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REGULAR ARTICLE

Beliefs About Medicines Predict Side-Effects of Placebo Modafinil

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Abstract

Background Patients receiving placebo in clinical trials often report side-effects (nocebo effects), but contributing factors are still poorly understood.

Purpose Using a sham trial of the cognition-enhancing "smart pill" Modafinil we tested whether medication beliefs and other psychological factors predicted detection and attribution of symptoms as side-effects to placebo.

Methods Healthy students (n = 201) completed measures assessing beliefs about medication, perceived sensitivity to medicines, negative affectivity, somatization, and body awareness; 66 were then randomized to receive Deceptive Placebo (told Modafinil–given placebo, 67 to Open Placebo (told placebo–given placebo, and 68 to No Placebo. Memory and attention tasks assessed cognitive enhancement. Nocebo effects were assessed by symptom checklist.

Results More symptoms were reported in the Deceptive Placebo condition (M = 2.65; SD = 2.27) than Open Placebo (M = 1.92; SD = 2.24; Mann–Whitney U = 1,654, z = 2.30, p = .022) or No Placebo (M = 1.68; SD = 1.75, Mann–Whitney U = 1,640, z = 2.74, p = .006). Participants were more likely to attribute symptoms to Modafinil side-effects if they believed pharmaceuticals to be generally harmful (incidence rate ratio [IRR] = 1.70, p = .019), had higher perceived sensitivity to medicines (IRR = 1.68, p = .011), stronger concerns about Modafinil (IRR = 2.10, p < .001), and higher negative affectivity (IRR = 2.37, p < .001).

Conclusions Beliefs about medication are potentially modifiable predictors of the nocebo effect. These findings provide insight into side-effect reports to placebo and, potentially, active treatment.

Keywords: Nocebo · Medication beliefs · Open-label placebo · Beliefs about Medicines Questionnaire (BMQ) · Necessity Concerns Framework (NCF) · Nocebo mechanisms

Introduction

The prescription of medicine is one of the most common interventions in health care systems. Although medicines have health benefits, they can also have a negative impact through the experience of side-effects. Medication side-effects are common [1] and distressing for patients, leading to decreased quality of life [2] and reduced adherence [3, 4].

A side-effect can be pragmatically defined as a symptom or unwanted effect that is attributed to the medicine [5]. Some side-effects are specific to a particular medicine and are an extension of the pharmacological effect of the medicine. Other side-effects (e.g., headache, fatigue, gastrointestinal symptoms) appear to be less specific and are common across different types of medicines [6]. Similar symptoms are also commonly reported as side-effects in the placebo arm of clinical trials [7–9] and are highly prevalent even in healthy untreated volunteers [10, 11].

Nocebo effects, which are often defined as adverse effects that follow the administration of pharmacologically inactive medication [12, 13], are surprisingly frequent. Meta-analyses examining side-effect data from clinical trials for the treatment of Parkinson's disease [14], Alzheimer's disease [15], and fibromyalgia [16] found that many patients in the placebo arm of trials (sometimes >50%) report side-effects. In some cases, these nocebo effects are so burdensome that patients subsequently withdraw from the trial [13, 14]. Nocebo effects are important in clinical practice as

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they can add to the perceived side-effect burden in patients taking active medication, thereby reducing patients' willingness to take their treatment as prescribed [17].

While there is abundance of studies documenting these apparent nocebo side-effects (i.e., symptom reporting following placebo administration) either through examination of data from patients in the placebo arm of randomized controlled trials (RCTs) or from participants receiving pharmacologically inactive substances in experimental settings [18–20], there is a distinct lack of studies using appropriate control groups [21]. Yet without an appropriate control group it is impossible to tell whether patients receiving placebo treatment would have experienced symptoms regardless of any placebo administration. In addition, little is known about nocebo mechanisms or psychological characteristics that distinguish between high and low nocebo responders [20, 22]. There is growing evidence that mechanisms influencing placebo responses such as conditioning [23], expectations [17, 24], and cognitive reappraisal [25] may also be relevant to nocebo responses, could interact with psychological patient characteristics [25] and that it may be possible to reduce the nocebo effect by targeting these mechanisms [26, 27].

Experimental Design and the Nocebo Effect

One common test for the nocebo effect is to randomize participants to either a nocebo (typically a placebo labeled as an active treatment and described as having negative effects) or a no treatment (Natural History) group and to assess whether participants report more symptoms in the placebo group than natural history [28, 29]. It is then assumed that any difference between groups arises from the effect of the placebo condition with the natural history group controlling for unrelated "everyday" symptom reports. However, volunteering for a trial of an active treatment and then being randomized to receive nothing may also influence participants' expectations of symptoms, emotions, or other mechanisms linked to the nocebo effect [28]. It is also not possible to probe attribution of symptoms as side-effects in this group as no drug is given to which symptoms could be attributed to. Potentially, receiving a placebo could increase symptom reporting but not increase the attribution of these symptoms as side-effects. Other researchers [30, 31] have suggested that an open-label placebo group (i.e., whereby individuals are correctly informed that the administered pill is pharmacologically inactive) could serve as another potential control group. For example, in the half-balanced placebo design, all participants are given placebo but are explicitly told that it is either a placebo (Open Placebo) or the active drug (Deceptive Placebo) [32]. Differences in negative outcomes between these groups can be interpreted as evidence for nocebo effect, assuming that participants believe and understand the information given in the Open Placebo condition [30]. A three-arm design was therefore chosen for the present study: Deceptive Placebo–Open Placebo–Natural History.

