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A qualitative study of the impact of severe asthma and its treatment showing that treatment burden is neglected in existing asthma assessment scales

Hyland, ME

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Bias in the assessment of quality of life in severe asthma due to the burden of oral
corticosteroids

Michael E. Hyland^{1,2}, Ben Whalley^{1,2}, Rupert C. Jones^{2,3}, Matthew Masoli^{2,4}

1. School of Psychology, Plymouth University, UK
2. Plymouth Respiratory Psychology Partnership
3. Plymouth University Schools of Medicine and Dentistry, Plymouth University, UK
4. Department of Respiratory Medicine, Plymouth Hospitals NHS Trust, UK

Corresponding author: Professor Michael Hyland, School of Psychology, Plymouth University, Plymouth PL4 8AA, UK. email: mhyland@plymouth.ac.uk, direct tel: +44 (0)1752584834, Sec tel +44 (0) 1752544800, Fax +44 (0) 1752 233362

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Abstract

Purpose

People with severe asthma experience significant respiratory symptoms and suffer adverse effects of oral corticosteroids (OCS), including disturbed mood and physical symptoms. The impact of OCS on health-related quality of life (HRQoL) has not been quantified. Asthma HRQoL scales are valid as outcome measures for patients requiring OCS only if they assess the deficits imposed by OCS. This study compared the burden of disease and treatment in patients with severe asthma with items in 8 asthma specific HRQoL scales.

Methods

23 patients with severe asthma recruited from a severe asthma clinic were interviewed about the impact of their respiratory symptoms and the burden of their treatment. Patients' reports were compared with the items of eight established asthma-specific HRQoL scales.

Results

In addition to the burden caused by symptoms, ten domains of OCS impact on HRQoL were identified: depression, irritability, sleep, hunger, weight, skin, gastric, pain, disease anxiety, medication anxiety. Impact varied and for some was substantial. Although all HRQoL scales include some OCS-relevant items, all eight scales fail to adequately assess the several types of burden experienced by some patients while on OCS.

Conclusion

Existing asthma HRQoL scales provide an over-positive estimation of HRQoL in patients with frequent exposure to OCS and underestimate the benefit of interventions that reduce OCS exposure. Apart from global HRQoL scale usage, bias can be avoided *either* by designing burden-specific questionnaires to be used alongside existing scales *or* by designing scales where the burdens of symptoms and medication are compared using equivalent response scales.

Keywords: Severe asthma; difficult asthma; quality of life; QALY; validity; assessment

Bias in the assessment of quality of life in severe asthma due to the burden of oral corticosteroids

Health related quality of life (HRQoL) is one of several outcome measures used to inform treatment guidelines for asthma, and is unique amongst outcome measures in that it informs whether treatment is worthwhile from the perspective of the patient[1]. Asthma-specific HRQOL scales have content validity to the extent that items in the scale assess the range of deficits experienced by patients with asthma. Content validity confers sensitivity to changes following an intervention: treatment benefit will be underestimated if content validity and sensitivity to change are poor. Asthma-specific HRQoL scales tend to be more sensitive to change than generic scales because they exclude items which are unlikely to change following treatment, and because generic scales do not include specific items relating to potential asthma improvement[2, 3].

The majority of patients with asthma have mild-to-moderate disease and the potential to be well-controlled with existing therapies (inhaled corticosteroids and bronchodilators). However, severe asthma is a much more heterogenous condition and is increasingly recognised as qualitatively different from mild-to-moderate asthma. These patients are more challenging to manage and are more likely to require treatment with oral corticosteroids (OCS). If the HRQoL deficits of asthma vary only in degree between mild, moderate and severe patients, then a scale which has shown to be valid and sensitive to change in mild and moderate patient should also be valid for patients with severe asthma – assuming that items are chosen to avoid floor or ceiling effects. However, if severe asthma patients have uniquely different types of HRQoL deficits,

then a scale that omitted those deficits would not be valid for severe patients, even though it might be valid for mild or moderate patients.

