Validating self-report and proxy reports of Dexamethasone Symptom Questionnaire for the evaluation of longer-term corticosteroid toxicity

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Abstract

Purpose

In brain tumours, brain metastases, or advanced cancer treatment with corticosteroids, side effects can add to symptoms. These are best assessed by patients, complementing clinical assessment. We assessed the feasibility and validity of Dexamethasone Symptom Questionnaire–Chronic (DSQ-Chronic), patient and caregiver versions.

Methods

A longitudinal cohort study was conducted, collecting clinician-rated toxicity, performance status, dexamethasone dose and DSQ-Chronic (patient and caregiver versions) at baseline, then 2, 4, and 8 weeks later. Patients had a primary malignant brain tumour, brain metastases, or advanced cancer, Karnofsky Performance Status ≥40, and predicted survival ≥8 weeks. Analysis included completion rates, frequency and severity of dexamethasone-attributable side-effects, agreement between patient and caregiver ratings, comparison with clinician-rated toxicity, and correlation with performance status.

Results

Sixty-six patients were recruited (mean age 60 years), with their caregivers. Completion of questionnaires was over 90% for the dyad at baseline but dropped over time, with caregivers completion rates higher at all timepoints. Agreement between patients and proxies was fair to moderate, and while proxies systematically overestimated symptom severity on DSQ-chronic total scores, the bias was less than 10 points. Patient and clinician agreement was higher for more objective symptoms.

Conclusion

The DSQ-Chronic is feasible when the patient is relatively well. As capacity to complete the DSQ-Chronic diminishes, caregivers can be proxy-raters. Clinicians capture corticosteroid toxicities, which may not be obvious to the patient. The DSQ-Chronic, patient and caregiver versions, are useful tools to be used with clinician assessment.

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Introduction

A large proportion of patients with high-grade glioma (HGG) or brain metastases will at some point have symptoms of raised intracranial pressure due to the mass of the tumor and related peritumoral edema.[1]

Corticosteroids, usually dexamethasone, are used to manage neurological deficits and symptoms (headache, nausea and vomiting) caused by raised intracranial pressure. Response rates of 30-80% have been reported.[1 2] Other benefits attributed to corticosteroids in advanced cancer include palliation of pain, fatigue, and anorexia.[3-8]

Clinical experience suggests that adverse events from corticosteroids can be severe, especially with prolonged use, but relationships to dose and duration of exposure have not been comprehensively documented. Side-effects include myopathy, weight gain, osteoporosis, hyperglycemia, and mood or personality changes.[9-11] Dexamethasone doses above 24 mg in malignant spinal cord compression are associated with serious acute gastrointestinal toxicity.[1 12] Proximal myopathy has been reported in 10–60% of brain metastases patients on corticosteroids for more than 3 weeks for cerebral edema, and high doses were related to cushingoid features and steroid-induced hyperglycemia.[1 13] Hence, dexamethasone treatment is a double-edged sword for people with advanced cancer or intracranial malignancies, worsening the exact problems it aims to treat, such as mood disturbance and functional decline.

These impacts are best assessed by patients, complementing assessment of toxicity by clinicians.[14] However, self-report may be challenging for people with advanced cancer, particularly those with high-grade glioma or brain metastases, because these patients are

often cognitively impaired.[15] Proxy ratings are a potential alternative, with sources including physicians, nurses, or family caregivers. Proxies tend to report lower levels of functioning, health, and quality of life and more symptoms than the patients themselves; the difference is generally modest.[16] Arguably, if the size and direction of bias is known, the information obtained from proxies is better than no information at all.

A self-report questionnaire (Dexamethasone Symptom Questionnaire (DSQ)) for acute symptoms related to dexamethasone as an antiemetic for chemotherapy has been developed and validated, however focuses on acute symptoms and does not have a proxy version.[17] We therefore revised the DSQ to create a version that included longer-term side-effects (Dexamethasone Symptom Questionnaire–Chronic (DSQ-Chronic)) and also allowed for caregiver proxy ratings.

The aim of this study was to assess the feasibility and validity of the DSQ–Chronic, patient and caregiver versions. The primary objective was to assess the feasibility of obtaining patient and caregiver–proxy ratings of side-effects that may be related to long-term use of dexamethasone.

Secondary objectives were to: 1) evaluate the face validity of the DSQ-Chronic patient and caregiver versions; 2) determine patient and caregiver ratings of the prevalence and severity of symptoms that may be attributable to dexamethasone; 3) compare patient and caregiver ratings in terms of degree of agreement and direction and size of proxy bias; 4) compare patient and caregiver side-effect ratings with corresponding clinician-rated toxicity on Common Terminology Criteria for Adverse Events version 4 (CTCAE v4) [18] criteria; 5) assess the association between clinician-rated patient performance status and

the patient- or proxy-rated burden of symptoms that may be attributable to dexamethasone.

