.531	.596					
Ethnicity	-1.646	0.670	-2.458	.015					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.168	9.969	4	198	<.001
Condition	3.581	0.836	4.281	<.001					
Ethnicity	-0.789	0.922	-0.856	.393					
Condition x Ethnicity	-1.827	1.322	-1.382	.168					
Age	-0.129	0.038	-3.420	.001					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.162	7.604	5	197	<.001
Condition	2.815	0.840	3.350	.001					
Employment	-0.655	1.064	-0.616	.539					
Condition x Employment	0.237	1.361	0.174	.862					
Age	-0.119	0.043	-2.783	.006					
Ethnicity	-1.710	0.677	-2.527	.012					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.161	7.555	5	197	<.001
Condition	2.794	0.807	3.460	.001					
Education	0.309	0.981	0.315	.753					
Condition x Education	0.124	1.366	0.091	.928					
Age	-0.131	0.038	-3.405	.001					
Ethnicity	-1.648	.671	-2.456	.015					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.183	8.833	5	197	<.001
Condition	2.915	0.643	4.536	<.001					
Anxiety	0.358	0.260	1.373	.171					
Condition x Anxiety	0.192	0.384	0.501	.617					
Age	-0.133	0.038	-3.544	<.001					
Ethnicity	-1.760	.661	-2.661	.008					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.204	10.100	5	197	<.001
Condition	2.810	0.634	4.431	<.001					
Optimism	-0.024	0.128	-0.187	.852					
Condition x Optimism	-0.361	0.173	-2.081	.039					
Age	-0.123	0.037	-3.309	.001					
Ethnicity	-1.528	0.654	-2.337	.020					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.230	11.790	5	197	<.001
Condition	2.753	0.624	4.414	<.001					
Somatisation	0.187	0.127	1.478	.141					
Condition x Somatisation	0.409	0.194	2.110	.036					
Age	-0.112	0.037	-3.055	.003					
Ethnicity	-1.386	0.645	-2.147	.033					
Effects	B	SE	t	*p*	R^2	F	df1	df2	*p*
Model					0.172	8.208	5	197	<.001
Condition	2.882	0.647	4.457	<.001					

Somatosensory amplification	0.061	0.086	0.711	.478					
Condition x Somatosensory amplification	0.045	0.108	0.417	.677					
Age	-0.134	0.038	-3.558	<.001					
Ethnicity	-1.825	0.671	-2.720	.007					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.241	12.502	5	197	<.001
Condition	3.103	0.622	4.992	<.001					
Symptoms 24 hours	0.323	0.153	2.120	.035					
Condition x Symptoms 24 hours	0.403	0.233	1.731	.085					
Age	-0.109	0.036	-2.995	.003					
Ethnicity	-1.342	0.641	-2.095	.037					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.206	10.219	5	197	<.001
Condition	2.905	0.633	4.58	<.001					
MHW	0.053	0.023	2.328	.021					
Condition x MHW	0.004	0.031	0.130	.897					
Age	-0.165	0.038	-4.330	<.001					
Ethnicity	-2.052	0.661	-3.106	.002					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.161	7.557	5	197	<.001
Condition	2.837	0.651	4.357	<.001					
BMQ Overuse	0.065	0.147	0.441	.660					
Condition x BMQ Overuse	-0.014	0.200	-0.073	.942					
Age	-0.139	0.039	-3.520	.001					
Ethnicity	-1.668	0.673	-2.479	.014					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.161	7.541	5	197	<.001
Condition	2.843	0.651	4.36	<.001					
BMQ Harm	0.075	0.173	0.436	.664					
Condition x BMQ Harm	-0.030	0.243	-0.123	.902					
Age	-0.138	0.040	-3.478	.001					
Ethnicity	-1.709	0.676	-2.529	.012					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.175	8.362	5	197	<.001
Condition	2.892	0.646	4.476	<.001					
PSM	-0.002	0.164	-0.014	.989					
Condition x PSM	0.319	0.232	1.372	.172					
Age	-0.147	0.038	-3.823	<.001					
Ethnicity	-1.612	0.667	-2.417	.017					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					0.170	8.082	5	197	<.001
Condition	2.906	0.649	4.481	<.001					
Trust in Medicine	-0.033	0.213	-0.155	.877					
Condition x Trust in Medicine	-0.321	0.310	-1.036	.301					
Age	-0.130	0.038	-3.431	.001					
Ethnicity	-1.646	0.668	-2.464	.015					
Effects	**B**	**SE**	**t**	***p***	***R²***	**F**	**df1**	**df2**	***p***
Model					.191	9.323	5	197	<.001
Condition	2.895	0.639	4.530	<.001					
Trust in Pharma	-0.291	0.262	-1.112	.268					
Condition x Trust in Pharma	-0.472	0.396	-1.190	.236					
Age	-0.124	0.037	-3.310	.001					
Ethnicity	-1.447	0.663	-2.182	.030					

