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Running Head: SIDE EFFECT ATTRIBUTION SCALE

When symptoms become side effects: Development of the Side Effect Attribution Scale (SEAS)

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Abstract

Objectives: Symptom misattribution is a central process in the nocebo effect but it is not accurately assessed in current side effect measures. We have developed a new measure, the Side Effect Attribution Scale (SEAS), which examines the degree to which people believe their symptoms are treatment side effects.

Methods: The SEAS was tested in three New Zealand studies: a vaccination sample (n = 225), patients with gout or rheumatoid arthritis (n = 102), and patients switching to a generic medicine (n = 69). The internal reliability of the scale was examined using Cronbach's alpha. To assess validity, the Side Effect Attribution Total Score and Side Effect Attribution Binary Score were related to a number of psychological measures associated with side effect reporting.

Results: The scale showed good internal reliability across the three studies, with Cronbach alphas ranging from .840 to .943. Analysis of the effect sizes showed that the Attribution Total Score was generally more strongly associated with nocebo responding than Attribution Binary Score. Participants had greater Side Effect Attribution Total Scores if they had higher expectations for vaccination side effects (r = .18, p = .028), more worry about future vaccine effects (r = .16, p = .046), a higher perceived sensitivity to medicines (r = .50, p < .001), greater anxiety (r = .25, p = .016), greater intentional non-adherence (r = .30, p = .003), greater medicine information seeking (r = .26, p = .010), lower trust in pharmaceutical agencies (r = -.29, p = .026), and lower medicine efficacy beliefs (r = -.46, p < .001).

Conclusions: The SEAS provides a more nuanced assessment of symptom attribution beliefs. It appears to be more sensitive measure than just a side effect total, as it is associated with a greater number of relevant psychological variables. Future research should examine the scale in other populations and settings.

Keywords: side effect attribution; measurement; nocebo effect

Introduction

Medications can have many side effects but these are not always due to the pharmacological action of the drug; instead side effects can be the result of the nocebo effect (Petrie & Rief, 2019). A key process in nocebo responding is the misattribution of common symptoms to a medication, due to an individual's expectation that they are going to experience side effects (Barsky, Saintfort, Rogers, & Borus, 2002). In every-day life, it is normal to experience symptoms that do not have an underlying medical cause, such as back pain, fatigue or headaches (Petrie, Faasse, Crichton & Grey, 2014). It has been estimated that 70-80% of side effects are not caused by the active treatment and are actually symptoms misattributed to medications by patients (Mahr et al., 2017). Common symptoms are often listed as side effects in medicine information leaflets (Tan, Petrie, Faasse, Bolland, & Grey, 2014) and are regularly reported as adverse drug reactions by patients (de Langen, van Hunsel, Passier, de Jong-van den Berg, & van Grootheest, 2008).

The attribution of side effects to a treatment can have serious consequences. Parents who perceived serious side effects in their children following influenza vaccination are less likely to re-vaccinate the next year (Smith, Amlôt, Weinman, Yiend, & Rubin, 2020). Nocebo-induced adverse reactions can make changing medicines difficult (Weissenfeld, Stock, Lüngen, & Gerber, 2010). The experience of side effects is also a leading cause of treatment non-adherence (Kardas, Lewek, & Matyjaszczyk, 2013) and greater healthcare utilisation (Rodriguez-Monguio, Otero, & Rovira, 2003). As such, when measuring the nocebo effect and side effect reporting, it is important to consider the extent to which people believe their current symptoms are caused by a medication.

There are a number of symptom and side effect measures used in the literature. A systematic review identified 40 symptom scales with the majority assessing symptom frequency and severity (Zijlema et al., 2013). Scales such as the General Assessment of Side Effects (Rief et al., 2011) typically ask people to indicate whether they have experienced a symptom in a given timeframe and, if present, to rate whether they believe this

is a side effect of a medication they are taking by responding either yes or no. The number of 'yes' responses is summed to create a total side effect score.