Methods

Setting and sample

Participants were recruited from five cancer and palliative care services in New South Wales (NSW), Australia, from both outpatient and inpatient services. Inclusion criteria for patients were: adults 18 years or older with a primary malignant brain tumour, brain metastases or advanced cancer (without brain involvement); informed consent, on ≥4 mg dexamethasone total daily dose for at least 48 hours (any route); Karnofsky Performance Status (KPS)[29] of ≥40 at baseline; and predicted survival of ≥8 weeks. Each eligible patient was invited to nominate a caregiver. Exclusion criteria included clinically significant neurological conditions (patients), non-English speaking or inability to complete assessments (patients and caregivers). Potential participants were approached by their primary treating oncologist or palliative care physician to seek their interest in participating in the study. The study was approved by the Cancer Institute NSW and Sydney Local Health District Human Research Ethics Committees.

Study design and assessments

This longitudinal cohort study followed patients and caregivers at baseline, then 2, 4, and 8 weeks later. At each time, patients and caregivers independently completed health-related outcome questionnaires, and the treating clinician independently assessed a specific list of toxicities that were potentially attributable to dexamethasone (derived from the Common Terminology Criteria for Adverse Events version 4.0 criteria), KPS score, and documented current dexamethasone use and planned future dexamethasone

treatment. For every toxicity, the clinician was asked to rate their opinion about the extent to which they felt the symptom was attributable to dexamethasone.

The assessments were undertaken as an outpatient, inpatient or at a community home visit, depending on the clinical status of the patient, to allow participants to continue participation in the study even if they did not feel well enough to attend a study clinic visit follow-up.

KPS[19 20] is a clinician-rated classification of a cancer patient's functional status. A score between 100 and 0 is assigned on the basis of the patient's ability to undertake a range of daily tasks.

The following information (participant report) was collected at baseline only: age of patient, caregiver relationship, number of hands-on caregiving hours/day, and whether the caregiver lived in same house as the participant. Details of the primary tumour and current anticancer treatment were elicited from the medical record.

Health-related outcome questionnaires

The DSQ-Chronic contains 18 side-effects that may be due to oral dexamethasone (patient version in appendix). The recall period for each item is the past week. The item stem for the patient version is "Did you …" while for the caregiver version, it was "Did the person you care for …". Patients and caregivers were asked to complete their version of DSQ-chronic separately, without knowledge of each other's responses.

The DSQ-Chronic retains the style (descriptive measure to measure incidence and severity of side effects), scoring (four-point Likert scale with same anchors) and recall period of the original DSQ[17] from which it was derived. A consensus group of clinicians

and researchers expert in development of patient reported measures, performed item generation for the additional side-effects associated with longer term dexamethasone use to include in the DSQ-Chronic, which were not already included in DSQ. These were based on clinical experience, literature review and consultation with oncologists and palliative care clinicians involved in the care of patients with brain tumours who regularly prescribe dexamethasone. The descriptors of these side effects were chosen to ensure they would be understandable for patients and caregivers.

Semi-structured interviews

Participants and their nominated caregivers also took part in semi-structured interviews aimed at evaluating the content validity of the DSQ-Chronic, using EORTC's phase 3 pretesting of new modules.[21] The interviews occurred within 2 weeks of completion of the last questionnaires, and were performed face-to-face (in the clinic or in the community). Participants were asked whether: the questionnaires offered an accurate and comprehensive description of the adverse effects experienced since beginning dexamethasone treatment; the items were easy to understand; and to comment on any items that are 'annoying' or upsetting. Items were added, reworded or removed in accordance with this advice.

Data analysis

Sample size and all analyses were prespecified. The study aimed to recruit 50 patient – caregiver dyads, with 50% (n=25) being patients with primary malignant brain tumours. Sample size was based on the precision of estimation of feasibility and reliability statistics, in terms of two-sided 95% confidence intervals (95% CI). A sample of 50

patients was determined to yield 95% CI for estimates of proportions with width at most ±15% and between-rater reliability and for the Kappa statistic[22] 95% CI precision of ±0.18 (assuming k=0.8, $P1$=$P2$=0.5).

To assess the feasibility of measuring dexamethasone-related side-effects by patient self-report and caregiver proxy report over time, we calculated the completion rates at each of the planned assessment times.

Face validity of the DSQ-Chronic was assessed by feedback from structured interviews with patients and/or caregivers using the interview schedule from the EORTC's phase 3 pretesting of new modules.[21] This involved six questions (were any items difficult, annoying, confusing, upsetting, intrusive, irrelevant; if so, which?) with the final question asking the respondent to nominate any "additional problems caused by the medications you are taking that are relevant for you but are not included in this questionnaire".

The frequency and severity of side-effects reported by patients and caregivers was described by the proportion of patients in each level of severity for each item via the following four response levels: ("not at all", "a little", "quite a bit", "very much").

