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ORIGINAL ARTICLE

Personality Influences the Reporting of Side Effects of Inhaled Corticosteroids in Asthma Patients

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Rationale. Negative affectivity is a measure of anxiety associated with increased reporting of symptoms. Few studies have explored this association with respect to drug-induced symptoms in patients taking medication for a chronic disease in real life. **Objectives.** In this cross-sectional study we examined the relationship between negative affectivity and self-reported side effects of inhaled corticosteroids in patients with asthma. We also investigated differential associations due to side effect type (subjective versus observable side effects) and treatment impact (i.e., hierarchical dosing). **Methods.** A total of 228 asthma patients, taking inhaled corticosteroids, completed scales measuring inhaled corticosteroid-induced side effects (Inhaled Corticosteroid Questionnaire scored: 0 = none; 100 = worst) and negative affectivity (Positive and Negative Affect Schedule scored: 10–50). Patients were grouped into low, average, and high negative affectivity groups based on published norms. **Results.** Patients high in negative affectivity reported significantly greater ($p < 0.001$) side effects (median score 20.5 (IQR: 11.4–33.0) than the groups of patients scoring lower on this measure (low negative affectivity: 7.1 (3.1–15.6); average: 13.3 (4.9–23.3)). The relationship between negative affectivity and side effects was stronger among patients taking low ($r = 0.40$ – 0.45) rather than mid to high inhaled corticosteroid doses ($r = 0.16$ – 0.28). **Conclusions.** Asthma patients with higher negative affectivity using inhaled corticosteroids report increased medication-induced symptoms. Clinicians should be aware that aside from inhaled corticosteroid dosage, the personality of the patient is an important factor in the reporting of drug-related side effects.

Keywords adverse effects, inhaled, glucocorticoids, anxiety, affect

INTRODUCTION

Mild side effects are often overlooked in clinical consultations (1). Many clinicians may instinctively feel that the reporting of mild side effects is driven predominantly by the personality of the patient making it unattractive to discuss side effects during a busy clinic. Certainly, psychological factors such as anxiety have been shown to influence patients' experiences and reporting of symptoms. Anxiety is a personality construct that represents a tendency towards fear, worry and perceived threat (2, 3). Negative affectivity is a major distinguishing feature of anxiety to which it is strongly related (2, 4). High negative affectivity is associated with increased reporting of symptoms (of up to 3 times higher) or general health complaints, compared to individuals scoring low on this measure (5–8). The relationship between negative affectivity and increased symptom-reporting exists among a large range of symptoms including bodily pain, itch, swollen joints, headaches, and nausea (5, 9).

Although many studies have investigated the relationship between somatic physical symptoms and anxiety measures, fewer studies have investigated the same relationship in medication-induced symptoms. Negative affectivity was associated with the self-reported side effects of radiation in

a randomized clinical trial of males receiving therapy for prostate cancer (10), but not with the side effects (total number) of analgesic medication in healthy men and women in a double-blind experimental study of pain perception (11). Trait anxiety was related to the reporting of tamoxifen-induced side effects in women participating in a randomized clinical trial of chemoprevention therapy (4).

Some studies suggest that the type of side effect may be an important factor in the association between anxiety measures and reporting. For example, trait anxiety and negative affectivity were associated with reports of vague (subjective) side effects but not concrete (observable) side effects of chemotherapy and inoculation (e.g. tetanus toroid), respectively (12, 13). Furthermore, it is hypothesized that the magnitude of the association between anxiety measures and "subjective" side effect-reporting may be proportionate to the impact of the drug treatment (12), although research is still needed to test this hypothesis.

No previous study, to our knowledge, has used a validated patient-report instrument to measure the side effect reporting of patients, and most existing studies have been conducted as part of a clinical trial or in healthy patients under experimental conditions.

Therefore in this observational cross-sectional survey of patients using inhaled corticosteroids (ICS) for the prophylactic treatment of asthma, we use a validated ICS-specific side effect scale (14–17) to examine the relationship between side effect-reporting and negative affectivity. We

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investigate any differential association due to the subjective or observable nature of side effects and examine the influence of medication impact with respect to the medication dose received.

METHODS

Ethical approval was sought but not required for questionnaire completion in The Netherlands. Patients (16 to 74 years of age; ≤ 20 pack years; with a physician diagnosis of asthma; taking ICS) from three asthma research cohorts in The Netherlands were invited to participate. Included patients reported no use of oral corticosteroids (previous 4 weeks), corticosteroid injections (previous 6 months), and no change in their ICS dose (previous 14 days).