As it is difficult to conduct experimental nocebo research in patients taking active medication, we set up a sham clinical trial in healthy students, who were told they were participating in a trial to examine the efficacy and safety of the cognition-enhancing "smart pill" Modafinil. This was chosen as a "cover story" because the off-label use of prescription stimulants like Modafinil and Adderall to boost cognitive performance has received extensive media attention, especially in relation to student groups [33]. However, the cognition-enhancing effects of Modafinil in healthy samples are still unclear [34], providing a convincing rationale for a trial. In the trial, we examined the number of symptoms individuals detected and attributed as side-effects when receiving either Deceptive Modafinil Placebo (told Modafinil–given placebo), Open Placebo (told placebo–given placebo), or no placebo (Natural History).

Symptom reporting in response to placebo varies wildly across individuals and conditions. To try to ensure that trial participants experienced a sufficient number of sensations that they could attribute to the effect of the placebo, we aimed to subtlety induce two symptoms (itch and dizziness) using visual stimuli in all three experimental groups. We also used objective measures of memory and sustained attention allowing us to test whether there was a placebo effect on cognitive performance.

Psychological Predictors of the Nocebo Effect

Another under-researched aspect of the nocebo effect is the putative contributing role of some psychosocial factors, in particular, the role of specific and general medication beliefs [35, 36] and perceptions of personal sensitivity to medicines [37], negative affectivity, somatization, and attention to bodily sensations.

Studies have demonstrated the importance of treatment beliefs in shaping treatment expectations [38], coping behaviors (e.g., adherence) [36, 39–41], and symptom appraisal [42]. Horne's model of cognitive representations of treatment proposes that attitudes to a particular medicine are shaped by how the individual judges their personal need for treatment (necessity beliefs) relative to their concerns about potential harms and other negative consequences of using it (Concerns; The Necessity Concerns Framework [36]).

These evaluations of specific medicines are influenced by more general pharmaceutical schemas [41, 43, 44]. Pharmaceutical schemas are beliefs that individuals have about pharmaceutical medicines as a class of treatment, for example, beliefs about harms, benefits and overuse of pharmaceuticals [41, 45, 46], and the self in relation to medicines (i.e., perceived sensitivity to the effects of medicines [37]).

In clinical studies, Horne's model of specific and general medication beliefs has proven useful in explaining variation in treatment adherence [44, 47–49]. The approach has also been applied to understanding variation in reporting of side-effects in response to pharmacological treatment with patients' concerns about treatment at baseline predicting the subsequent emergence of side-effects to active medication [5, 50]. A recent study in healthy volunteers all given a sham treatment demonstrated that negative medication beliefs, specifically worries about the effect of new technologies on health, perceptions of personal sensitivity to medicine and the belief that medicines generally cause harm, were associated with increased attribution of symptoms to the sham medicine [51]. However, no comparison with a control group was included in this study. Analog studies exploring mechanisms of nocebo effects have also identified the potential role of specific and general medication beliefs. For example, individuals reading a scenario in which they experienced a common symptom (headache) after starting a new treatment were more likely to misattribute it as a side-effect if they held more negative pharmaceutical schemas and had stronger concerns about the medication [52, 53].

There is considerable evidence for the role of psychological factors in symptom perception in general: negative affectivity [54], somatization [55], and attention to bodily sensations [56] have been shown to increase symptom reporting overall and in patients with medically unexplained symptoms [57]. It is thus plausible that these factors may lead to an increase in the detection of symptoms, which could be subsequently labeled as side-effects in individuals receiving placebo.

The aim of the proposed study is therefore twofold: (a) test whether there is a true nocebo effect by comparing symptom and side-effect reporting in participants receiving placebo treatment versus an appropriate control group; (b) explore the putative contributing role of psychological factors to nocebo side-effect reporting and symptom reporting.

This research design allowed us to test the following hypotheses:

H1: Participants randomized to receive deceptive Modafinil placebo would report more symptoms than those randomized to open-label placebo or no placebo.

H2: Participants with more negative pharmaceutical schemas (beliefs that pharmaceuticals are generally harmful, high perceived sensitivity to medicines) and concerns about the study pill would report more side-effects when receiving deceptive Modafinil placebo.

Methods

Participant Recruitment and Inclusion Criteria

Students were invited via posters and electronic newsletters to participate in a placebo-controlled trial to evaluate the efficacy and safety of Modafinil. Upon contacting the experimenter, participants were e-mailed an information sheet and a prescreening questionnaire to determine eligibility. Participants were eligible to participate if they were over 18 years of age, healthy, and not taking any medication (except hormonal contraceptives). Participants received £10 for their participation in the 60-min study.

Design and Randomization

The Qualtrics block randomization function was used to randomize participants to one of the following three (between-group) experimental conditions:

1) Deceptive Placebo: told Modafinil–given placebo
2) Open Placebo: told placebo–given placebo
3) Natural History: no placebo given

Participants were informed about their allocation by the computer but told to conceal the condition allocation (placebo arms only) from the experimenter by revealing only their randomization code, which was identical in both placebo conditions (see Fig. 1).

Materials

Before randomization to experimental conditions all participants were given information about Modafinil and the placebo pill, summarized below:

Modafinil patient information leaflet

The Modafinil patient information leaflet (see Supplementary Material A) was adapted from the leaflet of commercially available Modafinil and contained information about its indication, off-label uses, contraindications, and possible interactions with other medications and a list of possible side-effects (which included the induced symptoms itch and dizziness).