Using a clinimetric approach,[17 23] an index representing the total burden of side-effects was created by summing all 18 items, then converting linearly to a 0–100 range, such that 0 = "not at all" for all 18 side-effects and 100 = "very much" for all.

The degree of agreement between patient and caregiver ratings was assessed at the item level with the weighted Kappa statistic (applied to all four response levels), with magnitude interpreted after Landis and Koch[22] who characterized values <0 as indicating

no agreement and 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost perfect agreement; and the percentages of patients and caregivers who agreed that a patient either did not or did have a symptom (response dichotomised: "not at all" versus the remaining three levels of severity). The size and direction of proxy bias was assessed for the total side-effect score by subtracting the caregiver rating from the patient rating, such that a positive difference indicates the patient's rating was higher than the caregiver's (caregiver underestimated the side-effect burden) and a negative difference indicated the caregiver overestimated the burden of side-effects. The mean difference reflected the size and direction of proxy bias on average, and the pattern of individual differences was inspected via a Bland and Altman plot.[24] The mean difference was compared by using a paired sample *t* test, and both mean and individual differences of >10 points were considered to represent clinically significant bias.[25]

Patient and caregiver side-effect ratings were compared with corresponding clinician-rated toxicity on CTCAE criteria using the dichotomized symptoms as reported by the patient and caregiver ("not at all" versus the remaining three levels of severity) and the dichotomized symptoms as reported by the clinician (grade 0 vs all other grades) the level of agreement between the clinician and caregiver was assessed. The denominator in the percentage was calculated by the number of patients or caregivers who answered at baseline. If the clinician did not record a symptom for the patient, the patient was assumed to have a grade 0.

The association between clinician-rated KPS and patient and caregiver rating of side-effect burden (total score) was evaluated with a Spearman's correlation coefficient. Each

of the two symptom burden index scores was expected, *a priori*, to be correlated with KPS scores. In order to use KPS as an external anchor for clinical validity, a correlation of at least 0.3 is required.[26] Two groups of patients expected to be clinically distinct were defined using a KPS score of 60 as a cut-point (≥60 and <60).

Results

Sixty-six patients were recruited (mean age 60 years, range 31–62), with their caregivers, 25 (38%) with a primary brain tumour, 12 (18%) with brain metastases, and 29 (44%) with advanced cancer (no confirmed intracranial disease) (Table 1). Recruitment continued until 25 primary malignant brain tumour patients had been consented. There were slightly more male patients 36 (55%). Caregiver's age was similar to the patients (mean 57 years, range 25–82), 58 (88%) lived with the patient, with 39 (59%) providing hands-on care. Dexamethasone dosage over time is outlined in the supplementary table, with most patients on ≤ 8mg/day.

Questionnaires completion was over 90% for both patients and caregivers at baseline, but this dropped over time (Table 2). If they started the questionnaire, the proportion who answered all questions was higher for caregivers than for patients at all times. Patient and caregiver interviews (20 participant dyads) found that none of the questions where intrusive or upsetting, with questions perceived as easy to understand and not confusing. Additional symptoms not included in the DSQ-Chronic, suggested by participants, included muscle weakness (*n*=2), loss of energy (*n*=1), hand shaking/tremor (*n*=3), fluid retention/general swelling (*n*=2), hunger (*n*=1), increased amount of food (*n*=2), altered taste/bitterness in mouth (*n*=2), early morning wakening (*n*=2), difficulty getting out of bed (*n*=1), and scratching (*n*=1).

In response to the free text question "What other problems have you noticed due to steroids?", patient responses included sleep disturbances (trouble getting to sleep (*n*=8), broken sleep pattern (*n*=1), difficulty getting back to sleep once woken (*n*=2), being awake in middle of night (*n*=2) or sleep disruption (*n*=4)); weight gain (*n*=5); mobility

issues (*n*=3); fatigue or tiredness (*n*=4); skin changes (itch, easy bruising, *n*=3) and mood changes (not wanting to socialise, easy crying and lack of motivation (*n*=3)).

Caregiver's responses to the free-text question included noticing patient sleep disturbances (*n*=7) (e.g. sleep deprivation, sleeplessness, short duration of sleep, failure to sleep, sleeping during day rather than night or trouble getting to sleep due to specific reasons (funny dreams, light headedness)). Caregivers also reported patients having pins and needles (*n*=1), behaviours such as busyness (tidying up, washing up, walking around (*n*=2), and mobility issues (difficulty or slow walking stiffness, unsteadiness (*n*=5)). Mood changes noticed by caregivers included patient being emotional (*n*=1), irritable (*n*=4), short tempered or angry (*n*=3), and nervousness or anxiety (*n*=2). Sweet cravings was identified as a particular change in eating pattern. Confusion/absentmindedness (*n*=2), ankle swelling (*n*=2), fluid retention (*n*=1), face "puffed up"/bloating (*n*=2), abdominal bloating/bloating (*n*=5), loss of energy or fatigue (*n*=4), dry mouth (*n*=1), and itching (*n*=1) were also noticed by caregivers.