Self-Report Questionnaire

Patients consented to complete a self-report questionnaire, which included:

Drug-Induced Symptoms. The Inhaled Corticosteroid Questionnaire (ICQ) is a 57-item scale measuring self-rated ICS-induced side effects (e.g., voice and skin problems) in the previous 14 days (0 = "none" – 6 = "a very great deal"). The total and 15 domains of the ICQ are scored: 0 (best) – to 100 (worst) (see full list of items in Appendix).

Negative Affectivity. The negative affect scale of the Positive and Negative Affect Schedule (PANAS) (6, 18) is scored 10 (lowest) to 50 (highest). We used the time-frame "past few weeks."

Medication Use. Patients reported: daily dose of ICS (microgram dose, puffs taken per day); concomitant use of oral corticosteroid courses (past 12 weeks); corticosteroid injections (previous 6 months); current use of additional prescribed medications; date of first starting ICS treatment.

Asthma Status. Patients also reported the 6-item Asthma Control Questionnaire (ACQ) scored 0 to 6 (forced expiratory volume in 1 second question omitted) (19); number of emergency hospital visits for asthma (previous year); age when asthma was diagnosed.

Patient Demographics. Smoking status and educational level were also collected.

Procedure

Participants were categorized by their total score on negative affectivity (10–50) based on published norms (18) for healthy subjects: low NA (females [F]: ≤ 12 –15; males [M]: ≤ 12 –16); average NA (F: 16–23; M: 17–24) and high NA (F: ≥ 24 ; M: ≥ 25). The negative affectivity scores in our sample were similar to those of healthy patients. Participants were also categorized by their current daily ICS dose (low ≤ 400 μg ; medium 401–800 μg ; high > 800 μg (20); all stated doses are beclomethasone dipropionate (BDP) equivalent (1 μg of BDP/budesonide was equivalent to 0.5 μg fluticasone propionate irrespective of delivery device) (21, 22). As ICQ total scores were non-normally distributed all analyses were non-parametric and scores represented as medians and interquartile ranges. ICQ scores were subsequently logged in order that group means could be plotted onto a graph.

Six independent clinicians or researchers sorted the items of the ICQ into three categories: vague (subjective), concrete (observable), or neither (12). If four or more of the six raters agreed we allocated the item to the indicated category, otherwise the item was not allocated. We calculated overall rater-agreement: ([sum (percentage rater-agreement for each item)] / number of items rated [$n = 57$]).

The association between negative affectivity and subjective or observable side effects was examined using correlations. To carry out this part of the analysis the validated scoring system for the ICQ (total and domain scores 0–100) was abandoned, and correlations were conducted instead between total NA score (10–50) and the mean of ICQ item scores in each category (0–6) (12). This analysis was performed for the whole sample and after stratifying by dose group.

We also examined the relationship between negative affectivity and the 15 individual ICQ domains (see appendix) by correlating total NA score (10–50) with each of the 15 (validated) ICQ domain scores (0–100). All analyses were conducted using SPSS for windows version 14.

RESULTS

Patient characteristics can be seen in Table 1. Two hundred twenty-eight patients were eligible for analysis. One hundred five patients (46%) were using high daily doses of ICS, and the mean daily dose for the whole sample was 948 μg . Current asthma control was predominantly well-controlled (well-controlled is defined as scoring < 0.75 on the Asthma Control Questionnaire) (23) with only 21% of patients ($n = 47$) reporting uncontrolled asthma and 2 patients reporting an emergency hospital visit in the last 12 months.

We investigated the relationship between side effect reporting, negative affectivity, and ICS dose. Patients reported

TABLE 1.—Patient characteristics.

Self-reported patient characteristics	n = 228
Age in years – mean (SD)	43 (11.7)
Female sex	128 (56)
Medication use:	
Current daily dose ICS – mean μg (SD)	948 (653)
Duration of ICS use in years – mean (SD)*	13.3 (8.8)
Current use of nasal corticosteroid	59 (26)
Current use of eye or ear or dermal corticosteroid	9 (4)
Current use of short-acting β_2 -agonist	57 (25)
Current use of long-acting β_2 -agonist*	149 (67)
Current use of 1 or more concomitant drug	147 (65)
History of smoking:*	
Never smoked	125 (55)
Former smoker	85 (38)
Current smoker	16 (7)
Disease status and history:	
Current asthma control measured by the Asthma Control Questionnaire – median (IQR)	0.7 (0.21–1.5)
One or more emergency hospital visits for asthma in last year*	2 (1)
Age at diagnosis of asthma – median (IQR)*	15.4 (3.9–28.3)
Number of medical co-morbidities:	
None	79 (35)
1	96 (42)
2 or more	53 (23)
Education beyond high school	61 (27)

All data represent no. of subjects (%), unless otherwise specified. In calculating percentages for each characteristic, the number of subjects for whom there were complete data was used as the denominator. *Data were missing for the following variables: duration of ICS use in years ($n = 25$); use of long-acting β_2 -agonist ($n = 7$); history of smoking ($n = 2$); emergency hospital visits ($n = 1$); and age at diagnosis of asthma ($n = 10$).