However, the current measures of side effect reporting have not fully captured the range of side effect attribution beliefs and have a number of limitations. To date, the available measures have considered side effect attribution as a binary categorical construct and only provide two response options. The scales assume that respondents are able to neatly categorise their beliefs as either 'yes, this is a side effect' or 'no, it is not'. They also do not provide a neutral response, which may force respondents to select an option that doesn't truly reflect their beliefs (Saris & Gallhofer, 2014; Sturgis et al., 2014). The current measures only produce a total side effect score, whereas the extent to which people are likely to attribute their symptoms as treatment side effects may also be an important variable to investigate per se. Ultimately, the current side effect measures fail to accurately assess the *attribution* of symptoms to a medication and therefore the nocebo effect.

In this paper, we discuss the development of a new side effect measure, the Side Effect Attribution Scale (SEAS). This scale produces a Side Effect Attribution Total Score, indicating the degree to which people believe their symptoms are or are not side effects of a medication. The utility of the SEAS has been examined in three samples. These studies test the reliability of the symptom list and validity of the scale by examining the associations between the average attribution score and various psychological variables. These include attitudes towards vaccination, perceived sensitivity to medicine, non-adherence, seeking information about medicines and trust in pharmaceutical agencies. The aim of these studies is also to assess the usefulness of the side effect attribution score over and above a simple binary measure of side effects.

Method

Side Effect Attribution Scale Development

The side effects in the scale were generated using the 20 most commonly prescribed medicines and nine biologic drugs available in New Zealand in 2018. The generic version of biologics, biosimilars, are being increasingly used but are often perceived negatively,

meaning that nocebo responding is likely and supports the inclusion of biologic side effects in symptom measures (Rezk & Pieper, 2017). For each of the 29 medicines, a list of the common side effects was compiled based on the medicine data sheet, consumer information leaflet, and searching www.drugs.com. The side effect lists of the medications were merged and after combining the various terms used to describe the same symptoms (e.g. edema and swelling), a total of 285 unique side effects were identified. The list was further cleaned by removing symptoms that patients would not be able to perceive, for example 'low white blood cells', or broader illness labels that encompass a range of symptoms, such as upper respiratory infection or high blood pressure. The final scale version comprised the 50 most common medication side effects, which were listed in more than 10% of the drugs examined. For the full list of 50 side effects and frequency reported in four patient samples, see the supplementary material.

When administering the SEAS, patients are given the 50-item list and are first asked to indicate whether they have experienced each of these symptoms in a particular timeframe (usually in the past seven days). If present, they are then asked whether they think the symptom is a side effect of their medication or treatment (e.g. vaccination). As shown in Figure 1, the response option consists of five scale points: 1 = Definitely not a side effect, 2 = Probably not a side effect, 3 = Unsure, 4 = Probably a side effect, 5 = Definitely a side effect. For the Side Effect Attribution Total Score, the five response options are scored from one to five and averaged across the 50 symptoms for each individual. Attribution scores closer to five indicate greater side effect attribution – that overall an individual tends to believe their symptoms are side effects. Scores near three suggest that the person is mostly unsure about whether their symptoms are side effects, while scores closer to one show that the person does not believe their symptoms are side effects. A binary measure of the total number of side effects reported, similar to the yes/no categorisation of previous scales, was calculated by summing responses of 'Probably a side effect' and 'Definitely a side effect'. This is referred to as Side Effect Attribution Binary Score.

Symptom	Experienced in the past week		Do you think this symptom is a side effect of the medication?				
Headache	Yes	No	Definitely not a side effect	Probably not a side effect	Unsure	Probably a side effect	Definitely a side effect
Nausea	Yes	No	Definitely not a side effect	Probably not a side effect	Unsure	Probably a side effect	Definitely a side effect
Diarrhoea	Yes	No	Definitely not a side effect	Probably not a side effect	Unsure	Probably a side effect	Definitely a side effect
Muscle pain or discomfort	Yes	No	Definitely not a side effect	Probably not a side effect	Unsure	Probably a side effect	Definitely a side effect

Figure 1. Excerpt of the SEAS showing the response format for symptom reporting and side effect attribution.

The SEAS was tested in three studies. The first study comprised of a university student sample receiving an influenza (flu) vaccination. The second study comprised of a sample of patients with gout or rheumatoid arthritis (RA), while the third study consisted of patients with epilepsy or bipolar disorder who had recently switched to a generic version of their medication. Table 1 shows the demographic characteristics of each sample.

Table 1. Demographic characteristics of the three study samples.