All published asthma HRQoL scales contain items relating to the burden of asthma (i.e., activity restriction and emotional impact of asthma), and some include one or more items relating to the impact of treatment. The impact of OCS is known to be far greater than the impact of other asthma treatments[4, 5], and therefore severe patients, i.e., those who require maintenance or frequent bursts of high dose OCS, are likely to have a greater treatment burden than other patients. OCS are known to have direct effects on mood (e.g., depression, suicidal ideation, anxiety) as well as physical effects (e.g., weight gain) that also can have psychological implications[6-8]. It is unclear whether the burden of treatment is adequately measured by existing scales. If existing scales fail to assess the impact of OCS on HRQoL, then this will lead to overestimation of the effectiveness of OCS and underestimation of the benefit of steroid-sparing treatments.

The aim of this study was to characterise the burden of asthma and its treatment in this patient group, to determine the extent to which items in existing asthma-specific scales provide a valid assessment of the patient experience.

Methods

Patients were recruited from a specialist severe asthma clinic at Derriford hospital, Plymouth, UK if they were on Step 4 or 5 of British Thoracic Society treatment guidelines and invited to take part in a study where they would be asked about their experience of asthma and its treatment. Patients were purposefully sampled to represent

different age groups and social backgrounds. Patients were asked about their experience of asthma, their experience of medication and their treatment at the clinic, but with specific reference to the impact of OCS. The number of patients interviewed was determined by content saturation. Audio from interviews was recorded and transcribed, anonymised, and analysed by thematic analysis. Ethical approval and written informed consent were obtained.

Eight asthma-specific HRQoL scales were examined, of which six commonly feature in systematic reviews[9]. These are the Juniper Asthma Quality of Life Questionnaire (AQLQ^{Juniper})[10]; the mini AQLQ[11]; the Living with Asthma Questionnaire (LWAQ)[12]; the St George's Respiratory Questionnaire (SGRQ)[13]; the Marks Asthma Quality of Life Questionnaire (AQLQ^{Marks})[14]; the Asthma Questionnaire which is in two forms: the 30 item AQ30 and a 20 item subset, the AQ20[15]. We supplemented these six with two additional scales: The Asthma Bother Profile (ABP)[16] was developed for clinical use, where side effect concerns are relevant to adherence, and has additionally the been used as an outcome tool[17,18]. The Asthma Specific Quality of Life Scale (ASQLS)[19], is a recently-published scale, the development of which involved extensive qualitative research on asthma HRQoL domains.

Results

Patient characteristics

53 patients were identified as suitable for interview; 40 patients were contacted, 28 agreed to take part, 23 were interviewed, and 12 declined to take part for several reasons, including work commitments, child care, and health. Patients are labelled P1 to P23 in order of interview. Characteristics of the 23 patients interviewed are shown in Table 1.

Results of the thematic analysis

The content of interviews revealed two overarching themes: the *impact of asthma*, and the *impact of medication*. Impact of asthma could be divided into three domains: *activities, emotional impact, and hospitalisation*. OCS created the greatest impact on patients; patients reported only minor effects of other medications for their asthma or for other conditions. The effects of OCS could be divided into ten domains: *depression, irritability, sleep, hunger, weight, skin, gastric, pain, disease anxiety, medication anxiety*.

Impact of asthma

Many patients experienced activity restriction, activity avoidance and emotional impact of asthma but, while some were very severe, they were not qualitatively different from patients with mild or moderate asthma. A third domain of hospitalisation was reported by 19 patients: unpredictable repeated hospitalisation disrupted patients' lives,

particularly those with parental responsibilities, and made planning difficult. In addition, patients' disliked being in hospital and the associated treatment required, and felt less cared-for than when treated by staff at the severe asthma clinic who had a better understanding of their disease.

Impact of medication

Patients reported side effects only in association with OCS. Other asthma medication was perceived to have no or trivial effects.

Depression

P1, P10, and P15 experienced severe depression and attributed it to the effect of steroids (P1: "I know I was never depressed before I started on steroids"; P10 "I can't tell you how much I hate being on them because of the depression"). P15, P16, P19 reported the onset or increase in depression when reducing their OCS dose, and P10 reported that depression extended beyond the period in which they took OCS (P10: "it seems to last a good couple of weeks when I've come off them, even if I tail them off gently"). P5 and P8 reported depression but attributed it to their increased weight (P5: "I suppose it's where a lot of my depression comes from: because you get fat, your clothes don't fit"). P6 and P23 experienced depression but were unsure whether or not it was caused by OCS.