TABLE 2.—ICQ side effect score by negative affectivity (NA) and dose group.

ICS dose	n	All NA groups	n	Low NA	n	Average NA	n	High NA	value [†]
All doses	228	11.4 (4.0–23.3)	101	7.1 (3.1–15.6)	88	13.3 (4.9–23.3)	39	20.5 (11.4–33.0)	<0.001
Low	61	7.4 (2.5–14.1)	32	3.7 (1.1–8.0)	23	12.8 (4.7–20.0)	6	27.0 (8.7–53.5)	<0.001
Medium	62	10.2 (3.0–21.1)	24	5.1 (2.4–13.8)	28	14.2 (2.9–23.6)	10	16.6 (5.1–24.7)	0.042
High	105	14.6 (8.9–30.1)	45	13.7 (6.2–32.7)	37	12.5 (7.2–24.3)	23	24.5 (14.2–35.0)	0.053
<i>p</i> value [†]		<0.001		<0.001		0.539		0.439	

[†]Jonckheere-Terpstra test for comparison between low to high groups (highlighted bold); ICS = inhaled corticosteroid.

greater side effect scores by increasing negative affectivity with the high negative affectivity group reporting the highest side effect scores in all dose groups (see Table 2 rows: the high dose group bordered on statistical significance [$p = 0.053$]). Thus, side effect reports increased consistently with increasing negative affectivity.

With respect to ICS dose, patients reported greater side effect scores by increasing dose group in the total sample and the low negative affectivity group, but not in the average ($p = 0.539$) or high ($p = 0.439$) negative affectivity groups (see Table 2 columns). Thus, although side effect scores increased with increasing ICS dose for the total group of patients, this was not the case for the group of patients with average to high negative affectivity (logged group mean ICQ scores depicted in Figure 1).

We also carried out an investigation of the relationship between negative affectivity and side effect “type.” The level of rater-agreement was 77% for sorting the 57 ICQ items into the categories: subjective or observable. The 35 subjective side effects included: “feeling of exhaustion when talking,” “painful throat when talking,” “feeling thirsty,” “loss of appetite,” “mood swings,” “feeling tired.” The 15 observable side effects included “hoarseness of the voice,” “dry skin,” “oral thrush,” “swollen face or fluid around the face,” “bruising easily.” Seven items did not reach agreement as they were rated as “a bit a subjective and a bit observable” so we catego-

rized them as undifferentiated (see Appendix for the full list). No items were categorized by raters as “neither” subjective or observable.

We then examined the association between negative affectivity and reporting of subjective or observable side effects. Negative affectivity showed a positive association with both subjective and observable side effects overall, with correlations marginally higher between negative affectivity and subjective side effects (Table 3: “all doses”). We then stratified the sample by (hierarchical) dose (rows 3–5, Table 3). After stratification, differences in side effect type were most apparent in the mid- and high-dose groups, where although the subjective side effects were significantly associated with negative affectivity, the observable side effects were not.

We also investigated the association between total negative affectivity score and the 15 separate domain scores of the ICQ side effect questionnaire. Results showed that the 3 domains containing only observable side effects were not associated with negative affectivity, whereas the 11 domains containing subjective items were associated with negative affectivity, the most strongly associated being “Mood problems” ($r = 0.423$, $p < 0.01$) and “Tiredness” ($r = 0.301$, $p < 0.01$)—others included “Vision deterioration” ($r = 0.225$, $p < 0.05$), and “Oropharyngeal itching” ($r = 0.149$, $p < 0.05$) (data not shown).

DISCUSSION

The present observational findings provide an insight into the importance of personality on the reporting of drug-induced symptoms in patients with asthma. Data showed that in real-life, as in clinical trials or experimental studies, patients with high negative affectivity report significantly greater side effects than patients scoring lower on this anxiety measure. With respect to different side effect types, negative affectivity was consistently more strongly associated with subjective than with observable side effects, albeit that differences between correlation coefficients were rather small. Hence, although negative affectivity is associated with

FIGURE 1.—Side effect score (logged ICQ total score) by ICS dose and negative affectivity group.