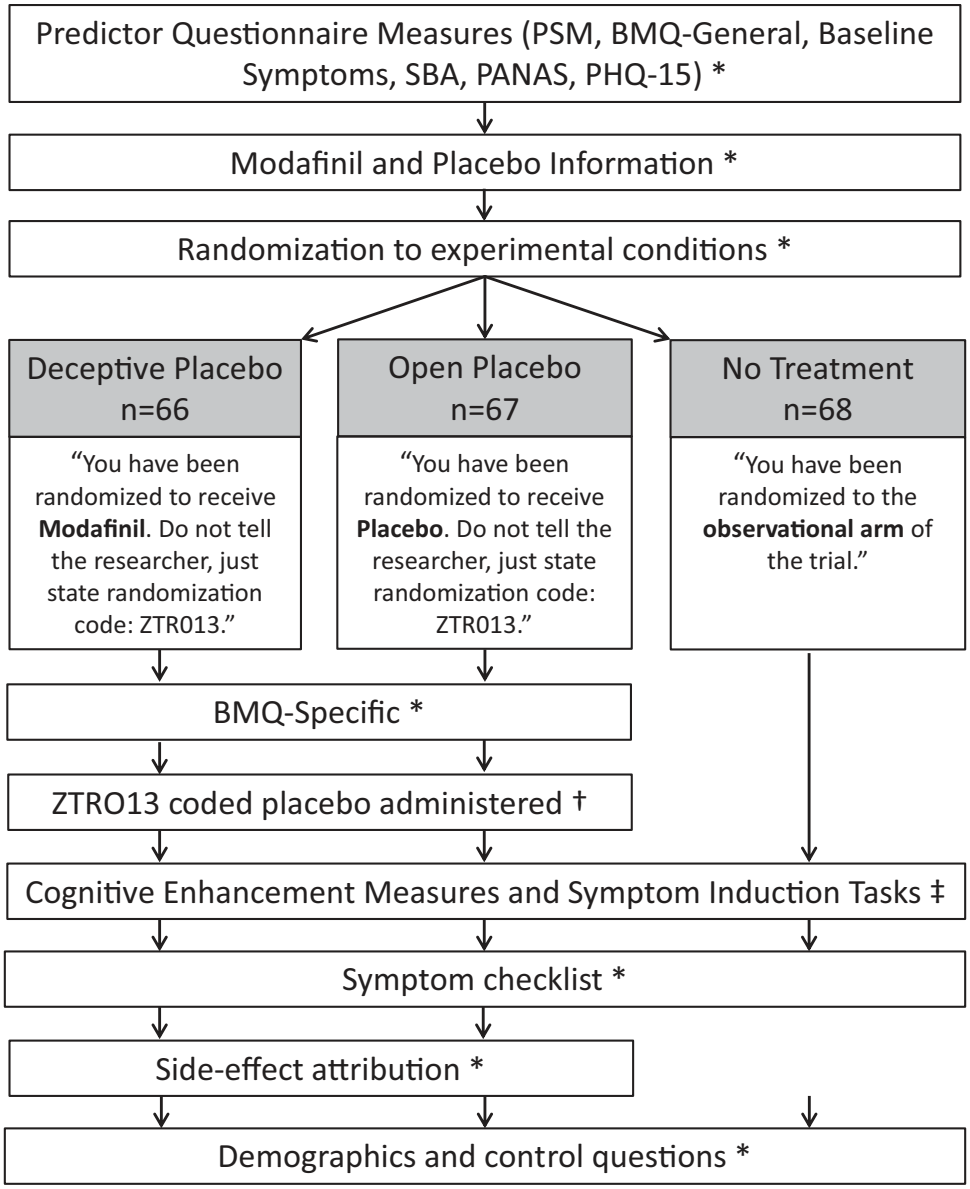

Fig. 1. Overview experimental design and measures. Mode of administration: *Qualtrics survey software, †experimenter, ‡E-prime; *BMQ* Beliefs about Medicines Questionnaire; *PANAS* Positive and Negative Affect Schedule; *PHQ-15* Patient Health Questionnaire—Somatization Scale; *PSM* Perceived Sensitivity to Medicines Scale; *SBA* Scale of Body Awareness.

Placebo information

Participants received the following information about the placebo pills, which was adapted from a review on typical descriptions of placebos in RCTs [58]: "A placebo is a 'dummy treatment', which looks like the genuine medicine but contains no active ingredient. It is used in clinical trials to assess the efficacy and safety of an active drug by comparing the outcomes in the placebo group to outcomes in the active treatment group. Please note that the placebo tablets used in this study contain sucrose (table sugar) and gelatin and no active medication. The placebo pills have been manufactured according to industry standards to ensure that they are not contaminated by any active ingredients in the manufacturing process." It should be noted that this manipulation differed from other Open Placebo manipulations (e.g., [32]) as it did not include a statement suggesting that the placebo might have a positive effect. We wanted to parallel information given in a usual clinical trial, where there would be little suggestion that the placebo would be effective.

Placebo pills

The placebo pills used in the study were sucrose filled gelatin caps.