Irritability and inability to rest or relax

Irritability caused by OCS was reported by P1, P2, P5, P6, P10, P16, P19, P20, P21, P22. (P10: “[I’m] Like a Rottweiler on heat! I am oh, it’s worse than any menopausal or premenopausal or anything like that. My poor husbandI’ve cried, I’ve said, I wish I was dead, you’d be better off without me”. P16: “I’ve been more irritable since I’ve been on steroids.”)

Sleep disturbance

Sleep disturbance due to the arousing effect of OCS was reported by P6, P7, P9, P12, P15, P19, P21 and P22. (P6: “I never sleep properly when I am on steroids”). P6 and P19 reported being easily woken (P6: “any sound wakes me up”). P9 and P15 reported not sleeping at all during the first night of a course of OCS (P15: I don’t sleep. I’m just hyper”). P17 reported that she used to experience sleep disturbance but had become used to it, and P20 reported sleep disturbance caused by severe hunger, that she attributed to OCS.

Hunger and disturbed eating patterns

Increased levels of hunger due to OCS were reported by 16 of the 23 patients (P1, P5, P6, P7, P8, P9, P10, P14, P15, P16, P18, P19, P20, P21, and P22). P22 reported hunger on 40mg but not 5mg prednisolone. P1 and P8 reported that the hunger was associated with a feeling of sickness (P8: “I get to feeling sick all day... it’s a really, really weird combination”), and both of these patients reported vomiting due to

overeating (P1: the amount of times I've been physical sick because of it, it's a complete nightmare"). P16 reported eating things she did not like when on OCS. P5 and P9 reported hunger for about one week after terminating OCS.

Impact of weight gain and Cushingoid appearance

Fourteen patients mentioned weight gain as a problem. P3, P14, P17 and P22 reported that they had not experienced weight gain and only slight weight gain was reported by P19. Patients reported that their increased weight was embarrassing (P5: "My weight thing is the big thing. It sounds so stupid, but I've had years of people going on about how fat I am"). P2 showed the interviewer a picture of herself before being put on steroids (P2: "Until then, 12 months ago I looked like this").

P6, P15 and P23 reported that the increased weight made the effects of asthma worse (P6: It doesn't help the breathing does it, when you've got more to carry..... Am I wheezing because I'm wheezing, or am I wheezing because I am carrying all this excess weight?". P15: "Obviously, the more weight you're carrying the more breathing problems you're having. So it's a Catch-22").

Impact of skin thinning

P10, P16, P18, P20 and P23 reported bruising easily, and P16 and P18 reported that they modified their behaviour to avoid bruising (P16: "I've got to be careful where I walk. You know like little handles on doors, corners on things ... I do just bump into

things because I sometimes don't think properly where I'm going. But a door handle will give me a bruise.”)

Gastric problems

P4, P5, P7, P8, P9 and P12 reported stomach bloating, P7 and P9 reported wind, and P8 and P9 reported constipation. P4, P8, P12, and P15 reported stomach pain.

Pain

P1, P2 and P21 reported pain attributed to fractures. P11, P15 and P19 reported pain when their OCS was reduced (P11: “If I suddenly went off prednisolone completely now, as I have done in the past, you find that all sorts of aches and pains come back”. P15: “I cannot manage without the maintenance dose. I can't let [husband] touch me because my skin feels as if it's all bruising”. P19: “If I take them off quickly, I get pain – really awful pains in my joints and muscles..... Basically, if someone just touches me, it hurts – I mean everywhere”).

Anxiety about future disease course

P5, P6, P10 and P16 expressed concerns about the future (P5: “I mean I just worry that I wouldn't be around with my kids when they're little”. P6: “Yes I do worry, you know, asthma kills, it does. You do worry about it sometimes”).

Medication anxiety

P4, P5, P6, P8, P9, and P13 expressed concerns about the long-term effects of OCS (P4: “I feel that it’s poisoning my system”. P9: “I’m getting immune to them I think”).

Additional comments

Some patients indicated that OCS had a greater impact on their lives than asthma symptoms. One patient (P2) indicated she would trade 15 years of life if she did not need to take OCS with asthma symptoms remaining constant, and two (P9, P16) would trade 10 years.

Comparison with existing asthma-specific HRQoL scales

All 8 HRQoL scales contain items assessing the impact of asthma symptoms in the domains of activities and emotions. No scale contains any items specifically referring to hospitalisation. Table 2 shows the number of items in each of the eight asthma-specific HRQoL scales that potentially could measure the impact of OCS in each of the 10 OCS domains of impact identified in this study. All scales could potentially measure the impact of sleep disturbance, but measurement of other domains is either absent for all scales or limited to a few. Three scales contain non-specific items relating to the general negative effect of medication on HRQoL.