	Study Sample		
	Vaccination *N* (%)	Gout/RA *N* (%)	Medicine switch *N* (%)
Gender			
Male	59 (26.2%)	68 (66.7%)	21 (30.4%)
Female	164 (72.9%)	34 (33.3%)	48 (69.6%)
Ethnicity			
NZ European	167 (74.2%)	66 (64.7%)	47 (68.1%)
Māori	23 (10.2%)	6 (5.9%)	12 (17.4%)
Pacific Islander	7 (3.1%)	12 (11.8%)	-
Asian	14 (6.2%)	9 (8.8%)	3 (4.3%)
Other European	7 (3.1%)	-	4 (5.8%)
Other	7 (3.1%)	9 (8.8%)	1 (1.4%)
	M (*SD*)	*M* (*SD*)	*M* (*SD*)
Age	18.71 (2.62)	62.75 (13.28)	41.88 (12.60)

The reliability of the 50-item symptom list was assessed in each study. To examine the validity of the scale and the utility of the Side Effect Attribution Total Score compared to the Side Effect Attribution Binary Score, we correlated these scores to the relevant psychological variables in each of the study samples. Variables that were seen as not being associated with side effect reporting were used to determine discriminant validity.

Vaccination Study

Participants and Procedure

Participants in the first study were 225 students receiving the 2019 flu vaccination at Victoria University of Wellington, New Zealand. Students were approached at temporary vaccination clinics at four university halls of residence and were invited to participate in a study investigating side effects from vaccination. Interested students were provided with a participant information sheet and if they were eligible and agreed to participate, they were then given a written consent form to sign. Eligible participants were aged 18 years of age or older, students of the university, and were able to receive the vaccination. Before participants received the vaccination, they completed a baseline questionnaire assessing demographics, symptoms experienced in the past four weeks (which used the symptom list from the SEAS), vaccination attitudes and expectations. One week after the vaccination, participants completed another questionnaire, which used the SEAS to measure symptoms in the past seven days and side effects attributed to the vaccination. Of the 225 participants, 195 (87%) completed the follow-up assessment. The majority of the sample was female (73%) and the average age was 19 years. The study was approved by the University of Auckland Human Participants Ethics Committee (reference number 022819).

Validation Measures

Vaccination Attitudes. Participants' attitudes about vaccination were assessed using the Vaccination Attitudes Examination Scale (VAX; Martin & Petrie, 2017). The scale is comprised of four 3-item subscales: mistrust of vaccine benefit, worry about future effects, concerns about commercial profiteering, and preference for natural immunity. Participants rate their level of agreement with each item using a 6-point scale from 1 'Strongly disagree'

to 6 ‘Strongly agree’. For each subscale, items were summed to create a total score with higher scores indicating stronger vaccination attitudes in line with the subscale theme.

Since concerns about the safety and side effects of vaccination are quite common (Kata, 2010), the validity of the SEAS was tested by examining whether the greatest correlation was between the Side Effect Attribution Total Score and worry about the future effects of vaccination. This VAX subscale is more directly related to side effect reporting with an example item being “Although most vaccines appear to be safe, there may be problems that we have not yet discovered”. To demonstrate discriminant validity, we hypothesised that the other subscales would have a weaker relationship and there would be no significant correlations for the Side Effect Attribution Binary Score.

Side Effect Expectations. Participants’ expectations about side effects from vaccination were measured using a question adapted from previous research (Smith, Weinman, Amlôt, Yiend, & Rubin, 2019). Participants were asked how concerned they were about the side effects they might get from the vaccination and answered using a 10-point scale ranging from 1 ‘Not at all’ to 10 ‘Extremely’. Participants with higher expectations for side effects were hypothesised to have a greater Side Effect Attribution Total Score.

Gout and Rheumatoid Arthritis Study

Participants and Procedure

In the second study, participants were 102 patients diagnosed with either gout or rheumatoid arthritis (RA) and prescribed medication to manage their condition. To be eligible to participate, patients needed to be 18 years of age or older and taking the medication for at least one year. Patients of a rheumatology clinic in Auckland, New Zealand were invited to participate in a study investigating their perceptions of treatment. They were invited either directly by their rheumatologist or sent a letter by the Auckland District Health Board. In both cases, patients were given a participant information sheet to read and signed a written consent form if they agreed to participate. The study consisted of a questionnaire assessing demographics, perceived sensitivity to medicines, anxiety, intentional non-adherence, medicine information seeking behaviour, and the SEAS. Sixty percent of the sample had

gout and were being treated with the medication allopurinol, while the remaining 40% had RA and were on methotrexate to manage their condition. The average age of the sample was 63 years and 67% were male. The study was approved by the New Zealand Health and Disability Ethics Committee (reference number 19/CEN/148).