Predictor Questionnaire Measures

Perceived Sensitivity to Medicines

The Perceived Sensitivity to Medicines (PSM) [37] assesses beliefs about personal susceptibility to the effects of medication with 5 items (e.g., My body is very sensitive to medicines), which are rated on 5-point Likert scales (1 = strongly disagree to 5 = strongly agree). As per standard analysis a mean PSM score was computed by dividing the sum of item ratings by the number of scale items. Higher scores indicate greater PSM. Internal consistency was high (Cronbach's $\alpha = .85$).

Beliefs about Medicines Questionnaire

Participants' beliefs about the study pill they were randomized to (after allocation information) were assessed with the Beliefs about Medicines Questionnaire (BMQ)-Specific and general beliefs about pharmaceutical medicines as a class of treatment with the BMQ-General. The BMQ-Specific [45] comprises two scales capturing individuals' beliefs about the necessity of a specific treatment (Specific Necessity, e.g., "Without this pill I would perform poorly") and concerns about potential adverse consequences of taking it (Specific Concerns, e.g., "Having to take this pill worries me"). The BMQ-General comprises three scales assessing views about pharmaceutical medicines as a whole. The General Harm scale assesses beliefs about the degree to which medicines are perceived as 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. The General Benefit scale assesses views about the benefits of medicines (e.g., "In most cases the benefits of medicines outweigh the risks"). All items are rated on 5-point Likert scales (1 = strongly disagree to 5 = strongly agree). As per standard analysis scale scores were computed by summing scale item scores and dividing it by the number of scale items. Higher scores indicate stronger endorsement of scale constructs. All BMQ scales had adequate internal consistency (Cronbach's αs ranging between .64 and .75).

Baseline symptoms

A symptom checklist proposed by Pennebaker [56] was used to ascertain whether participants differed on baseline symptoms they were experiencing prior to randomization. Participants were asked to indicate on 7-point bipolar rating scales (e.g., 1 = no headache to 7 = headache) whether they were currently experiencing any of 12 listed symptoms (e.g., headache, itch, dizziness). A total baseline symptom score was computed by summing ratings (Cronbach's $\alpha = 0.77$).

Positive and Negative Affect Schedule

State Negative Affect (NA) was assessed with the short form of the Positive and Negative Affect Schedule (PANAS) [59]. Participants were asked to indicate to what extent (from 1 = not at all to 5 = extremely) they generally experience 10 negative (e.g., distressed, upset) and 10 positive feelings (e.g., excited, relaxed). State NA and Positive Affect (PA) scores were computed by summing scores for all negative and positive adjectives, respectively. Internal consistency was high (Cronbach's αs > .83).

Patient Health Questionnaire

Somatization was assessed with the Patient Health Questionnaire (PHQ-15) [57]. The PHQ-15 contains a list of 15 symptoms and participants are asked to indicate whether they have been bothered by each symptom during the past 4 weeks on a 3-point Likert scale (0 = not bothered at all, 1 = bothered a little, 2 = bothered a lot). For the purposes of the study, the female only item (menstrual cramps) was replaced with "racing heart." Individual item scores were summed to form a total score. Internal consistency was good (Cronbach's $\alpha s = 0.71$).

Scale of Body Awareness

Individuals' cognitions about bodily sensations were assessed with the Scale of Body Awareness (SBA) [60]. The SBA contains four items (e.g., How much do you think about how your body feels?) which are rated on 5 Likert scales ranging from 1 = very little to 5 = very much. An SBA score was computed by summing item scores (Cronbach's $\alpha s = 0.83$).

Baseline Variables

Demographics

Participants were asked to indicate their age, gender, ethnic background, and first language.

Self-focused attention

Participants indicated on a 7-point Likert scale (from 1 = not at all to 7 = very much) how closely they had paid attention to changes in bodily sensations during the study.

Symptom Induction Tasks

Itch induction

Itch sensations were induced using six mages of insects crawling on skin that were embedded among other stimuli

(i.e., pictures of flowers, positive and negative affective pictures) in an alleged reaction time task involving the categorization of images. Functional magnetic resonance imaging studies have shown that this type of imagery can be effective in inducing itch [61] by activating neural regions linked to the physical perception of itch [62].

Dizziness/vertigo induction

Dizziness/vertigo was induced using black and white concentric circles as a background picture in another bogus reaction time task (see Supplementary Material B). Similar black and white patterned stimuli [62, 63] have been used to examine visually induced vertigo. Participants were instructed to press the spacebar as soon as a blue dot that moved across the patterned background changed to red.

Symptom and Side-Effect Reporting Measures

Symptom checklist

Participants were shown a checklist which was based on a highly modified version of the Illness Perception Questionnaire Identity scale [64]. It contained 25 symptoms (17 of which had been listed in the Modafinil leaflet and the remainder of which were common symptoms) and two textboxes allowing participants to specify other symptoms. The order of the 25 symptoms was randomized. Participants were asked to indicate (yes/no) whether they had noticed each symptom, and the number of symptoms they reported was summed.

Side-effect attribution

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

Scratching

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

Cognitive Enhancement Measures

Both subjective (perceived improvement) and objective (standardized cognitive tasks) outcome data were collected.

Perceived cognitive enhancement

Participants were asked to rate their alertness, ability to concentrate, and ability to remember on 100-point visual analog scales (VASs) ranging (0 = less than usual, 50 = no change, 100 = more than usual). A mean perceived cognitive enhancement score was computed by averaging the responses across the three VASs (Cronbach's $\alpha = 0.86$).

