Beliefs about medicines predict side-effects of placebo Modafinil

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Abstract

Background

Many patients in the placebo arm of clinical trials report side-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 the detection and attribution of symptoms as side-effects to placebo (nocebo effects).

Methods

Healthy students (*n*=201) completed validated measures assessing beliefs about medication, perceived sensitivity to medicines, negative affectivity, somatization and body awareness before being randomized to receive Deceptive Placebo (told Modafinil – given placebo *n*=66), Open Placebo (told placebo – given placebo *n*=67) or no placebo *(*Natural History *n*=68). Memory and sustained attention tasks were used to assess cognitive enhancement. The detection and attribution of symptoms as side-effects was assessed with a checklist.

Results

Participants receiving Deceptive Placebo Modafinil reported significantly more symptoms (M= 2.65; SD=2.27) than those receiving Open Placebo (M=1.92; SD=2.24; Mann Whitney U=1654, z=2.30, p=.022) or no placebo (M = 1.68; SD=1.75, Mann Whitney U=1640, z=2.74, p=.006). Side-effects of Deceptive ‘Modafinil’ were predicted by specific and general medication beliefs. Participants were significantly more likely to attribute symptoms to Modafinil side-effects if they believed pharmaceuticals to be

generally harmful (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

Specific and general beliefs about medication are potentially modifiable predictors of the nocebo effect. These findings provide insight into psychological determinants of side-effect reporting to placebo and, potentially, to 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 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 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 labelled 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 behaviours (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, e.g. 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 (47-50). 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, 51). 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 (52). However, no comparison with a control group was included in this study. Analogue 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 (53, 54).

There is considerable evidence for the role of psychological factors in symptom perception in general: Negative affectivity (55), somatization (56) and attention to bodily sensations (57) have been shown to increase symptom reporting overall and in patients with medically unexplained symptoms (58). It is thus plausible that these factors may lead to an increase in the detection of symptoms, which could be subsequently labelled as side-effects in individuals receiving placebo.

The aim of the proposed study is therefore two-fold: 1) 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 2) 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.

Method

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 pre-screening 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-minute 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 Figure 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).

Placebo information: Participants received the following information about the placebo pills, which was adapted from a review on typical descriptions of placebos in RCTs (61): “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 (PSM): The 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 perceived sensitivity to medicines. Internal consistency was high (Cronbach's α=.85)

Beliefs about Medicines Questionnaire (BMQ): Participants' beliefs about the study pill they were randomized to (after allocation information) were assessed with the 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 (57) was used to ascertain whether participants differed onbaseline symptoms they were experiencing prior to randomization. Participants were asked to indicate on 7-point bipolar rating scales (e.g. 1=no headache – 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 α=.77).

Positive and Negative Affect Schedule (PANAS): State Negative Affect was assessed with the short form of the PANAS (62). Participants were asked to indicate to what extent (from 1=not at all to 5=extremely) they generally experience ten negative (e.g. distressed, upset) and ten positive feelings (e.g. excited, relaxed). State Negative (NA) and Positive Affect (PA) scores were computed by summing scores for all negative and positive adjectives respectively. Internal consistency was high (Cronbach's αs >.83)

Patient Health Questionnaire (PHQ-15): Somatization was assessed with the Patient Health Questionnaire (PHQ-15) (58). 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 αs =.71).

Scale of Body Awareness (SBA): Individuals' cognitions about bodily sensations were assessed with the Scale of Body Awareness (SBA) (63). 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 αs =.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. FMRI studies have shown that this type of imagery can be effective in inducing itch (65) by activating neural regions linked to the physical perception of itch (66).

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 (66, 67) 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 (68). 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 were 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 was collected.

Perceived cognitive enhancement: Participants were asked to rate their alertness, ability to concentrate, and ability to remember on 100-point visual analogue scales (VAS) 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 VAS (Cronbach's α=.86).