Validation Measures

Perceived Sensitivity to Medicines. The degree to which people believe they are particularly sensitive to the effect of medicines was measured using the Perceived Sensitivity to Medicines Scale (PSM; Horne et al., 2002). A greater perceived sensitivity to medicines has been shown to be associated with greater side effect reporting after taking a placebo described as a "well-known tablet" (Webster, Weinman, & Rubin, 2018). The scale consists of five statements, for example "My body overreacts to medicines", and participants were asked to indicate their agreement using a 5-point scale from 1 'Strongly disagree' to 5 'Strongly agree'. Scores for each item are summed to create a total score ranging from 5 to 25, with higher scores representing a greater perceived sensitivity to medicines. Higher perceived sensitivity to medicines was expected to correspond with a greater Side Effect Attribution Total Score.

Anxiety. In this study, state anxiety was assessed using the short-form Spielberger State-Trait Anxiety Inventory (STAI-6; Marteau & Bekker, 1992). The scale comprises of three anxiety present and three anxiety absent statements which participants are asked to rate their level of agreement with using a 4-point scale from 1 'Not at all' to 4 'Very much'. Scores for each item are summed to give a total anxiety score from 6 to 24. It was hypothesised that people with higher levels of anxiety would have a greater Side Effect Attribution Total Score.

Intentional Non-Adherence. The study specifically investigated the degree to which patients intentionally do not take their medication due to the perception of side effects. This was measured using the item "Because I don't like the side effects" from the first version of the Intentional Non-Adherence Scale (INAS; Weinman et al., 2018). The response option was a five-point scale from 1 'Strongly disagree' to 5 'Strongly agree'. It was hypothesized

that participants with greater intentional non-adherence due to side effects would also have a greater Side Effect Attribution Total Score.

Medicine Information Seeking. The extent of participants' medicine information seeking behaviour was measured with two questions, which have been used in previous research (Faasse, Grey, Horne, & Petrie, 2015; Kleinstäuber, MacKrill, & Petrie, 2018). Participants were asked how often they read the information sheets in medicine packs as well as how often they look up medicine information on the Internet. The response options consisted of an 11-point scale from 0 'Never' to 10 'Always'. To create a total score of medicine information seeking, a participant's responses to the two questions were summed. It was hypothesised that participants with higher medicine information seeking would have a greater Side Effect Attribution Total Score.

Medicine Brand Change Study

Participants and Procedure

The nocebo effect frequently occurs in medicine brand changes (Weissenfeld et al., 2010) so the final study comprised of 69 patients who had recently switched to a generic version of the medication lamotrigine. Due to a change in drug funding implemented by the New Zealand government Pharmaceutical Management Agency (PHARMAC), approximately 11,000 patients taking either the Lamictal or Arrow-Lamotrigine brands of lamotrigine had to switch to a generic version called Logem. This medication is primarily used to treat epilepsy and bipolar disorder. In this study, 61% of participants were taking lamotrigine to treat epilepsy, 33% to treat bipolar disorder, and 6% for other reasons. The majority of the sample was female (70%) and the average age was 42 years.

The study consisted of an online questionnaire, live from May 2019 to March 2020 and accessed via the PHARMAC lamotrigine brand change webpage. On the webpage, patients were invited to complete a brief survey about their perceptions and experiences of the medicine switch. To be eligible to participate, patients had to be at least 18 years of age and currently taking either Lamictal or Arrow-Lamotrigine. The first page of the survey provided interested respondents with information about the study and they were informed

that completing and submitting the questionnaire indicated consent to participate. The questionnaire also assessed medicine efficacy beliefs, trust in pharmaceutical agencies and used the SEAS to measure side effects attributed to Logem. The study was approved by the University of Auckland Human Participants Ethics Committee (reference number 022839).