Note:

* Controlling for each term in the interaction and age and ethnicity which significantly correlates with warned side-effects

MHW = modern health worries, BMQ = beliefs about medicines, PSM = perceived sensitivity to medicine

Continuous predictors have been mean centred

After correcting for multiple testing using the Benjamini & Hochberg procedure, none of the interactions remain significant

Interactions* between each predictor variable and leaflet condition on non-warned side-effect expectations

Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.037	5.358	3	.147
Condition	0.675	0.393	2.944	.086				
Gender	0.387	0.492	0.619	.431				
Condition x Gender	-0.074	0.661	0.012	.911				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.048	6.972	3	.073
Condition	0.643	0.320	4.051	.044				
Age	-0.024	0.031	0.78	.447				
Condition x Age	-0.015	0.042	0.120	.729				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.053	7.688	3	.053
Condition	1.067	.420	6.451	.011				
Ethnicity	0.367	.475	0.597	.440				
Condition x Ethnicity	-1.124	.661	2.889	.089				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.039	5.587	3	.134
Condition	0.933	0.406	5.292	.021				
Employment	0.387	0.492	0.619	.431				
Condition x Employment	-0.747	0.649	1.326	.250				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.040	5.706	3	.127
Condition	0.796	0.405	3.852	.050				
Education	0.567	0.487	1.357	.244				
Condition x Education	-0.417	0.649	0.413	.521				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.056	8.053	3	.045
Condition	0.721	0.326	4.888	.027				
Anxiety	0.279	0.150	3.471	.062				
Condition x Anxiety	-0.308	0.198	2.431	.119				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.044	6.372	3	.095
Condition	0.623	0.317	3.853	.050				
Optimism	-0.033	0.068	0.241	.623				
Condition x Optimism	-0.041	0.087	0.219	.640				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.086	12.635	3	.005
Condition	0.646	0.326	3.918	.048				
Somatisation	0.143	0.066	4.721	.030				
Condition x Somatisation	-0.011	0.097	0.014	.907				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.042	6.001	3	.112
Condition	0.057	0.321	4.581	.032				
Somatosensory amplification	-0.045	0.045	1.579	.209				
Condition x Somatosensory amplification	-1.275	0.054	0.698	.404				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.088	12.867	3	.005
Condition	0.791	0.332	5.667	.017				
Symptoms 24 hours	0.213	0.080	7.110	.008				
Condition x Symptoms 24 hours	-0.122	0.115	1.130	.288				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.090	13.184	3	.004
Condition	0.764	0.332	5.291	.021				
MHW	0.031	0.012	7.142	.008				
Condition x MHW	-0.018	0.015	1.426	.232				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***

Model					0.092	13.578	3	.004
Condition	0.745	0.335	4.963	.026				
BMQ Overuse	0.229	0.082	7.843	.005				
Condition x BMQ Overuse	-0.181	0.103	3.071	.080				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.071	10.311	3	.016
Condition	0.719	0.327	4.840	.028				
BMQ Harm	0.210	0.089	5.577	.018				
Condition x BMQ Harm	-0.248	0.119	4.365	.037				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.054	7.836	3	.050
Condition	0.690	0.321	4.602	.032				
PSM	0.122	0.079	2.348	.125				
Condition x PSM	-0.040	0.108	0.135	.713				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.080	11.678	3	.009
Condition	0.779	0.334	5.445	.020				
Trust in Medicine	-0.268	0.117	5.228	.022				
Condition x Trust in Medicine	0.130	0.156	0.699	.403				
Effects	**B**	**SE**	**Wald**	***p***	***R²***	**X²**	**df**	***p***
Model					0.098	14.467	3	.002
Condition	0.774	0.338	5.235	.022				
Trust in Pharma	-0.412	0.155	7.068	.008				
Condition x Trust in Pharma	0.201	0.210	0.922	.337				

Note:

* Controlling for each term in the interaction

MHW = modern health worries, BMQ = beliefs about medicines, PSM = perceived sensitivity to medicine

Continuous predictors have been mean centred

After correcting for multiple testing using the Benjamini & Hochberg procedure, none of the interactions remain significant