Discussion

OCS use in asthma is known to be associated with psychological and physical side effects[4, 5]. While patients may or may not be correct when attributing the causes of symptoms, these attributions are likely to affect satisfaction with treatment and

adherence. The type of impact of OCS varied between patients, but emotional impacts were comparatively common. Ten patients reported irritability, five reported depression directly attributed to the use of steroids, and a further two reported depression as a consequence of weight gain. Eight patients reported sleep disturbance due to the arousing effects of OCS, with a further one patient reporting sleep disturbance due to the effects of hunger. Of the 14 patients reporting hunger, two reported vomiting due to overeating, and one reported indiscriminate eating. OCS had an impact on patients' lives also when the dose was reduced or discontinued, with three patients reporting pain sensitisation under these circumstances, and three reporting depression. Three patients reported that the increased weight caused by OCS exacerbated their asthma symptoms. These results are broadly consistent with previous research showing that the burden of treatment in severe asthma is primarily due to the impact of OCS, and the major form of impact is in terms of psychological disturbance[4]. Additionally, this research highlights the dynamical interaction between OCS and depression, the disturbed eating patterns rather than just hunger, the effect of central pain sensitisation (in 3/23 patients) when reducing OCS dose, and gastric symptoms attributed by patients to OCS.

With the possible exception of hospitalisation, we found little evidence that the burden of asthma symptoms is qualitatively different in the severe asthma population compared to other populations and existing scales are valid for the severe population in that respect.

With regard to the burden of asthma treatment, the results are more complex. All of the existing scales had items relating to sleep disturbance. Sleep disturbance can arise for

at least two reasons – due to breathlessness/cough and due to the arousing effect of oral steroids (or less commonly, due to increased hunger). The sleep items of four of the scales (including the AQLQ^{Juniper} and the mini-AQLQ) are worded in such a way that either cause would be reported. Depression was not assessed in either the AQLQ^{Juniper} or mini-AQLQ, but was assessed in some other scales (see Table 2). Depression was a major impact in some patients and is a recognised side effect of OCS. Depression in asthma can result from three causes – depression due to limitations caused by asthma symptoms; a direct effect of OCS on depression; and the indirect, depressive effects of altered body image and self-concept. For those scales where depression is assessed (i.e., Living with Asthma Questionnaire, the AQLQ^{Marks}, and the Asthma Bother Profile), any cause of depression would elicit a patient response.

Although we identified 10 domains of HRQoL deficit caused by OCS, it is possible that these deficits are measured by items in existing scales that refer more generally to ‘medication’. Neither the mini-AQLQ nor the AQLQ^{Marks} have items relating to medication. The SGRQ has two items and the Asthma-Specific Quality of Life Scale has one item relating to the effect of medication on life. Other scales had items relating to medication embarrassment or bother, but not to their impacts. The AQLQ^{Juniper} has one item relating to concern about use of medication, but not related to impact. Only the LWAQ has an item that could relate to weight gain, and none have items relating to hunger or disturbed patterns of eating, the impact of skin thinning, gastric problems, and pain. Irritability was found to be a common and troubling symptom, but only the

LWAQ and the AQ30 have items that measure this aspect of the patient's experience, and then only by referring to restlessness and an inability to relax.

The impact of OCS is entirely or almost entirely neglected in the scales most frequently used in clinical trials (ACLQ^{Juniper} and mini-AQLQ). Other outcome measures, including spirometry and asthma control questionnaires, fail to measure the impact of treatment as perceived by the patient, and therefore fail to assess that uniquely important feature of HRQoL measurement: whether the treatment is worthwhile from the perspective of the patient[1].

HRQoL scales are used for two purposes: as an outcome measure and which can be used to make resourcing decisions and as a guide to clinical practice. Both purposes are better served if the impact of asthma symptoms and asthma medication are assessed together. In the short term it seems advisable to use a global HRQoL scale alongside existing scales. However, global scales tend to be less sensitive to change than disease specific scales as the latter (should) optimise items in relation to quality of life burden. For the future, two strategies are possible. One is to develop treatment burden scales that can be used alongside an existing asthma HRQoL scale, and which has the potential to be used for other diseases where OCS is used in severe cases. The other is to develop a new scale where the burdens of symptoms and medication are simultaneously measured along equivalent scales. For example, sleep disturbance can be caused by either asthma symptoms or the effect of OCS, and measurement on separate equivalent scales allows the clinician to compare how patients perceive the

advantages and disadvantages of medication. Figure 1 shows a possible design of such a questionnaire, a design that could help clinicians manage non-adherence.