Validation Measures

Trust in Pharmaceutical Agencies. The degree to which people trust pharmaceutical-related agencies has been shown to be associated with side effect reporting experimentally (Webster, Weinman, & Rubin, 2018) and with adverse reactions in medicines switches (MacKrill & Petrie, 2018). In this study, participants were asked to rate how much they trusted medicine information from pharmacists, PHARMAC, Medsafe (New Zealand's medicines safety authority) and drug companies. Responses were measured on a scale from 1 'Do not trust' to 10 'Completely trust'. Responses for these items were significantly correlated (r = .325 to .718) and so were summed to create a total 'trust in pharmaceutical agencies' score, which had a good Cronbach's alpha in this study (α = .80). People with lower trust were hypothesised to have a greater Side Effect Attribution Total Score.

Medicine Efficacy Beliefs. To assess participants' belief about the efficacy of the new generic medicine, participants were asked to indicate how well the medicine was managing their condition on a scale from 0 'Not at all' to 10 'Extremely well'. Previous research has shown that patients' beliefs about the efficacy of a new medicine is associated with side effect reporting after switching to a generic drug (MacKrill & Petrie, 2018). Therefore, it was expected that people with a lower efficacy belief would have a greater Side Effect Attribution Total Score.

Statistical Analyses

The internal consistency of the 50-item symptom list was assessed in each study by calculating the Cronbach's alpha value based on participants general symptom reporting. For the student vaccination sample, the reliability of the symptom list was measured with both the baseline data of symptoms experienced in the previous four weeks and with the follow-up data of symptoms experienced in the past seven days. The Cronbach's alpha for the Side

Effect Attribution Total Score was also calculated in each study. For the patient studies, Cronbach's alphas were calculated for the overall sample as well as individual patient groups. Independent samples t-tests were conducted to examine whether there were any differences between patients with gout versus RA and patients with epilepsy versus bipolar disorder in general symptom reporting, the Side Effect Attribution Total Score and Binary Score.

To assess the validity of the SEAS we examined the correlations between VAX subscales and side effect expectations in the Vaccination Study and the SEAS Side Effect Attribution Total Score and Binary Score. In the Gout/RA study we looked at the associations between perceived sensitivity to medicine, anxiety, non-adherence due to side effects and medicine information seeking scale completed by participants and the SEAS side effect total and attribution score. In the Medicine Switch Study we examined the correlations between trust in pharmaceutical agencies and belief in the efficacy of new medicine and the SEAS Side Effect Attribution Total Score and Binary Score. It was hypothesised that the relationship with the Attribution Total Score would be stronger than those for the Attribution Binary Score. An alpha level of .05 was considered significant for all analyses.

Results

At baseline prior to the vaccination, the university student sample reported an average of 11 symptoms in the previous four weeks and then five symptoms in the seven days following the vaccination (see Table 2 for exact means and standard deviations). In the collective sample of patients with gout or RA, the average number of symptoms in the previous week was 13. There was no significant difference in symptom reporting for people with gout or RA, $t(100) = -1.69$, $p = .09$. The sample of patients who had switched to the generic medicine experienced an average of 14 symptoms and there was also no significant difference in symptom reporting for people with epilepsy or bipolar disorder, $t(62) = -1.41$, $p = .16$.

Reliability

The Cronbach's alphas for each study are shown in Table 2. The alphas range from .840 to .943, which shows that the list of 50 symptoms has good internal consistency. The reliability

is consistent across the three study samples as well as within each study patient group. The vaccination results show that the symptom list is also stable when assessing symptoms in either the past four weeks or seven days.

Table 2. Cronbach's alphas and total number of symptoms, Side Effect Attribution Total Score and Attribution Binary Score for each study.