Figure 1a and 1b rank the symptoms reported by patients and caregivers, respectively, in order of those with higher frequencies of "very much", or "quite a bit" severity ratings. The six top-ranked symptoms by the patient included the top five of the caregivers, but in a slightly different order. Similarly, the four lowest-ranked symptoms were the same for patients and caregivers.

Ten symptoms had moderate agreement (0.41–0.60) between patient and caregiver: trouble getting to sleep, lack of appetite, loss of weight, weight gain, thrush, roundness of face, depression, anger, trouble getting out of a low chair, bruising and headaches (Table

3). Six symptoms had fair agreement (0.21–0.40): indigestion, vomiting, increased appetite, hiccups, agitated and rash. The remaining symptom, feeling nauseated, had substantial agreement (0.65).

Figure 2 shows the pairwise comparison of patient and caregiver reporting of symptoms. For 55 of the pairs (83%), the difference fell within the difference of 10 units that was deemed to be clinically important. Reassuringly, there was no obvious pattern of increasing difference with increasing symptom burden. The mean of these paired differences showed that patients systematically scored the dexamethasone symptoms with lower severity than their caregivers. At baseline, the mean difference (patient score minus caregiver score) was -2.8 (-5.0 to -0.5), P=0.02; week 2, -2.6 (-4.4 to -0.8), P=0.01; week 4, -2.2 (-3.9 to -0.5), P=0.01; and week 8, -1.5 (-4.4 to +1.5), P=0.31. All means and 95% confidence intervals were well within the difference of 10 units that was deemed to be clinically important.

Clinician-rated toxicities based on CTCAE are listed in Table 4.

The two groups were compared with patients categorised by their baseline KPS (<60 versus ≥60) and DSQ-chronic scores. Patients with baseline KPS<60 (n=16) had mean DSQ-Chronic scores almost 5 points higher (mean DSQ-Chronic 43.7, SD 11.7) than those with higher baseline KPS (n=45, mean DSQ-Chronic 39, SD 7.3), but this difference did not reach statistical significance (P=0.06). There was little correlation between KPS and DSQ scores at baseline within each of these two patient groups (Spearman coefficient 0.22, P=0.09).

Discussion

This study has demonstrated that completing the DSQ-Chronic tool is feasible for both patients and caregivers when the patient is relatively well. However, their capacity to complete the DSQ-Chronic diminishes over time, mainly because of patient deterioration, and caregivers withdrawing from the study at this time also. Caregivers consistently had higher rates of commencing and completing the questionnaires than patients. The top ranked symptoms for patients were similar to those of caregivers, with only the order differing. Agitation, the top symptom for caregivers, was ranked lower by patients, possibly because it had more impact on caregivers. The lowest ranked symptoms were the same for patients and caregivers. Agreement between patients and proxies was generally fair to moderate, and while proxies systematically overestimated severity of the patients' symptoms, the size of the bias was less than the clinically important threshold of 10 points in the 0–100 point range.

Our data confirm that dexamethasone is associated with multiple symptoms, often moderate to severe. These results extend our understanding of the symptoms seen over time with dexamethasone use in cancer patients, including in a population of people with primary or secondary brain cancers. In acute use, in a population receiving dexamethasone for moderately emetogenic chemotherapy (50% of whom had metastatic disease) sleep difficulties, indigestion, agitation, increased appetite, and weight gain were reported.[17] This would suggest that people taking dexamethasone in the cancer setting are likely to experience side effects from the outset, with the pattern of symptoms varying depending on duration of use or other individual factors. Agitation, sleep difficulty and

increased appetite seem to be symptoms that are highly prevalent in both acute[17] and chronic use.

Interestingly the symptoms seen in our cohort do not seem to be related to decline in functional status. This may be because functional status is more affected by neurological impairments than symptom burden.

Despite some lack of agreement at the individual level, at the group level, caregivers provide a reasonable proxy rating for symptoms that may be attributable to corticosteroids. For some of these symptoms, caregivers can use direct observation to inform their ratings, for example, agitation, difficulty getting out of a chair, or sleep disruption. The literature remains contradictory about the concordance of proxy ratings of patient-reported outcomes and the merit of proxy ratings when the patient is unable to report. It is known that proxy raters tend to report greater symptom experience and poorer function than do the patients themselves, and our results confirm this.[16 27-29] For symptoms with corresponding CTCAE criteria, percentage of patient and clinician agreement was higher for more objective symptoms (e.g. hiccups, vomiting, weight gain), and less so for mood and personality changes. Clinicians also could rate other important adverse effects for which there is no straightforward symptom question (for example, osteoporosis and psychosis).