Wechsler Auditory Digit Span Test

A computerized version of the Wechsler Auditory Digit Span Test (WDST) [65] was used to measure short term memory performance. Digit span tests have been utilized in previous studies testing the effectiveness of active Modafinil [66, 67]. Both forward and backward auditory digit span were assessed: In the forward digit span procedure participants heard a series of digits and had to reproduce the digits in order by typing the numbers on a keypad. Digit sequences were chosen randomly, starting with three digits and increasing to nine digits with two trials per digit length. In the backward digit span procedure, participants were instructed to type the digits in reverse order (e.g., 134 would be 431). Presentation and randomization of digits were identical to the forward procedure, but the sequence started with two digits, increasing to eight digits. The total number of items correctly repeated forwards (forward digit span) and backwards (backward digit span) were computed.

Continuous Performance Test

The Continuous Performance Test (CPT) has been previously used to assess effects of Modafinil on sustained attention in sleep deprived emergency room physicians [68] and healthy volunteers [69]. Participants saw sequences of letters (one letter per screen) and were instructed to make a target response (press 2) whenever the stimulus "X" immediately followed the presentation of the letter "A" and to make a nontarget response (press 1) to all other stimuli. Stimuli were presented for 200 ms. Participants were given visual feedback (green tick or red x for 100 ms) after each response (see Supplementary Material C). The intertrial interval length varied randomly between 1,000, 1,500, and 2,000 ms. Participants completed 40 practice trials (with 20% targets). The 150 main trials contained 20% targets. Reaction times were measured from the end of the stimulus presentation until a response was detected. Responses over 1,500 ms and under 200 ms were coded as incorrect [70]. The number of correct target responses and average reaction times for correct target responses (in ms) was computed.

Procedures

The study was approved by the UCL School of Pharmacy Research Ethics Committee (ID: 4716/002).

The study was carried out at a research lab in the Pharmacy Department of a large UK university. After obtaining informed consent the experimenter (M.H.) seated participants (one participant per experimental session) in front of a computer terminal and entered the anonymous participant ID on a Qualtrics survey that contained the predictor questionnaire measures (see Fig. 1) and Modafinil and placebo information. Participants were left alone at the computer but told to call the experimenter (who was seated at a desk in the same room) in case they had any questions. After participants completed this first section, the survey software randomized participants to the experimental conditions (see Fig. 1). Participants in the two placebo conditions received a placebo pill (from the same pill bottle, thereby blinding the experimenter) or no pill (Natural History condition). Participants were asked to wait for approximately 10 min for the drug to take effect (or simply to wait in the Natural History group). Participants then completed the WDST, CPT, and the two symptom induction tasks, which were administered via E-prime. They then rated perceived cognitive enhancement and were given the symptom checklist, which included the side-effect attribution measure in the two placebo conditions. Finally, participants completed the demographic questions and were immediately debriefed about the deception at the end of the experimental session.

Statistical Analysis and Sample Size Calculation

An a priori sample size analysis was conducted using GPower version 3.1.9. It showed that Wilcoxon Mann–Whitney test we would need 67 participants per condition to achieve 80% power with an alpha error probability of 5%, assuming a moderate effect size of $d = 0.5$. Required sample size for a parametric test was substantially lower.

Analysis of variance and chi-square tests were used to assess whether participants differed in baseline symptoms, demographic factors, or predictor measures prerandomization. The distribution of outcome data was examined graphically and numerically. Across the sample only very few participants reported the induced symptoms of itch ($n = 12$; 6%) and dizziness ($n = 19$; 9.5%) making it impossible to compare differences in participants who did or did not attribute these symptoms as side-effects. The total number of reported symptoms and side-effects (count data) were not normally distributed so between-group differences were examined with nonparametric tests (Kruskal–Wallis, Mann–Whitney *U*-tests). Chi-square tests were used to examine whether there were differences in the number of participants reporting at least one symptom/side-effect in the experimental groups. Between-group differences in continuous outcomes were examined with one-way analyses of variance and *t*-tests. Associations between treatment beliefs/psychological predictors and the number of reported symptoms/side-effects were examined with univariate negative binomial regression models. Results are reported using incidence rate ratios (IRRs). An IRR of 1.5 indicates that the expected count is multiplied by a factor of 1.5 with every single unit increase in the predictor.

Results

Sample Characteristics and Exclusions

The majority (61.2%) of the 201 participants were white (31.3% White British/Irish, 29.9% other White background; 2.5% black British; 1.5% other black background; 5.5% Indian/Pakistani/Bangladeshi; 5.0% other Asian background; 15.9% Chinese; 6.5% mixed; 2.0% other) with a mean age of 22.9 years ($SD = 4.97$, range 18–54). Most participants (62.2%) stated that English was their first language. Just under half of the sample (47.2%) reported that they held an undergraduate or postgraduate degree. The sample was 44.3% male and 55.7% female. We did not collect data on socioeconomic status.

Demographic characteristics, the number of reported baseline symptoms and predictor measures did not differ significantly between experimental groups (all ps > .11). Two participants in the Open Placebo condition indicated that they had experienced all the prespecified 25 symptoms (including vomiting, which was not observed by the experimenter). They also failed to follow instructions for other tasks. Their data were excluded.