Wechsler Auditory Digit Span Test (WDST): A computerized version of the WDST (69) was used to measure short term memory performance. Digit span tests have been utilized in previous studies testing the effectiveness of active Modafinil (70, 71). 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 3 digits and increasing to 9 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 was 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 (CPT): The CPT has been previously used to assess effects of Modafinil on sustained attention in sleep deprived emergency room physicians (72) and healthy volunteers (73). Participants saw sequences of letters (one letter per screen) and were instructed to make a target response (press 2) whenever the

stimulus “X” immediately followed the presentation of the letter “A” and to make a non-target response (press 1) to all other stimuli. Stimuli were presented for 200 msec. Participants were given visual feedback (green tick or red x for 100 msec) after each response (see supplementary material C). The inter-trial interval length varied randomly between 1000, 1500 and 2000 msec. 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 1500 msec and under 200 msec were coded as incorrect [78]. The number of correct target responses and average reaction times for correct target responses (in msec) were 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 (MH) 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 Figure 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 Figure 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 minutes 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 pre-randomization. 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 non-parametric

tests (Kruskall-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 ANOVAS 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 (IRR). 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 pre-specified 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=1640, z=2.74, p=.006) and Open Placebo group (Mann Whitney U=1654, 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%) (χ^2(1)=4.66, p=.031) and marginally more than in the Open Placebo group (70.8%, χ^2(1)=3.77, p=.052, see Figure 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 (χ^2(2)=0.91, p=.63).

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=1189, z=5.144, p<.001; see Table 1) and the number of participants reporting at least one side-effect (χ^2(1)=31.32, p<.001) was 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% 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. Perceived sensitivity to medicines (PSM scale) was associated with increased symptom reporting only when participants were led to believe they were taking active Modafinil, whereas negative affect, 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], *ps*<.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 perceived sensitivity to medicines (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 *ps*>.05).

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 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 *p*s>.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 symtoms and side-effects when given Modafinil placebo. Negative affect, somatization and self-reported attention to bodily sensations also predicted symptom reporting across all three experiemental groups, i.e. 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 (74). Although comparisons between a placebo group and a natural history group are now commonly used to demonstrate placebo effects (29, 75), there is a dearth of studies extending this methodology to the study of nocebo effects (28). Labelling 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, 52, 76). 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 (77). As one would expect from the literature on medically unexplained symptoms (58), 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 isn't working.

In contrast to previous studies suggesting that placebos may be effective without deception (8,79), 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 (80) the present study did not include a positive message surrounding the placebo (e.g. the placebo effect is powerful (78) as we wanted to minimze 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 towards 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 stiumli 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), clinicans 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 (81) and personal sensitivity could be potentially effective in reducing nocebo related side-effects.