A review of 23 studies (1991 to 2002) concluded that judgments made by significant others and health-care providers about various patients' health-related quality of life are reasonably accurate, with large patient-proxy differences infrequent and modest.[16] This has since been replicated in patients with advanced cancer (n=51) with good patient-

proxy agreement on EORTC QLQ-C30 scores, if the proxy is a family caregiver.[30] Other authors state reliance on proxy assessments leads to different conclusions about the effect of cancer treatments on quality-of-life. A study using the Spitzer QL-Index in patients with brain metastases, found family proxies were a poor substitute for the patient's perspective.[28] Similarly, poor concordance for all quality-of-life domains in the Functional Assessment of Cancer Therapy–Brain questionnaire was found, in a population of 60 patients with brain metastases.[27] Variables that may influence the degree of concordance include patient parameters such as sex, age, and caregiver parameters such as the proxy's self-reported lack of family support for themselves and the patient, health problems, and self-esteem.[31]

Despite the challenges, a need for instruments that can be reliably rated by proxies remains, particularly for patients with brain involvement. In a study of patients with primary brain tumours (n=42) and their significant others using the EORTC QLQ-C30 and brain cancer module, the QLQ-BN20, fairly good agreement was seen, with median correlation 0.46.[32] A recent study of the DEGRO brain module (DBM), a 10-item questionnaire rating the general condition as well as functions and impairment by symptoms in areas relevant to patients with brain metastases, found patient and proxy ratings had high correlation and similar mean changes over time, suggesting that proxies can be used as an alternative when patients are unable to self-complete questionnaires.[33] We have drawn the same conclusion from our results.

Strengths of the study

This study adapted an existing patient-reported outcome tool (the DSQ) to provide a measure for a highly prevalent and distressing adverse effects of a pharmacological

therapy. Cohabiting patient-caregiver dyads predominated, so the caregiver was likely to have direct experience of the toxicities experienced by the patient.

Study limitations

Clinicians were asked to measure corticosteroid toxicity using a different tool, and hence it was not possible to directly compare these assessments with those of patients and caregivers. The rationale for this was to reduce burden on clinicians, to ensure comprehensive reporting by using a familiar tool, and to utilise a clinical method that was more robust than a symptom description. The DSQ-Chronic could only be administered in English so the experiences of people from non-English speaking backgrounds were not captured (up to 60% of the clinic population at participating sites). It is also difficult to determine whether caregivers included the impact of the patient's symptom on themselves in their ratings, for symptoms such as agitation, difficulty getting out of a chair, and sleep disturbance. The dexamethasone dosage was only captured by self-report every 2 weeks, resulting in a less accurate reflection of dose exposure over time, compared to the potential results with a daily or weekly dose diary. A limitation was the use of a heterogeneous patient sample that included primary malignant brain tumours, brain metastases and other cancers.

Implications for the DSQ-Chronic questionnaire

Our findings have led to further refinement of the DSQ-Chronic. Specifically, the questions have been reordered according to importance and severity from the patient's perspective (Figure 1a), but the less prevalent items have been retained, as these symptoms can be highly distressing when they do occur. On the basis of qualitative responses, several questions have been reworded to "Have you felt

agitated/nervous/anxious?"; "Have you had trouble sleeping?"; "Have you experienced low mood, such as depression or easy crying?"; and "Have you had increased appetite/hunger?". It was decided not to alter the question about ability to get out of a chair or to include other mobility problems, as this was deemed harder to attribute directly to corticosteroids and is often due to the underlying cancer. While the DSQ-Chronic includes symptoms that are potentially attributable to corticosteroid toxicity, it is not designed to be a diagnostic tool and a full clinical assessment is always required to determine potential causes.

Implications for future research

This study has demonstrated that patients are able to report toxicities that may be attributable to dexamethasone. The DSQ-Chronic provides a standardised, systematic way of doing this in clinical studies of cancer-related conditions where corticosteroid treatment is used, rather than reliance on clinician assessment. Though the DSQ- chronic was devised for use in clinical settings of longer-term use, it would be interesting to evaluate whether patients also report these side effects during acute use. Wherever possible, the patient should be asked to report this directly; however, the caregiver is a reasonable substitute where the patient is unable to report. Owing to the tendency of the caregiver partner to withdraw from a study when the patient deteriorates, studies that rely on proxy report need to ensure caregivers understand their role and its importance if and when the patient can no longer self-report.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments. The study was approved by

the Cancer Institute NSW and Sydney Local Health District human research ethics committees.

Authors' disclosures

The authors declare that they have no conflict of interest.

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Figure legends

Figure 1

Symptoms at baseline, ranked by severity, on the Dexamethasone Symptom Questionnaire–Chronic: A. reported by patients (*n*=61); and B. reported by caregivers (*n*=66).