Differences in Symptom Reporting Between Experimental Groups

Participants reported on average 2.65 symptoms in the Deceptive Placebo, versus 1.92 and 1.68 in the Open Placebo and Natural History group, respectively (see Table 1). Participants in the Deceptive Placebo group reported significantly more symptoms than those in the Natural History (Mann–Whitney $U = 1{,}640$, $z = 2.74$, $p = .006$) and Open Placebo group (Mann–Whitney $U = 1{,}654$, $z = 2.30$, $p = .022$). Chi-square tests showed that more participants reported ≥1 symptom in the Deceptive Placebo (84.8%), than in the Natural History group (69.1%) ($\chi^2(1) = 4.66$, $p = .031$) and marginally more than in the Open Placebo group (70.8%, $\chi^2(1) = 3.77$, $p = .052$, see Fig. 2). The experimenter witnessed scratching in 16 participants in the Deceptive Placebo, 13 in the Open Placebo and 12 participants in the Natural History group ($\chi^2(2) = 0.91$, $p = .63$).

Table 1. Differences in experimental groups

Outcomes (*M*, *SD*)	Deceptive Placebo (*n* = 66)	Open Placebo (*n* = 65)	No treatment (*n* = 68)
Symptom-related outcomes			
Symptoms	2.65 (2.27)[1,2]	1.92 (2.24)[1]	1.68 (1.75)[2]
Side-effects	1.41 (1.97)[3]	0.27 (0.86)[3]	NA
Cognitive enhancement WDST			
Forward digit span	10.79 (2.04)[4]	9.97 (2.42)[4]	10.09 (2.33)
Backward digit span	10.41 (2.08)[5]	9.57 (2.59)[5]	10.35 (2.15)
CPT-AX			
Correct target responses	25.94 (3.70)	24.46 (5.98)	25.54 (3.10)
RT in ms	175.06 (60.27)	195.96 (98.99)	171.61 (64.33)
Perceived cognitive enhancement	57.14 (12.15)	53.38 (12.22)	57.53 (14.73)

[1–5] denote significant between-group differences ($p < .05$, two-sided), all other comparisons $p > .05$; Mann–Whitney was used for comparison of symptom-related outcomes, pairwise *t*-tests for cognitive enhancement; *CPT-AX* Continuous Performance Test-AX version; *RT* reaction time; *WDST* Wechsler Digit Span Test.

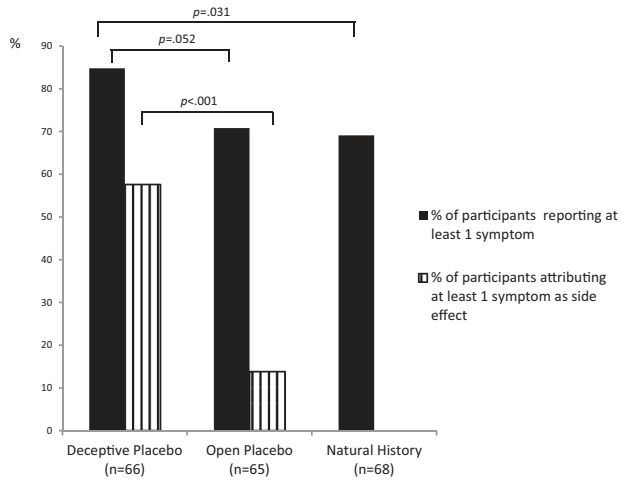

Fig. 2. Percentages of participants reporting symptoms and side-effects.

Differences in Side-Effect Reporting in the Two Placebo Groups

Of the 175 symptoms that were reported in the Deceptive Placebo group 93 (53.14%) were attributed as side-effects, whereas only 18 of the 126 symptoms (14.29%) in the Open Placebo group. Both the number of reported side-effects (Mann–Whitney $U = 1{,}189$, $z = 5.144$, $p < .001$; see Table 1) and the number of participants reporting at least one side-effect ($\chi^2(1) = 31.32$, $p < .001$) were significantly higher in the Deceptive Placebo than the Open Placebo group.

Predictors of Symptom Reporting

Participants who had stronger concerns (BMQ-Concerns IRR = 1.22, 95% confidence interval [CI; 1.03, 1.45], $p = .023$) and higher necessity beliefs (BMQ-Necessity IRR = 1.46, 95% CI [1.13, 1.87], $p = .003$) about the study pill in the placebo conditions reported significantly more symptoms. PSM scale was associated with increased symptom reporting only when participants were led to believe they were taking active Modafinil, whereas NA, somatization, and self-focused attention increased symptom reporting across all three experimental groups (see Table 2). Body awareness (SBA) was associated with symptom reporting in the Open Placebo group only.

Predictors of Side-Effect Reporting

Participants who had stronger concerns (BMQ-Concerns IRR = 2.10, 95% CI [1.43, 3.06]) and necessity beliefs (BMQ-Necessity IRR = 2.64, 95% CI [1.49, 4.65], *p*s < .001) about the study pill (across both Open and Deceptive Placebo groups) reported significantly more side-effects. Participants who believed they were taking active Modafinil reported more side-effects if they had greater PSM (PSM IRR = 1.68, 95% CI [1.13, 2.52], $p = .011$) and believed pharmaceutical medicines to be generally harmful (BMQ General-Harm IRR = 1.70, 95% CI [1.09, 2.67], $p = .019$]). The number of reported side-effects in the Deceptive Placebo group was also higher for participants with greater negative affectivity (IRR = 2.37, $p < .001$) and those who reported having paid closer attention to their bodily sensations during the study (IRR = 1.37, 95% CI [1.11, 1.69], $p = .003$), but not those with higher somatization (IRR = 1.08, 95% CI [0.99, 1.67], $p = .069$). Only self-reported attention to bodily sensations (IRR = 2.12, 95% CI [1.23, 3.64], $p = .006$) was associated with side-effect reporting in the Open Placebo group (all other predictors *p*s > .05; Table 3).