References

1. Davies EC, Green CF, Taylor S, et al.: Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS one.* 2009, *4:*e4439.
2. Larsen EB, Gerlach J: Subjective experience of treatment, side-effects, mental state and quality of life in chronic schizophrenic out-patients treated with depot neuroleptics. *Acta Psychiatr Scand.* 1996, *93:*381-388.
3. Ammassari A, Murri R, Pezzotti P, et al.: Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *JAIDS.* 2001, *28:*445-449.
4. DiBonaventura M, Gabriel S, Dupclay L, Gupta S, Kim E: A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. *BMC Psychiatr.* 2012, *12:*20.
5. Nestoriuc Y, Orav EJ, Liang MH, Horne R, Barsky AJ: Beliefs about medicines predict non-specific side effects in rheumatoid arthritis patients. *Arthr Care Res.* 2010, *62:*791.
6. Tan K, Petrie KJ, Faasse K, Bolland MJ, Grey A: Unhelpful information about adverse drug reactions. *BMJ.* 2014, *349:*g5019.
7. Rief W, Nestoriuc Y, von Lilienfeld-Toal A, et al.: Differences in adverse effect reporting in placebo groups in SSRI and tricyclic antidepressant trials. *Drug Safety.* 2009, *32:*1041-1056.
8. Poitras P, Gougeon A, Binn M, Bouin M: Extra digestive manifestations of irritable bowel syndrome: Intolerance to drugs? *Dig Dis Sci.* 2008, *53:*2168-2176.
9. Petrie KJ, Rief W: Psychobiological mechanisms of placebo and nocebo effects: pathways to improve treatments and reduce side effects. *Ann Rev Psychol.* 2019, *70:*599-625.
10. Reidenberg M, Lowenthal D: Adverse nondrug reactions. *NEJM.* 1968, *279:*678-&.
11. Meyer FP, Troger U, Rohl FW: Adverse nondrug reactions: An update. *Clin Pharmacol Ther.* 1996, *60:*347-352.
12. Barsky AJ, Saintfort R, Rogers MP, Borus JF: Nonspecific medication side effects and the nocebo phenomenon. *JAMA.* 2002, *287:*622.
13. Mitsikostas DD, Mantonakis LI, Chalarakis NG: Nocebo is the enemy, not placebo. A meta-analysis of reported side effects after placebo treatment in headaches. *Cephalalgia.* 2011, *31:*550-561.
14. Stathis P, Smpiliris M, Konitsiotis S, Mitsikostas D: Nocebo as a potential confounding factor in clinical trials for Parkinson's disease treatment: a meta-analysis. *Eur J Neurol.* 2013.
15. Amanzio M, Benedetti F, Vase L: A systematic review of adverse events in the placebo arm of donepezil trials: the role of cognitive impairment. *Int Psychogeriatr.* 2012, *24:*698-707.
16. Häuser W, Bartram C, Bartram-Wunn E, Tölle T: Adverse events attributable to nocebo in randomized controlled drug trials in fibromyalgia syndrome and painful diabetic peripheral neuropathy: Systematic review. *Clin J Pain.* 2012, *28:*437-451.
17. Faasse K, Petrie KJ: The nocebo effect: patient expectations and medication side effects. *Postgrad Med J.* 2013, *89:*540-546.
18. Link J, Haggard R, Kelly K, Forrer D: Placebo/nocebo symptom reporting in a sham herbal supplement trial. *Eval Health Prof .* 2006, *29:*394-406.
19. Schweiger A, Parducci A: Nocebo: The psychologic induction of pain. *Pavlov J Biol Sci.* 1981, *16:*140-143.