Figure 2

Pairwise comparison of patient and caregiver at baseline, on the Dexamethasone Symptom Questionnaire–Chronic total score. *A difference >0 indicates that the patient responded with a higher rating for the symptoms than the caregiver and <0 indicates the patient provided lower ratings than the caregiver.

Table 1: Patient and caregiver characteristics

Characteristic	Primary brain tumour (*n*=25)	Brain metastases (*n*=12)	Advanced cancer (*n*=29)
Patients			
Age (years), mean (SD)	55.8 (10.1)	59.2 (10.4)	63.5 (9.11)
Sex			
Male	13 (20)	7 (11)	16 (24)
Female	12 (18)	5 (8)	13 (20)
KPS			
30	1 (2)	0	1(2)
40	0	1 (2)	4 (6)
50	4 (6)	2 (3)	5 (8)
60	3 (5)	4 (6)	8 (12)
70	6 (9)	1 (2)	6 (9)
80	7 (11)	3 (5)	1 (2)
90	4 (6)	0	5 (8)
Caregivers			
Age (years), mean (SD)	55.5 (12.8)	57.8 (14.1)	58.0 (10.5)
Relationship			
Spouse or partner	21 (32)	8 (12)	22 (33)
Sibling	1 (2)	0	2 (3)
Parent	2 (3)	2 (3)	0
Child	1 (2)	2 (3)	3 (5)
Other relation	0	0	1 (2)
Friend	0	0	1 (2)
Resides in same house	24 (36)	9 (14)	25 (38)
Provides hands-on care	13 (20)	9 (14)	17 (26)

Numbers are mean (standard deviation), or *n* (%) with denominator the total number of patients or caregivers (66).

Table 2: Patients and caregiver compliance with completion of questionnaires by time

Time point	Patients still on study (*n*)	Started the questionnaire, of patients still on study (%)		Answered all the questions, of those who started the questionnaire (%)		Did not answer all the questions on the previous questionnaire and did not attempt next questionnaire (%)	
		Patients	Caregivers	Patients	Caregivers	Patients	Caregivers
Baseline	66	61/66(92%)	60/66(91%)	42/61(69%)	49/60(82%)	NA	NA
Week 2	63	46/63(73%)	46/63(73%)	28/46(61%)	40/46(87%)	5/17(29%)	3/17(18%)
Week 4	54	34/54(63%)	3/53(62%)	22/34(65%)	24/33(73%)	6/20(30%)	2/20(10%)
Week 8	44	26/44(59%)	26/44(59%)	17/26(65%)	23/26(88%)	4/18(22%)	3/18(17%)

NA=not applicable

Table 3: Comparison of patient and caregiver reporting of prevalence of each DSQ-Chronic symptom at baseline, and reliability of caregivers as proxies

DSQ-Chronic items (patient/caregiver)[a]	Patients reporting symptom (*n*, %)	Caregivers reporting symptom (*n*, %)	Weighted Kappa coefficient	Caregivers and patients who agree (%)
Have you experienced low mood, depression and/or easy crying?	42 (69)	42 (70)	0.45	83
Have you had increased appetite?	41 (67)	39 (65)	0.32	65
Did you have trouble getting to sleep?	38 (62)	29 (48)	0.53	69
Have you had difficulty getting out of a low chair?	35 (57)	39 (65)	0.51	75
Have you felt agitated/nervous?	34 (56)	49 (82)	0.26	65
Have you experienced increased levels of anger or irritability?	32 (52)	36 (60)	0.51	74
Have you had problems with your skin being fragile or easily bruised?	28 (46)	25 (42)	0.52	80
Did you have indigestion/heartburn/reflux or discomfort in the upper abdomen?	27 (44)	28 (47)	0.39	74
Have you lost weight?	26 (43)	30 (50)	0.53	82
Have you felt nauseated?	23 (38)	24 (40)	0.65	86
Have you lacked appetite?	21 (34)	23 (38)	0.43	72
Have you had headaches?	20 (33)	22 (37)	0.54	81
Have you gained weight?	19 (31)	17 (28)	0.44	82
Have you noticed increased roundness of your face?	18 (30)	19 (32)	0.54	83
Have you vomited?	10 (16)	9 (15)	0.38	86
Have you had hiccups?	9 (15)	7 (12)	0.33	88
Have you had thrush/yeast infection in your mouth?	8 (13)	9 (15)	0.52	87
Have you had a rash/acne on your face?	6 (10)	8 (13)	0.33	87
Have you had trouble controlling your blood sugars? (if diabetic (n=15))	4 (67)	3 (38)		80

[a] Symptoms presented in same order as DSQ-chronic questions.