Study	Cronbach's α for symptom total	Cronbach's α for Attribution Total Score	Symptom total *M* (*SD*)	Attribution Binary Score *M* (*SD*)	Attribution Total Score *M* (*SD*)
Vaccination					
Baseline	.855	-	10.84 (6.57)	-	-
Follow-up	.840	.865	4.55 (4.48)	1.51 (2.67)	2.30 (1.18)
Gout/RA	.943	.964	12.70 (10.76)	2.71 (5.80)	2.33 (0.97)
Gout	.879	.954	11.23 (9.52)	1.93 (3.83)	2.15 (0.91)
RA	.914	.970	14.88 (12.18)	3.90 (7.78)	2.56 (1.02)
Medicine Switch	.913	.908	13.99 (8.80)	9.06 (7.02)	3.88 (0.68)
Epilepsy	.913	.924	12.54 (9.09)	8.45 (7.72)	3.97 (0.67)
Bipolar	.895	.895	15.70 (8.18)	10.52 (6.03)	3.85 (0.67)

Note: The baseline symptom total for the vaccination study is from a 4-week timeframe. The vaccination follow-up symptom total and all other studies measure symptoms in the past seven days.

Validity

Table 2 shows the average Side Effect Attribution Total Score and Binary Score for each study sample. The binary score indicated that the vaccination sample reported 1.51 side effects one week after receiving the vaccination. The average Side Effect Attribution Total Score was 2.30, indicating that in general this sample tended to believe that their symptoms were not vaccination side effects. The gout/RA study reported an average of 2.73 side effects. The two patient groups did not differ significantly in the number of side effects reported, $t(53.13) = -1.50$, $p = .14$. There was a significant difference in the average Attribution Total Score, with RA patients having a greater score (2.56) than those with gout (2.15), $t(93) = -2.07$, $p = .042$. This indicates that the RA patients were more uncertain about whether their symptoms were side effects. The medicine brand change sample reported 9.06

side effects. There was no difference in the side effect reporting by patients with epilepsy or bipolar disorder, $t(61) = -1.11$, $p = .27$. The Side Effect Attribution Total Score was 3.88 and there was no significant difference between the two patient groups, $t(59) = 0.66$, $p = .51$. This suggests that participants were leaning towards their symptoms possibly being side effects of the new generic medicine.

We examined the correlations between the Side Effect Attribution Binary Score and Attribution Total Score and relevant measures in the three studies and these results are presented in Table 3. It was hypothesised that these relationships would be stronger for the SEAS Attribution Total Score than for the Binary Score. In the Vaccination Study there were significant associations between the Attribution Total Score and the VAX worry about future effects and concerns about commercial profiteering subscales. There was also a significant correlation between the SEAS Attribution Total Score and participants' expectations for side effects from the flu vaccine. The Attribution Binary Scores was not significantly associated with the VAX subscales or expectations for side effects.

In the Gout/RA Study both the Side Effect Attribution Total Score and Binary Score were significantly correlated with perceived sensitivity to medicines, anxiety, intentional non-adherence due to side effects, and greater medicine information seeking. The SEAS Attribution Total Score generally had stronger relationship with these variables apart from anxiety, which was more significantly associated with the Binary Total. In the Medicine Switch Study, the SEAS Attribution Total Score was significantly associated with both a lower belief in the efficacy of the new medicine and trust in pharmaceutical agencies. Across all samples the findings also show that on the whole, the Attribution Total Score was more strongly related to the validation outcomes than the binary total number of side effects.

Table 3. Correlations between relevant measures in vaccination study, Gout/RA study, and medicine switch study

	Attribution Binary Score		Attribution Total Score	
Measure	*r*	*p*	*r*	*p*
Vaccination Study				
Vax Subscales				
Mistrust of vaccine benefit*	-.01	.92	.04	.64
Worry about future effects	.09	.26	.16	**.046**
Concerns about commercial profiteering*	.09	.27	.18	**.028**
Preference for natural immunity*	.13	.12	.11	.17
Expectations for vaccination side effects	.15	.07	.18	**.028**
Gout/RA Study				
Perceived sensitivity to medicines	.31	**.001**	.50	**<.001**
Anxiety	.34	**<.001**	.25	**.016**
Non-adherence due to side effects (INAS)	.25	**.010**	.30	**.003**
Medicine information seeking	.23	**.021**	.26	**.010**
Medicine Switch Study				
Trust in pharmaceutical agencies	-.08	.56	-.29	**.026**
Belief in the efficacy of new medicine	-.26	**.033**	-.46	**<.001**

Note: * indicates measure is used for discriminant validity

Discussion

The aim of these studies was to develop and test a new measure of side effect reporting that provides a greater focus on the process of symptom misattribution. While previous measures tend only to assess the total number of side effect reported, this new scale also examines people's overall predisposition to believe that their symptoms are or are not side effects. The three studies provide evidence that the Side Effect Attribution Scale is reliable and valid in both a healthy vaccination sample and patients taking medicines. The findings also point to the fact that measurement of this attributional bias may offer valuable new insights into side effect reporting and non-adherence.