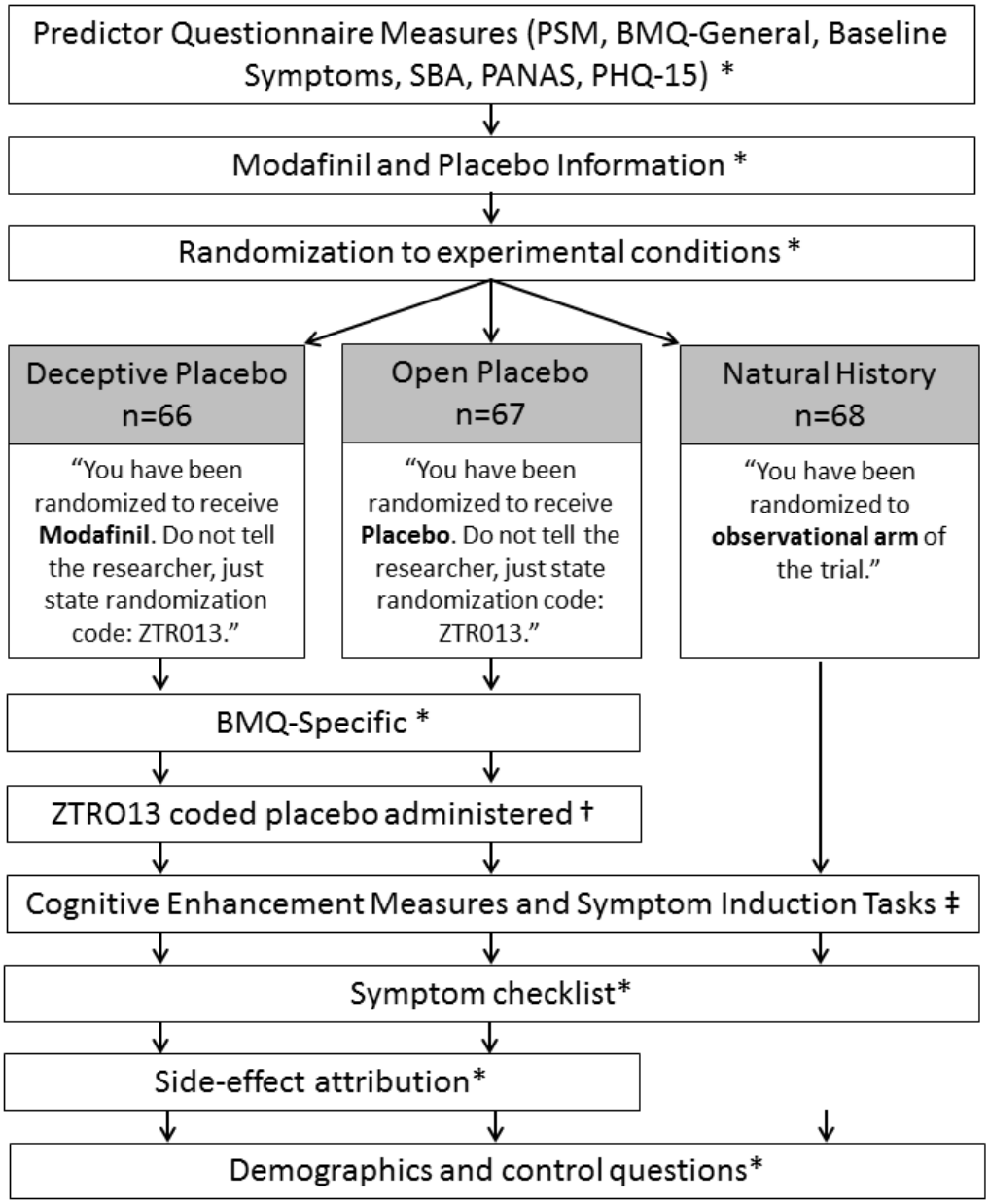
20. Webster RK, Weinman JA, Rubin GJ: A systematic review of factors that contribute to nocebo effects. *Health Psychol.* 2016, *35:*1334-1355.
21. Neukirch N, Colagiuri B: The placebo effect, sleep difficulty, and side effects: a balanced placebo model. *J Behav Med.* 2014.
22. Benedetti F, Lanotte M, Lopiano L, Colloca L: When words are painful: unraveling the mechanisms of the nocebo effect. *Neurosci.* 2007, *147:*260-271.
23. Benedetti F, Pollo A, Lopiano L, et al.: Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci.* 2003, *23:*4315-4323.
24. Häuser W, Hansen E, Enck P: Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch Arztebl Int.* 2012, *109:*459.
25. Tracey I: Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat Med.* 2010, *16:*1277-1283.
26. Colagiuri B, Park J, Barnes K, et al.: Pre-exposure, but not overshadowing, inhibits nocebo hyperalgesia. *J Pain.* 2021, *22:*864-877.
27. MacKrill K, Morrison Z, Petrie KJ: Increasing and dampening the nocebo response following medicine-taking: A randomised controlled trial. *J Psychosom Res.* 2021, *150:*110630.
28. Hróbjartsson A: What are the main methodological problems in the estimation of placebo effects? *J Clin Epidemiol.* 2002, *55:*430-435.
29. Gøtzsche P: Is there logic in the placebo? *Lancet.* 1994, *344:*925-926.
30. Horing B, Weimer K, Muth ER, Enck P: Prediction of placebo responses: a systematic review of the literature. *Frontiers in Psychology.* 2013, *5:*1079-1079.
31. Enck P, Klosterhalfen S, Zipfel S: Novel study designs to investigate the placebo response. *BMC Med Res Methodol.* 2011, *11:*90.
32. Meeuwis SH, van Middendorp H, Lavrijsen APM, Veldhuijzen DS, Evers AWM: Open- and closed-label placebo and nocebo suggestions about a sham transdermal patch. *Psychosom Med.* 2021, *83:*33-42.
33. Partridge BJ, Bell SK, Lucke JC, Yeates S, Hall WD: Smart drugs "as common as coffee": media hype about neuroenhancement. *PLoS one.* 2011, *6:*e28416.
34. Smith ME, Farah MJ: Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychol Bull.* 2011, *137:*717.
35. Horne R: Treatment perceptions and self-regulation. *The self-regulation of health and illness behaviour*: Routledge, 2003, 138-153.
36. Horne R, Chapman S, Parham R, et al.: Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: A meta-analytic review of the Necessity-Concerns Framework. *PLoS one.* 2013, *8:*e80633.
37. Horne R, Faasse K, Cooper V, et al.: The perceived sensitivity to medicines (PSM) scale: An evaluation of validity and reliability. *Brit J Health Psychol.* 2013, *18:*18-30.
38. Webster RK, Rubin GJ: Predicting expectations of side-effects for those which are warned versus not warned about in Patient Information Leaflets. *Annal Beh Med.* 2021.
39. Leventhal H, Brissette I, Leventhal EA: The common-sense model of self-regulation of health andillness. *The self-regulation of health and illness behaviour*. London: Routledge, 2003, 42-65.