Differences in Cognitive Enhancement Between Experimental Groups

Participants recalled on average 10 (out of a possible 14) forward and 10 (out of a possible 14) backward

Table 2. Univariate negative binomial regression models predicting symptom reporting in each experimental group

IRR [95% CI]	Deceptive Placebo (n = 66)	Open Placebo (n = 65)	Natural History (n = 68)
PSM	1.45 [1.11, 1.89]**	1.33 [0.90, 1.96]	1.17 [0.77, 1.77]
BMQ General-Harm	1.31 [0.99, 1.73]†	0.87 [0.61, 1.24]	1.37 [0.87, 2.15]
BMQ General Overuse	1.16 [0.88, 1.54]	1.11 [0.77, 1.58]	1.39 [0.94, 2.04]
BMQ General Benefit	0.92 [0.64, 1.34]	1.36 [0.78, 2.35]	0.68 [0.43, 1.11]
NA	1.77 [1.28, 2.44]**	1.58 [1.08, 2.30]*	1.66 [1.15, 2.38]**
PHQ-15	1.08 [1.02, 1.13]**	1.13 [1.04, 1.23]**	1.12 [1.05, 1.92]**
SBA	0.96 [0.75, 1.24]	1.89 [1.30, 2.75]**	1.01 [0.74, 1.34]
Self-focused attention	1.19 [1.05, 1.36]***	1.31 [1.10, 1.56]**	1.22 [1.06, 1.41]**

BMQ Beliefs about Medicines Questionnaire; *CI* confidence interval; *IRR* incidence rate ratio; *NA* Negative Affect; *PHQ* Patient Health Questionnaire; *PSM* Perceived Sensitivity to Medicines Scale; *SBA* Scale of Body Awareness; *self-attention* self-reported attention to bodily sensations during study.

$^{\dagger}p < .10$.

*$p < .05$.

**$p < .01$.

*** $p < .001$.

Table 3. Univariate negative binomial regression models predicting side-effect reporting in the two placebo groups

IRR [95% CI]	Deceptive Placebo (n = 66)	Open Placebo (n = 65)
PSM	1.68 [1.13, 2.52]*	1.11 [0.36, 3.36]
BMQ General-Harm	1.70 [1.09, 2.67]*	1.50 [0.57, 3.93]
BMQ General Overuse	1.36 [0.88, 2.10]	1.89 [0.66, 5.41]
BMQ General Benefit	0.77 [0.42, 1.41]	0.28 [0.05, 1.49]
NA	2.37 [1.44, 3.89]**	1.95 [0.51, 7.46]
PHQ-15	1.08 [0.99, 1.17]†	1.25 [0.84, 1.86]
SBA	0.76 [0.49, 1.15]	1.26 [0.28, 5.67]
Self-focused attention	1.37 [1.05, 1.36]*	2.12 [1.23, 3.64]*

BMQ Beliefs about Medicines Questionnaire; *CI* confidence interval; *IRR* incidence rate ratio; *NA* Negative Affect; *PHQ* Patient Health Questionnaire; *PSM* Perceived Sensitivity to Medicines Scale; *SBA* Scale of Body Awareness; *self-attention* self-reported attention to bodily sensations during study.

$^{\dagger}p < .10$.

*$p < .05$.

**$p < .01$.

digit sequences. Participants in the Deceptive Placebo group recalled significantly more forward digit sequences than participants in the Open Placebo group ($t(129) = 2.09$, $p = .039$) and but not the Natural History group ($t(132) = 1.84$, $p = .067$). Backward digit span was also significantly higher for participants in the Deceptive Placebo than the Open Placebo group ($t(129) = 2.05$, $p = .042$), but not the Natural History group ($t(132) = 0.15$, $p = .88$). There was no difference in recalled forward ($t(131) = 0.29$, $p = .80$), and backward digits ($t(131) = 1.90$, $p = .059$) between the Open Placebo and Natural History group. Performance in the CPT did not differ between the three experimental groups (see Table 1, all ps > .05). Participants rated their cognitive performance as better than usual (50 scale midpoint equaling no change, see Table 1) in all experimental groups, but perceived cognitive enhancement was not significantly higher in the Deceptive Placebo condition group to the Open Placebo ($t(129) = 1.76$, $p = .080$) and Natural History groups ($t(132) = 0.16$, $p = .87$). The difference between Open Placebo and Natural History groups also was not significant ($t(131) = 1.76$, $p = .080$).

Discussion

This study is the first to demonstrate that nocebo effects are predicted by medication beliefs using a design that compared Deceptive Placebo against both open-label placebo and no treatment (Natural History): There were significant differences in side-effect reporting across the three conditions. Participants who believed that they were given active Modafinil reported significantly more symptoms than participants given open-label placebo or no placebo. Side-effect reporting (i.e., attribution of these symptoms as side-effects) was more frequent in the Deceptive Placebo ("Modafinil") than Open Placebo group. Specific medication beliefs and general pharmaceutical schemas predicted nocebo responding. Participants who had stronger concerns and necessity beliefs about the study pill and who indicated that they were more sensitive to the effects of pharmaceuticals reported more symptoms and side-effects when given Modafinil placebo. NA, somatization, and self-reported attention to bodily sensations also predicted symptom reporting across all three experimental groups, that is, even when no drug was administered. There was also evidence for

a placebo effect on short-term memory, confirming the validity of the experimental manipulation.

