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Research Report

Development of a New Self-Reporting Instrument Measuring Benefits and Side Effects of Corticosteroids in Duchenne Muscular Dystrophy: Report from a Pilot Study

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Abstract.

Background: There is no cure for Duchenne Muscular Dystrophy (DMD); treatment is symptomatic and corticosteroids slow the progression. Side effects of corticosteroids – especially the physical effects – have been described, however patients' and caregivers perception on chronic corticosteroid treatment and their side effects is less well known, in particular with regards to cognition, behaviour, and emotional functioning.

Objective: The primary aim of this pilot study was to (i) construct a self-report questionnaire to assess the perceived benefits and side effects of corticosteroids for patients with DMD and their parents. Furthermore we aimed to (ii) investigate the psychometric qualities of this questionnaire, (iii) whether there was a difference between parents' and patient's perceptions, and finally (iv) to what extent reported side effects may alter over time.

Methods: A 23-item questionnaire (SIDE-CORT: *side effect of corticosteroids*) was constructed to assess the perception of these benefits and side effects in a systematic manner.

Results: In total, 86 patients (aged 5 – 28 years) and 125 of their parents completed the questionnaire. Internal consistency was good. Using factor analyses on the side effect items as reported by parents, two underlying factors were found, with the first factor describing cognitive, behavioural and emotional functioning, and the second factor describing physical functioning. The potential benefits of corticosteroids were highly rated among both parents and patients, although parents rated the importance of the benefits higher than their sons ($p=0.002$). Similarly, parents rated the severity of the side effects generally higher than their sons ($p=0.011$), especially with regards to the physical side effects ($p=0.014$). Based on the parent's perception, the neurodevelopmental side effects generally appeared to decline the longer corticosteroids were used.

Conclusions: To our knowledge, this is the first explicit study on perceived cognitive-, behavioural-, and emotional side effects and the allocation of benefits to corticosteroids in DMD. On the basis of our research we suggest a short form questionnaire, which proves to be reliable and valid for research- and clinical practice. This questionnaire could provide useful insights for the care of boys and men with DMD.

Keywords: Duchenne muscular dystrophy, corticosteroids, side effects, benefits, questionnaire-study

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ABBREVIATIONS

BMI	Body mass index
CNS	central nervous system
DMD	Duchenne Muscular Dystrophy
QoL	quality of life
SD	standard deviation

INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disorder, which occurs in approximately 1 in 3,500–5,000 live male births [1–4] and is caused by mutations in the *DMD* gene that encodes the dystrophin protein. Dystrophin is a large anchoring protein that connects the muscle fiber cytoskeleton to the surrounding extracellular matrix [5]. The absence of dystrophin results in progressive muscle wasting, respiratory-, and cardiac complications [6]. DMD becomes clinically detectable secondary to muscle weakness, which generally presents between the ages of 2 and 4 years [7]. Most boys lose ambulation and become usually wheelchair dependent around their teens [8, 9]. However, DMD is not limited to skeletal, respiratory, and cardiac muscle involvement, as dystrophin is also distributed throughout certain brain regions [10]. The absence of dystrophin has furthermore been associated with an increased risk for neurodevelopmental disorders and epilepsy [11–15].

Currently, corticosteroids are the only treatment that has been shown to slow the somatic progression of DMD despite extensive research for a more effective treatment for DMD [16, 17]. Favourable effects have been demonstrated with both prednisone and deflazacort, including slowing muscle deterioration resulting in prolonged ambulation and upper extremity strength, and a delayed onset of cardiomyopathy [7, 18–26]. Fewer respiratory tract infections, fewer hospitalizations in teenage years, and a delayed onset of respiratory muscle weakness have also been demonstrated [23, 27]. Besides this, corticosteroid treatment significantly reduces the number of individuals requiring spinal surgery for scoliosis [28, 29]. Consequently, a natural history without corticosteroids is rather uncommon in patients with DMD.

In addition to the well documented benefits of corticosteroid treatment, there are numerous potential side effects – especially when a daily steroid regime is implemented [17] – and a small group of patients appear to be non-responders to symptomatic corticos-

teroid treatment [21]. Side effects, secondary to the long-term use of corticosteroids, have been described for both prednisone and deflazacort in studies that have followed DMD patients for 12 weeks to 14 years [7, 18, 21–23, 30]. The most common side effect reported is decreased height [7, 21, 23, 29, 30] with weight gain being the second most common side effect [7, 21, 22, 30]. The latter side-effect has furthermore been reported as the most common cause of discontinuation of corticosteroids [30]. Excessive weight gain, however, was also found in DMD patients who are not treated with corticosteroids [20]. In a double blind randomized control study evaluating deflazacort and prednisone, there were more adverse events in those treated with prednisone compared to deflazacort. Specifically weight gain [31], cushingoid appearance, and erythema were more frequently noted with prednisone [32]. Nonetheless, there are conflicting reports regarding deflazacort treatment resulting in less weight gain compared to prednisone [33]. Prednisone is associated with fewer cataracts [7, 17, 23, 30, 32]. Delayed puberty [21], hirsutism, and increased fracture risks [7, 23, 30] have also been described as side effects with both corticosteroids [33]. A varying spectrum of corticosteroid side effects thus exists for both deflazacort and prednisone, however full consensus has not been achieved.