40. Leventhal H, Diefenbach M, Leventhal EA: Illness cognition: using common sense to understand treatment adherence and affect cognition interactions. *Cogn Ther Res.* 1992, *16:*143-163.
41. Horne R, Parham R, Driscoll R, Robinson A: Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease. *Inflamm Bowel Dis.* 2009, *15:*837-844.
42. Leventhal, H, Leventhal, EA, & Contrada, RJ (1998). Self-regulation, health, and behavior: A perceptual-cognitive approach. *Psychol Health*, 13(4), 717-733.
43. Chapman SC, Barnes N, Barnes M, et al.: Changing adherence-related beliefs about ICS maintenance treatment for asthma: feasibility study of an intervention delivered by asthma nurse specialists. *BMJ Open.* 2015, *5:*e007354.
44. Chapman SC, Horne R, Chater A, Hukins D, Smithson WH: Patients' perspectives on antiepileptic medication: relationships between beliefs about medicines and adherence among patients with epilepsy in UK primary care. *Epilepsy Behav.* 2014, *31:*312-320.
45. Horne R, Weinman J, Hankins M: The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol Health.* 1999, *14:*1-24.
46. Horne R, Weinman J: Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res.* 1999, *47:*555-567.
47. Holmes EA, Hughes DA, Morrison VL: Predicting adherence to medications using health psychology theories: a systematic review of 20 years of empirical research. *Value Health.* 2014, *17:*863-876.
48. Chapman SCE, Horne R, Chater A, Hukins D, Smithson WH: Patients' perspectives on antiepileptic medication: Relationships between beliefs about medicines and adherence among patients with epilepsy in UK primary care. *Epilepsy Behav.* 2014, *31:*312-320.
49. Chater AM, Parham R, Riley S, Hutchison AJ, Horne R: Profiling patient attitudes to phosphate binding medication: a route to personalising treatment and adherence support. *Psychol Health.* 2014, *29:*1407-1420.
50. Chapman S, Dale P, Svedsater H, et al.: Modelling the effect of beliefs about asthma medication and treatment intrusiveness on adherence and preference for once-daily vs. twice-daily medication. *NPJ Prim Care Respir Med.* 2017, *27:*61.
51. Horne R, Chapman S, Glendinning E, et al.: Mind matters: Treatment concerns predict the emergence of antiretroviral therapy side Effects in people with HIV. *AIDS Behav.* 2018*:*1-10.
52. Webster RK, Weinman J, Rubin GJ: Medicine-related beliefs predict attribution of symptoms to a sham medicine: A prospective study. *Br J Health Psychol.* 2018, *23:*436-454.
53. Heller MK, Chapman SC, Horne R: Beliefs about medication predict the misattribution of a common symptom as a medication side effect—Evidence from an analogue online study. *J Psychosom Res.* 2015, *79:*519-529.
54. Heller MK, Chapman SC, Horne R: No blank slates: Pre-existing schemas about pharmaceuticals predict memory for side effects. *Psychol Health.* 2017. *32*(4): 402-421
55. Watson D, Clark LA: Negative affectivity: the disposition to experience aversive emotional states. *Psychol Bull.* 1984, *96:*465.
56. Kroenke K, Spitzer RL, Williams JB: The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med.* 2002, *64:*258-266.
57. Pennebaker JW: *The Psychology of Physical Symptons*: James Pennebaker, 1982.