Conclusions:

The use of existing asthma-specific scales in populations of severe asthma patients creates two kinds of bias. First, in cross-sectional studies, the total burden of asthma on HRQoL in these patients will be underestimated in comparison with less severe patients. Second the benefit of OCS on HRQoL will be overestimated and the benefit of steroid sparing agents underestimated. These biases have implications for treatment recommendations in terms of resources allocated to severe asthma patients and choices made about the use of modern steroid sparing agents, these being substantially more expensive than OCS. The bias in current measurement can be remedied in part by the use of global HRQoL scales (global HRQoL questionnaires typically fail to measure, for example, the effects of abnormal hunger), *or* preferably by developing treatment burden questionnaires *or* by developing a new type of HRQoL scale for severe asthma where the burden of symptoms and treatment can be compared using equivalent response scales.

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Table 1 Characteristics of patients of the 23 patients interviewed.

N (gender)	23 (19 female, 4 male)
Mean age – years (age at diagnosis)	50.95 years (28-70) (20 years)
Mean FEV1 – Litres (range)	1.74 L (0.56 – 2.78)
Mean FEV1 %Predicted (range)	62% (30-90)
N prescribed maintenance OCS	15/23
Mean daily dose for those on maintenance OCS (mg/d) (range)	15.3 mg/d (5-60mg)
N adherence with oral steroids measured by serum prednisolone/cortisol (%)	12 tested of whom 11 (92%) were compliant, 1 partially compliant.
Mean BMI – Kg/m ² (range)	30.1 (21.1 – 48.4)
Mean MiniAQLQ* score (range)	4.54 (1.7 – 5.7)
Mean ACT** score (range)	14.47 (5 - 23)

*mini asthma quality of life questionnaire

**asthma control test

Table 2. Number of questions in 8 asthma specific quality of life scales corresponding to each of the 10 domains of OCS impact.

Domains	AQLQ^{Juniper}	MiniAQLQ	LWAAQ	SGRQ	AQLQ^{Marks}	ABP*	AQ30**	ASQLS
No. of items in questionnaire	32	15	68	76	20	15	30	112
Depression	0	0	1	0	1	2	0	1
Irritability	0	0	1	0	0	0	1	0
Sleep	1	1	1	1	1	1	1	4
Hunger	0	0	0	0	0	0	0	0
Weight	0	0	1	0	0	0	0	0
Skin	0	0	0	0	0	0	0	0
Gastric	0	0	0	0	0	0	0	0
Pain	0	0	0	0	0	0	0	0
Disease anxiety	0	0	1	0	2	1	0	2
Medication anxiety	1	0	1	0	0	0	1	1
Non-specific items about medication	0	0	0	3	0	2	0	1

AQLQ^{Juniper}: Asthma Quality of Life Questionnaire[10]; MiniAQLQ: Mini Asthma Quality of Life Questionnaire[11]; LWAAQ: Living With Asthma Questionnaire[12]; SGRQ: St Georges Respiratory Questionnaire[13]; AQLQ^{Marks}: Asthma Quality of Life Questionnaire[14]; AQ30: Asthma Questionnaire-30[15]; ABP: Asthma Bother Profile[16]; ASQLS: Asthma specific quality of life scale[19].

*The ABP has an additional 7 management items. **The AQ20 has 20 items comprising a subset of the AQ30.

Figure 1: Design of questionnaire to measure asthma symptoms and medication symptoms using equivalent scales.

	<i>Patients respond on scale:</i>						
	1	2	3	4	5	6	7
	Not at all			Makes life a misery			
<i>List of items relating to domains identified for both asthma symptoms, effects of medication, or both</i>	Because of my asthma symptoms...			Because of my asthma medicines....			
I am restricted in my social life	_____			_____			
I am restricted in my personal life	_____			_____			
I get depressed	_____			_____			
I get irritable	_____			_____			
Etc.	_____			_____			
Etc.	_____			_____			
Etc.	_____			_____			

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