TABLE 3.—Association between negative affectivity and side effects, stratified by side effect type and inhaled corticosteroid dose.

ICS dose group	n	Subjective side effects (n = 35) [†]	Observable side effects (n = 15) [†]
All doses	228	0.35**	0.26**
Low dose	61	0.45**	0.40**
Mid dose	62	0.28*	0.19
High dose	105	0.26**	0.16

Correlation coefficients (Spearman's rho) represent associations between NA score (10–50) and the mean of summed ICQ item scores (0–6) in each side effect “type” category: * $p < 0.05$ ** $p < 0.01$; [†]7 of the 57 ICQ items could not be categorized.

increased side effect reports, the strength of the association may be partly dependent on the relative subjectivity of the side effect reported.

Although it is not possible to determine the cause of differences in reporting due to the cross-sectional study design used, results invite speculation. One frequently posited explanation for the differential symptom-reporting associated with anxiety is the symptom perception hypothesis. Under this hypothesis, patients with high anxiety over-report unfounded subjective symptoms, owing to increased encoding (noticing or vigilance) and inaccurate recall of symptoms, leading to erroneous attribution of somatic symptoms to medical causes (2, 5, 24). However, at least with respect to treatment-induced symptoms, elegantly designed prospective studies have begun to provide evidence to refute this theory (4, 12, 13, 25). This has lead some researchers to test an alternative veridical reporting hypothesis, which proposes that differences in reporting in different anxiety groups may reflect true differences in experiences of side effects. Anxiety may influence the reactivity of body systems (e.g., endocrine system, immune system), with increased reactivity occurring in anxious persons. For example, subjective side effects such as mood swings caused by the effects of chemotherapy on the endocrine system are reported more in anxious persons (25). In the present data, the subjective side effects of ICS affecting the endocrine system, such as mood problems and tiredness (e.g., due to adrenal insufficiency) (26) were significantly (and most strongly) correlated with negative affectivity. This data could support the hypothesis that increased reporting in high negative affectivity persons reflects true increases in endocrine-associated side effects. However, without objective or prospective data we cannot rule out the possibility that the differential reporting of subjective and observable side effects is cognitive in origin, occurring as a result of the differential ambiguity of side effects (i.e., patients may encode and recall subjective and observable symptoms differently) rather than as a result of true differences in side effect occurrence.

In this study we also explored the proposition that the relationship between subjective side effects and negative affectivity is influenced by the impact (dose) of the treatment. We compared the association between negative affectivity and subjective side effects at different ICS doses. At low doses the association was stronger ($r = 0.45$) than at mid and high doses ($r = 0.28$, $r = 0.26$). However, this was also true for observable side effects, so treatment impact is probably important for the relationship between negative affectivity and side effect reporting regardless of relative subjectivity. Thus, it appears that the impact of ICS is greater in patients with higher negative affectivity taking relatively low doses.

Cognitive or physiological processes may provide an explanation for this. With respect to the cognitive (symptom perception) hypothesis: Patients taking the lowest doses have few disease symptoms (presently or in the past) making drug side effects more noticeable for high negative affectivity persons with a propensity to vigilantly scan and encode symptoms. In comparison, patients taking high treatment doses may have a number of disease symptoms (such as breathlessness), which take precedent cognitively due to their greater health threat. With respect to the physiological

(veridical reporting) hypothesis, it may be that greater disease severity may in some way mediate drug-related symptoms. For example, asthma patients with milder disease may have greater systemic bioavailability of ICS than those with more severe disease (27, 28). Mortimer (2006) compared the plasma concentrations of four different ICS in 30 asthma patients (between 18 to 70 years of age) with differing disease severity. Compared to patients with severe disease (50% predicted FEV₁) taking the same moderate ICS dose (~800 μ g) patients with milder disease (100% predicted FEV₁) had up to 2.2 times higher plasma concentrations of ICS (27). Thus, if patients with high negative affectivity have higher reactivity of the endocrine or other body systems as a result of their greater anxiety, this may lead to greater reporting of side effects at low than at higher doses. This is demonstrated somewhat in Figure 1, where patients with average to high negative affectivity (but not low negative affectivity) taking the lowest doses had such inflated side effect scores that a dose response was no longer significant.