58. Rief W, Broadbent E: Explaining medically unexplained symptoms-models and mechanisms. *Clin Psychol Rev.* 2007, *27:*821-841.
59. Symon A, Williams B, Adelasoye QA, Cheyne H: Nocebo and the potential harm of 'high risk'labelling: a scoping review. *J Adv Nurs.* 2015, 71(7), 1518-1529.
60. Colloca L, Finniss D: Nocebo effects, patient-clinician communication, and therapeutic outcomes. *JAMA.* 2012, *307:*567-568.
61. Bishop FL, Adams AE, Kaptchuk TJ, Lewith GT: Informed consent and placebo effects: a content analysis of information leaflets to identify what clinical trial participants are told about placebos. *PLoS one.* 2012, *7:*e39661.
62. Mackinnon A, Jorm AF, Christensen H, et al.: A short form of the Positive and Negative Affect Schedule: Evaluation of factorial validity and invariance across demographic variables in a community sample. *Pers Indiv Dif.* 1999, *27:*405-416.
63. Hansell S, Sherman G, Mechanic D: Body awareness and medical care utilization among older adults in an HMO. *J Gerontol.* 1991, *46:*S151-S159.
64. Lloyd D, Hall E, Hall S, McGlone F: Can itch-related visual stimuli alone provoke a scratch response in healthy individuals? *Brit J Dermatol.* 2013, *168:*106-111.
65. Ward J, Burckhardt V, Holle H: Contagious scratching: shared feelings but not shared body locations. *Front Hum Neurosci.* 2013, *7:*122.
66. Adjamian P, Holliday IE, Barnes GR, et al.: Induced visual illusions and gamma oscillations in human primary visual cortex. *Eur J Neurosci.* 2004, *20:*587-592.
67. El Shakankiry HM, Kader AAA: Pattern sensitivity: a missed part of the diagnosis. *Neuropsychiatr Dis Treat.* 2012, *8:*313.
68. Moss-Morris R, Weinman J, Petrie K, et al.: The revised illness perception questionnaire (IPQ-R). *Psychol Health.* 2002, *17:*1-16.
69. Wechsler D: *WAIS-IV: Wechsler Adult Intelligence Scale*: Pearson, 2008.
70. Pigeau R, Naitoh P, Buguet A, et al.: Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. *J Sleep Res.* 1995, *4:*212-228.
71. Wesensten NJ: Effects of modafinil on cognitive performance and alertness during sleep deprivation. *Curr Pharm Des.* 2006, *12:*2457-2471.
72. Gill M, Haerich P, Westcott K, Godenick KL, Tucker JA: Cognitive performance following Modafinil versus placebo in sleep-deprived emergency physicians: A double-blind randomized crossover study. *Acad Emer Med.* 2006, *13:*158-165.
73. Repantis D, Schlattmann P, Laisney O, Heuser I: Modafinil and methylphenidate for neuroenhancement in healthy individuals: a systematic review. *Pharmacol Res.* 2010, *62:*187-206.
74. Colloca L, Miller FG: The nocebo effect and its relevance for clinical practice. *Psychosom Med.* 2011, *73:*598-603.
75. Hróbjartsson A, Gøtzsche PC: Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *NEJM.* 2001, *344:*1594-1602.
76. Petrie KJ, Moss-Morris R, Grey C, Shaw M: The relationship of negative affect and perceived sensitivity to symptom reporting following vaccination. *Brit J Health Psychol.* 2004, *9:*101-111.
77. Put C, Van den Bergh O, Van Ongeval E, et al.: Negative affectivity and the influence of suggestion on asthma symptoms. *J Psychosom Res.* 2004, *57:*249-255.