DSQ, Dexamethasone Symptom Questionnaire

Table 4: Comparison of clinician-rated steroid toxicities (CTCAE) at baseline with corresponding patient report from DSQ-Chronic

Clinician-reported symptom (CTCAE)[a]	Corresponding DSQ-Chronic item (patient/caregiver)[b]	Clinicians reporting symptoms (*n*, %)	Patients and clinicians who agree on symptom (%)	Caregivers and clinicians who agree on symptom (%)
Depressed level of consciousness	nil	4 (6)	—	—
Duodenal ulcer	nil	0	—	—
Gastric ulcer	nil	0	—	—
Gastric hemorrhage	nil	0	—	—
Gastritis	nil	1 (2)	—	—
Gastroesophageal reflux disease	nil	8 (12)	—	—
Mucosal infection	nil	1 (2)	—	—
Pharyngitis	nil	2 (3)	—	—
Dry skin	nil	8 (12)	—	—
Psychosis	nil	1 (2)	—	—
Osteoporosis	nil	2 (3)	—	—
Mania	Depression, low mood, easy crying (Q14)	3 (5)	36	34
Euphoria	Depression, low mood, easy crying (Q14)	1 (2)	33	31
Dyspepsia	Indigestion/heartburn/reflux (Q1)	12 (18)	67	62
Insomnia	Sleep (Q2)	25 (38)	61	68
Nausea	Nauseated (Q3)	17 (26)	80	72
Vomiting	Vomited (Q4)	11 (17)	92	91
Hiccups	Hiccups (Q7)	7 (11)	87	89
Weight gain	Gain weight (Q9)	19 (29)	78	79
Agitation	Agitated (Q10)	12 (18)	57	32
Rash acneiform	Rash/acne (Q11)	0	90	87
Mucosal infection, candida	Thrush/yeast infection (Q12)	2 (3)	87	84
Cushingoid features	Roundness (Q13)	18 (27)	82	78

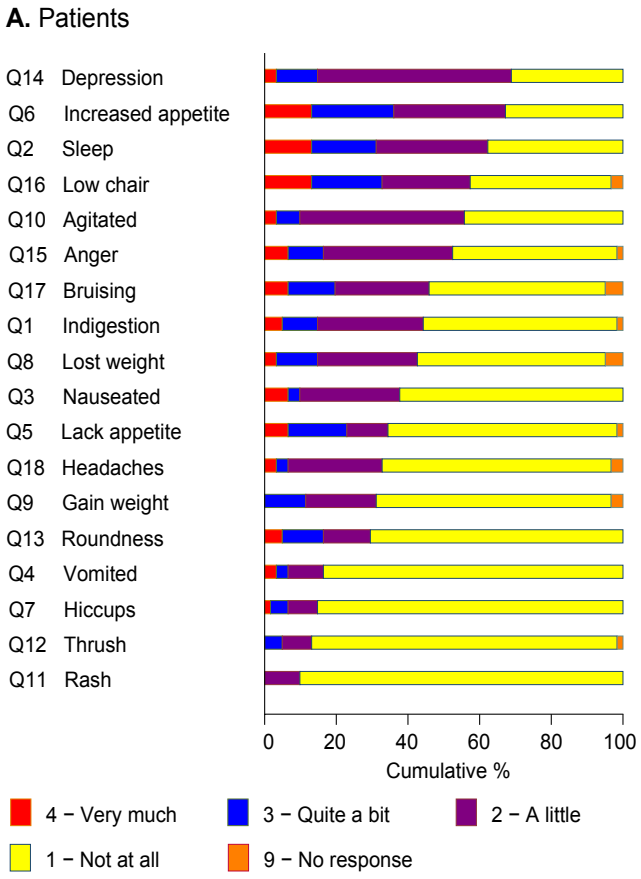
Clinician-reported symptom (CTCAE)[a]	Corresponding DSQ-Chronic item (patient/caregiver)[b]	Clinicians reporting symptoms (*n*, %)	Patients and clinicians who agree on symptom (%)	Caregivers and clinicians who agree on symptom (%)
Depression	Depression, low mood, easy crying (Q14)	9 (14)	43	44
Personality change	Anger or irritability (Q1)	9 (14)	45	36
Skin atrophy	Bruising/skin fragility (Q17)	1 (2)	53	58
Headache	Headaches (Q18)	11 (17)	78	71
Hyperglycemia	Problems with blood sugar control (Q20B)	5 (8)	100	89
Hypoglycemia	Problems with blood sugar control (Q20B)	1 (2)	50	78

[a] DSQ symptoms not covered by CTCAE: lack of appetite, increased appetite, weight loss, getting out of low chair.

[b] CTCAE not covered by DSQ: level of consciousness, dysgeusia (altered taste), duodenal ulcer, gastric ulcer, gastric hemorrhage, gastritis, gastro-oesophageal reflux, pharyngitis, skin atrophy, dry skin, osteoporosis, mania, euphoria.