This study makes an important contribution to the literature on nocebo effects as it provides rare evidence for what has been termed the "true" nocebo effect [71]. Although comparisons between a placebo group and a Natural History group are now commonly used to demonstrate placebo effects [29, 72], there is a dearth of studies extending this methodology to the study of nocebo effects [28]. Labeling all symptoms reported in the placebo arm as nocebo effects may overestimate nocebo effects. In the present study, the majority of participants in the Natural History group (69.1%) also reported symptoms and not all reported symptoms were subsequently attributed as side-effects in the placebo groups. Findings from the study also suggest that part of the efficacy of "smart pills" like Modafinil may be due to placebo effects.

There is compelling evidence that patients' beliefs about medication are associated with adherence to prescribed medications across a range of illness groups [36] and a growing number of clinical studies demonstrate associations between medication beliefs and side-effect reporting [5, 51, 73]. This is however one of the first studies to demonstrate their role in nocebo responding. Our findings further confirmed the importance of negative affectivity in symptom and side-effect perception. A previous study with asthmatic patients showed that those scoring higher on negative affectivity reported greater airway obstruction after inhaling from a placebo inhaler described as a bronchoconstrictor [74]. As one would expect from the literature on medically unexplained symptoms [57], somatization was also associated with increased symptom detection, but not the attribution of these symptoms as side-effects. Our findings suggest that there are likely to be different predictors of symptom reporting and side-effect reporting, with medication-related constructs being particularly important for side-effect reporting. Outside of the experimental context these relationships may well be complex and dynamic as experiencing some symptoms may reinforce need for medication or be interpreted as evidence that a medication is not working.

In contrast to previous studies suggesting that placebos may be effective without deception [8, 75], we failed to find differences between the open-label placebo and Natural History group in either subjectively reported or objectively measured cognitive enhancement. Unlike most other studies using open-label placebos [76] the present study did not include a positive message surrounding the placebo (e.g., the placebo effect is powerful [70] as we wanted to minimize both positive and negative expectations in this control group and ensure that our manipulation more closely resembled the information that would be given in a typical trial of a new medication. Our failure to find a nocebo effect in the open-label group suggests that side-effect reports in previous open-label studies may arise from the explanation given of the placebo/nocebo effect rather than from the experience of taking the placebo (perhaps indicating the role of processes such as expectation rather than conditioning). This might suggest that in placebo-controlled trials of active medication, symptom reports in the placebo arm are more likely to increase when participants believe they are taking the active treatment than when they believe they are taking an inactive placebo. Our participants were healthy students taking a novel medication and so may have been particularly unlikely to show a nocebo response to an Open Placebo presented without a rationale or statement of potential effects. Our study has several strengths and limitations. We used two different control groups (Natural History and Open Placebo) and assessed both symptom reporting and the attribution of symptoms as side-effects. The experimenter was blind to allocation in the two placebo conditions and both subjective (perceived cognitive enhancement) and objective outcome measures (WDST, CPT-AX) were used, reducing the likelihood of reporting bias. Participants in this study were healthy and not taking any medication, ruling out any concomitant pharmacological effects. Despite this advantage it is not clear whether our findings relating to symptoms experienced in our "laboratory" setting can be generalized to patients' everyday experience. In addition, students who volunteer for a study to assess drug safety have potentially more positive attitudes toward medicines and perceive themselves as less vulnerable to adverse medication effects. The inclusion of a variety of predictor measures may have led to false positive findings. Our induction of symptoms via visual stimuli did not produce a strong effect. The symptom induction techniques we used in this study were deliberately subtle (visual stimuli disguised as being part of reaction time tasks). While more heavy-handed symptom induction techniques (e.g., inducing sweating by making the room extremely hot) may produce more symptoms, it is arguably less likely that these would be attributed as side-effects to medication. We did not have a sufficient sample size to test whether our psychological variables predicted side-effects and symptom reports differently in the Open Placebo, Deceptive Placebo, and Natural History conditions. Further better powered studies are needed to examine multivariate associations between medication beliefs/psychological predictors and symptom/side-effect reporting in response to placebo.

Findings from the study have potential clinical applications. Side-effects, be they due to pharmacological or nocebo-related factors, are likely to reduce adherence [3]. This may lead to a loss in treatment benefit, which may consequently affect morbidity and mortality. Given the association between medication beliefs and both

adherence [36] and side-effects [5], clinicians may want to discuss any concerns patients have about their medication and probe perceptions of sensitivity to medicines when prescribing treatment. The BMQ and PSM may serve as templates to aid discussion. In addition, our findings suggest that interventions to modify unfounded concerns about the harmfulness of medications [77] and personal sensitivity could be potentially effective in reducing nocebo-related side-effects.

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Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards Authors Monika K. Heller, Sarah C.E. Chapman, and Rob Horne declare that they have no conflict of interest.

Authors' Contributions Monika Heller led study design, coordination and management of recruitment, preparation, analysis and interpretation of data, preparation and review of final manuscript. Sarah Chapman contributed to study design, coordination and management of recruitment, preparation, data analysis, interpretation of results, and preparation and review of final manuscript. Rob Horne initiated and obtained funding for the work and contributed to study design, interpretation of data and review of final manuscript.

Ethical Approval All procedures performed in this study I was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants in this study.

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