78. Kaptchuk TJ, Friedlander E, Kelley JM, et al.: Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One.* 2010, *5:*e15591.
79. Kelley JM, Kaptchuk TJ, Cusin C, Lipkin S, Fava M: Open-label placebo for major depressive disorder: A pilot randomized controlled trial. *Psychother Psychosom.* 2012, *81:*312–314.
80. Charlesworth JE, Petkovic G, Kelley JM, et al.: Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *J Evid Based Med.* 2017, *10:*97-107.
81. Petrie KJ, Perry K, Broadbent E, Weinman J: A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *Brit J Health Psychol.* 2012, *17:*74-84.

Figure 1: Overview experimental design and measures



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

Figure 2: Percentages of participants reporting symptoms and side-effects

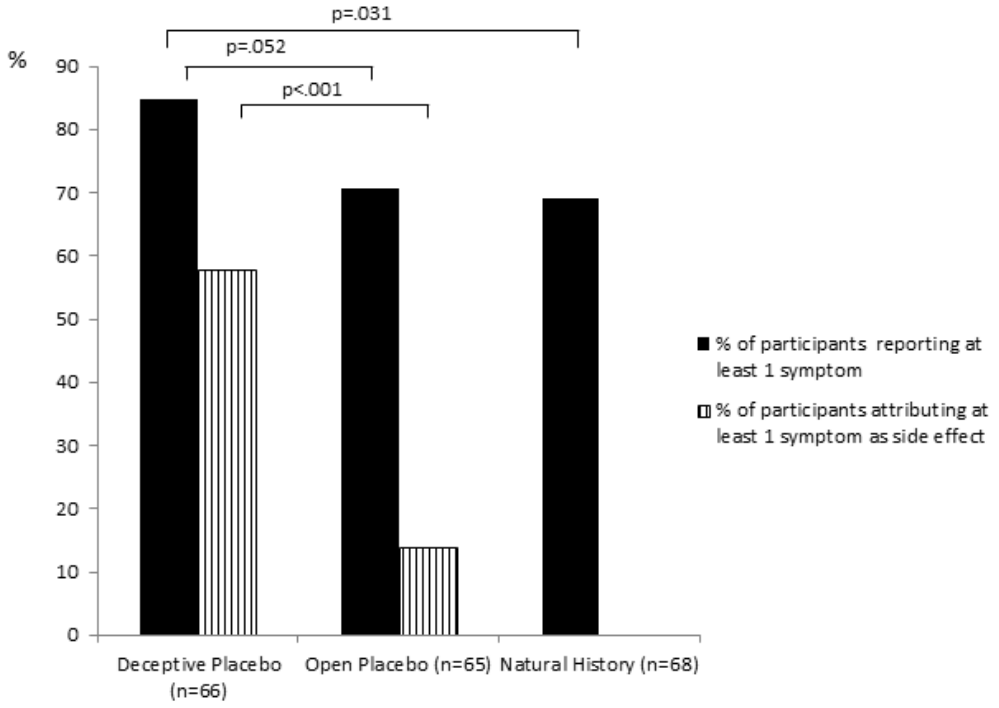


Table 1: Differences in experimental groups

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 msec	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)

Note. [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; WDST=Wechsler Digit Span Test, CPT-AX=Continuous Performance Test-AX version, RT=reaction time, msec=milliseconds.

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)	No Treatment (*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]**

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

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]*

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