The list of 50 symptom items showed good internal consistency and that the scale was answered consistently across different samples. The scale also appeared sensitive to timeframes, as was the case in the vaccination study where participants were asked to reflect on symptoms in the past seven days or four weeks. The list of symptoms is drawn

from side effects reported from the current most prescribed medicines and is the first general scale to include side effects from biologic drugs.

The SEAS Side Effect Attribution Total Score provides insight into how participants interpret their symptoms following treatment and is useful in identifying the attribution bias towards interpreting symptoms as treatment side effects. The student vaccination sample and patients with gout/RA had low attribution scores, which indicates that overall they tended to believe their symptoms were not side effects. Conversely, patients changing to a generic version of their medication had higher scores, indicating that they believed their symptoms were more likely to be side effects. This sample possibly had greater side effect attribution scores as patients can be concerned about medicine switches (Forbes, Davies, & Horne, 2011) and changing medicines can induce strong nocebo responding resulting in increased side effects (Faasse, Cundy, Gamble, & Petrie, 2013).

Regarding discriminant validity, it was expected that there would be no relationship between the Attribution Total Score and variables not directly associated with side effects. In line with this, there were no significant correlation between Attribution Total Score and the VAX 'mistrust of vaccine benefit' or 'preference for natural immunity' subscales. However, there was a correlation for the VAX subscale regarding concerns about commercial profiteering. As was expected, a higher level of worry about future effects of vaccination (i.e. side effects) was associated with a greater Attribution Total Score.

Generally the results supported the validity of the scale. Greater side effect expectations, greater perceived sensitivity to medicines, greater anxiety, lower trust in pharmaceutical agencies and lower medicine efficacy beliefs have been shown to be associated with greater nocebo responding and in the current study these measures corresponded with greater side effect attribution scores. The notable finding is that the attributional scale was more strongly related to the validation outcomes than the binary measure of total number of side effects, which has been the primary outcome of previous research but does not fully assess attribution beliefs. It has been found that scales with fewer response options, such as yes/no side effect measures, give less reliable data as they fail to

discriminate between respondents' strength of beliefs (DeCastellarnau, 2017). More response options, as is the case of the SEAS, allow for a greater assessment of belief intensity (Schaeffer & Presser, 2003). The pattern of results suggests that the Attribution Total Score is a more sensitive measure than binary side effect totals and may be tapping into something unique and separate to side effect reporting. Having a greater understanding of how people interpret symptoms as side effects is important since the misattribution of symptoms is central to the nocebo effect (Petrie & Rief, 2019).

It is important to note that the Side Effect Attribution Total Score and Attribution Binary Score will be highly correlated as they are measuring the same construct. The side effect total could be considered a cruder attribution score based on a binary measure of 'side effect present' versus 'absent'. While this study has demonstrated that the 1-5 attribution score is a more accurate measure of side effect beliefs, the side effect total is not redundant as it may be still useful to know the number of side effects people believe they have experienced. A potential limitation of the SEAS, compared to other side effect scales such as the GASE (Rief et al., 2011), is that it does not include an opportunity for reporting the severity of symptoms. It could be that the symptoms that are rated as being more severe are more likely to be attributed as a side effect. Future versions of the scale could examine the relationship between symptom severity and attribution score. Future research could also test a shorter list of side effect items, which could be produced by removing items that are present in less than 10% of respondents (see supplementary material). Symptoms that are not frequently reported in day-to-day life are unlikely to then be attributed as side effects. Further research is needed to establish the validity of the SEAS in other samples and could also test translations of the scale into other languages.

In conclusion, the SEAS provides a measure of an individual's attributional bias towards seeing symptoms as side effects. The degree to which people believe symptoms may or may not be side effects has been neglected in past research but we have demonstrated that it may be an important factor in investigating the nocebo response and non-adherence to treatment. The three studies show that the Side Effect Attribution Total

Score has significant associations with psychological variables known to predict side effect reporting. Future research should consider a brief version of the SEAS and validating the scale in diverse populations.

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