The limitations of this study include that data are cross-sectional preventing the determination of cause and effect. The research literature is predominantly focused on determining how increased anxiety drives inflated symptom reporting, although the opposite (i.e., that increased symptoms drive inflated anxiety) is also possible. Secondly, we recorded only self-reported side effects in this study, whereas objective measures of drug effect (e.g., adrenal suppression measured by plasma or urinary cortisol) may have provided evidence of the relationship between negative affectivity and physiological processes. Our data show that negative affectivity is consistently more strongly associated with subjective than observable side effects, but the magnitude of the difference between correlation coefficients was small in this study. It is possible that a more definitive measure of (state) negative affectivity is needed test for differences between these types of side effect, therefore in future research concurrent reporting (e.g., "today") might be used rather than the retrospective reporting ("past few weeks") used in this study.

The key clinical implication for these findings is that, as many clinicians instinctively believe, the personality of the patient influences patient-perceived side effects, potentially affecting adherence to medication regimens as a result. Patients with a high level of anxiety perceive more side effects. Randomized clinical trials show that provision of information about potential side effects, and how to manage them, may lower anxiety, reduce side effect reporting, and increase appropriate self-care behavior (10, 29). Patients consistently report that they wish to be informed of all potential side effects of their medication (30–32), and provision of this information is unlikely to lead to increased side effect reporting in itself (33). However, the format of information giving is crucial; asthma patients prefer one-to-one medication information tailored to their specific needs rather than generic leaflets that are often too difficult or confusing for the majority of patients (34).

In conclusion, our data show that in patients taking inhaled corticosteroids for the treatment of asthma, aside from inhaled corticosteroid dosage, the personality of the patient is an important factor in the reporting of mild side effects.

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Appendix.—Categorizations by type of side effect for the 57 items in the 15-domain ICQ.

Dental Deterioration – 1 item:			
• any form of dental decline (tooth decay, tooth staining etc.)	O		
Eye dryness – 1 item:			
• dry eyes	X		
Facial Oedema – 1 item:			
• a swollen face or fluid around the face	O		
Mood Problems – 3 items:			
• feeling ‘grumpy’	S		
• mood swings	S		
• feeling ‘easily irritated’	S		
Oral Candidiasis – 1 item:			
• oral thrush (fungal infection: sore throat covered with pustules, and difficulty swallowing)	O		
Oropharyngeal Itching – 2 items:			
• an itchy feeling on the roof of your mouth	S		
• an itchy feeling in the back of your throat	S		
Oropharynx Problems – 9 items:			
• coughing	O		
• coughing up phlegm	O		
• coughing up thick mucus	X		
• thick mucus coming up	X		
• thick mucus sticking at the back of your throat	S		
• a need to clear your throat	X		
• mucus in your throat	S		
• a ‘clump’ in your throat	S		
• a feeling that ‘a layer of mucus stays on the back’ of your throat	S		
Perspiration – 2 items:			
• sweating	S		
• sweating during the night	X		
Skin, Hair and Nails – 7 items:			
• dry skin on the face	O		
• dry skin	O		
• bruising easily	O		
• bruises that are painful for a long period	S		
• thinner skin or less flexibility in your skin	O		
• brittle nails, or your nails breaking easily	O		
• hair loss	O		
		Taste Disruption – 3 items:	
		• a change in your ability to taste	S
		• a loss of ability to taste	S
		• a loss of appetite	S
		Thirst – 2 items:	
		• feeling thirsty	S
		• wanting to drink liquid (because of a dry mouth)	S
		Tiredness – 2 items:	
		• difficulty sleeping	S
		• feeling tired	S
		Unpleasant Taste – 7 items:	
		• a terrible taste in your mouth	S
		• a ‘taste’ on the teeth	S
		• a ‘bad taste’ or unfresh feeling in your mouth	S
		• bad breath	O
		• wanting to rinse your mouth	S
		• wanting to brush your teeth	S
		• wanting to chew gum	S
		Vision Deterioration – 1 item:	
		• come kind of deterioration of your vision	S
		Voice Problems – 15 items:	
		• hoarseness of the voice	O
		• a ‘rough’ voice	O
		• a noticeable change to your voice	O
		• your voice feeling similar to how your voice feels when recovering from the flu	S
		• your voice feeling like it had ‘gone to the back of your throat’	S
		• not being able to sing	S
		• loss of speech volume so that you couldn’t talk as loudly as normal	X
		• a feeling of exhaustion when talking	S
		• a painful throat when talking	S
		• a feeling that other people couldn’t understand your speech because you speak too softly or not clearly enough	S
		• a breaking voice	O
		• a ‘rough’ throat	S
		• a sore throat	S
		• an unpleasant feeling in your throat	S
		• a dry throat	S

O = observable; S = subjective; X = these undifferentiated items were rated a bit observable and a bit subjective