CTCAE, Common Terminology Criteria for Adverse Events, DSQ, Dexamethasone Symptom Questionnaire

Figure 1


A. Patients
Q14 Depression
Q6 Increased appetite
Q2 Sleep
Q16 Low chair
Q10 Agitated
Q15 Anger
Q17 Bruising
Q1 Indigestion
Q8 Lost weight
Q3 Nauseated
Q5 Lack appetite
Q18 Headaches
Q9 Gain weight
Q13 Roundness
Q4 Vomited
Q7 Hiccups
Q12 Thrush
Q11 Rash
0 20 40 60 80 100
Cumulative %
4 − Very much
3 − Quite a bit
2 − A little
1 − Not at all
9 − No response

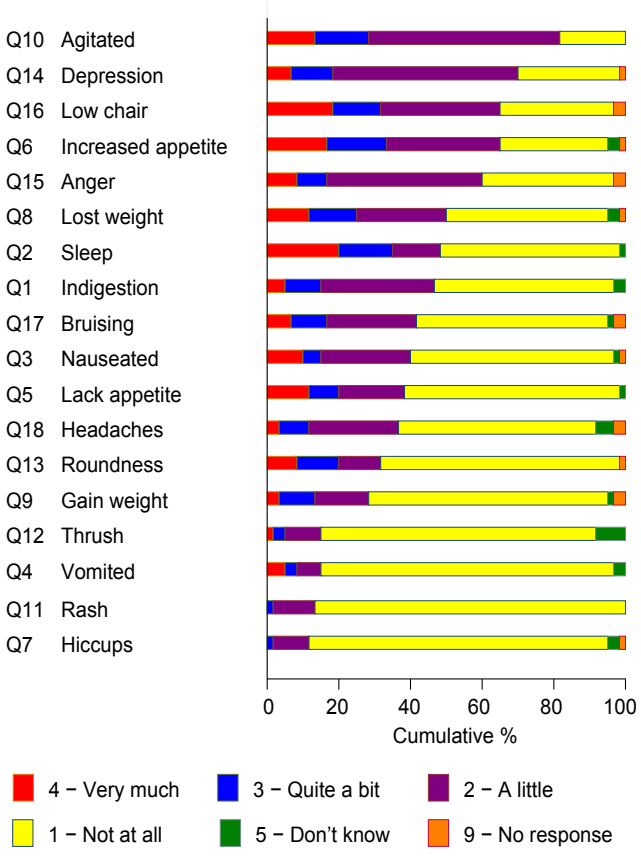
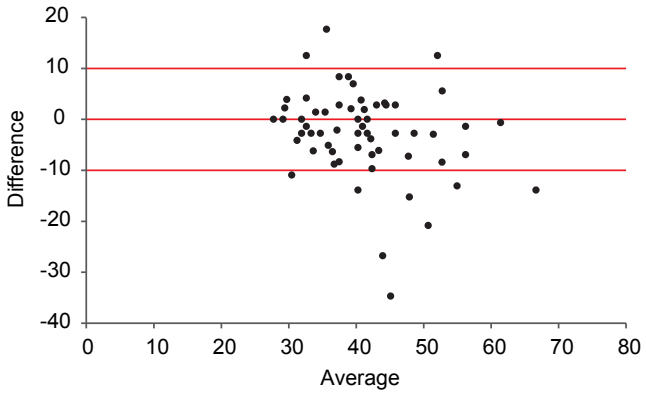

B. Caregivers
Q10 Agitated
Q14 Depression
Q16 Low chair
Q6 Increased appetite
Q15 Anger
Q8 Lost weight
Q2 Sleep
Q1 Indigestion
Q17 Bruising
Q3 Nauseated
Q5 Lack appetite
Q18 Headaches
Q13 Roundness
Q9 Gain weight
Q12 Thrush
Q4 Vomited
Q11 Rash
Q7 Hiccups
0 20 40 60 80 100
Cumulative %
4 − Very much
3 − Quite a bit
2 − A little
1 − Not at all
5 − Don't know
9 − No response

Figure 2



Validating self-report and proxy reports of Dexamethasone Symptom Questionnaire for the evaluation of longer-term corticosteroid toxicity

Supplementary table. Dexamethasone dosage from study entry to 8 weeks

	Number of participants on dosage at each time point (*n*=66)				
Dosage	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Total number on this dosage at any time point**
Dosage/24 hours (mg)					
0	0	3	5	7	15
>0–2	1[a]	13	19	10	43
>2–4	40	20	10	9	79
4–8	12	9	3	4	28
8–12	6	0	3	0	9
12–16	5	3	0	1	9
>16	1	0	0	0	1
Dosage missing					
Reason unknown[b]	1	2	1	1	5
Patient no longer on study	0	16	25	33	74
Dose missing as patient did not complete patient-reported measures	0	13	13	12	38
All	66	66	66	66	

[a] Steroid dose was reduced for clinical reasons between eligibility and consent, and the baseline measures.

[b] Steroid forms were not completed at certain time points and the reason is unknown.