In addition to these physical side effects of corticosteroids, behavioural, and emotional side effects of corticosteroid treatment in DMD have also been reported [17–20, 34, 35] including irritability, aggression [9], mood swings, hyperactivity, depression, and euphoria [2, 36]. Similarly, it was suggested that the increased risk of ADHD in DMD might be exacerbated by corticosteroids treatment [2]. It has been postulated that these side effects are more frequent with prednisone treatment compared to deflazacort [32]. Yet in other studies no statistical difference has been identified between the two corticosteroids [35]. However, long term studies have predominantly focused on physical side effects rather than evaluating cognitive, behavioural, and emotional changes associated with corticosteroid treatment in DMD.

As life expectancy has increased significantly in the last two decades secondary to changes in clinical care and corticosteroid treatment, new insights concerning the psychological wellbeing and functioning of these patients and the potential contribution of corticosteroid treatment is of growing importance. To determine the perceived side effects, a self-report questionnaire can provide useful information

to clinicians [37] since it has been suggested that the perception of possible side effects is captured best by using such means. However, most existing disease-specific questionnaires focus on quality of life (QoL) or on the treatment effect of steroids, and are not designed to detect treatment-related side effects. Therefore, the primary aim of this explorative pilot study was to (i) develop a questionnaire to assess benefits and both physical and neuropsychological side effects of corticosteroids. Such a tool is currently lacking in clinical practice and could therefore be implemented in the routine care for patients with DMD. This pilot study will serve as an incentive for its further development. However, as an initial measure of the concepts (construct) validity and reliability we aimed to (ii) establish these psychometric qualities from the traditional perspective. Apart from the abovementioned clinical aims, we also aimed to use it here for research purposes: that is, we wanted to find out (iii) whether parents' and patients' perception differed with regards to the report of benefits and side effects of corticosteroids in DMD. Finally, we were also interested in (iv) whether these side effects would change over time for patients taking daily corticosteroids, i.e. with increasing treatment duration.

METHODS

Measures

Two parallel versions of the SIDECORT (*side effects of corticosteroids*) questionnaire were constructed: one version for parents (SIDECORT-P) and one version for boys/young men with DMD (SIDECORT-CY, i.e. child and youth). Both versions were available in English and Dutch. Native speakers carefully translated the original Dutch version into English and back. The items of the questionnaire were formulated after a thorough literature search resulting in a list of all possible reported side effects and benefits (see appendix A and B for more information on the rationale behind these items). This list was separately and independently presented to four experts in clinical and psychological care (JH, JV, LM, and DB). Items on which there was consensus were appended in the original questionnaire with 10 possible benefits and 33 possible side effects. In order to attain the best possible understanding for patients and parents, the items were designed to be short, straightforward, and with easy language describing the side effects and benefits from the parents' and boy's perspective.

In the construction of the SIDECORT we used an existing questionnaire (SIDAED) for the evaluation of side effects of other chronically used drugs, i.e. anti-epileptic treatment, as an example [38].

SIDECORT can be divided into 4 sections: general information, possible benefits from corticosteroids, possible side effects from corticosteroids, and overall impression. If there are general medical issues, the participant indicates when this started. When rating the potential benefits, a 3-point Likert scale is considered appropriate [39] and is therefore used (*not important, moderately important or very important*). When rating possible side effects participants indicate if it is not an issue or if it is an issue; a 4-point Likert scale is used (*no problem, mild problem, moderate problem or serious problem*) as well as duration of time it has been an issue. For the side effect section, we used the response-format of the SIDAED [38]. Finally in part four, overall impression, it is asked to assign an overall rating of corticosteroids on a 10-point Likert scale (a score of 0 implying "*not at all*" and a score of 10 meaning "*very much*") by means of two general questions that are used as a validation tool for the questionnaire presented here. The SIDECORT, which is included in appendices C and D, concludes with a question on steroid recommendation. The time frame used for the questions was current status.

Statistical analysis

Data analysis was performed using SPSS (version 21). Demographic variables and external characteristics including age, height, and weight were initially calculated. A principal component analysis was performed to identify the underlying structure of the SIDECORT. Principal component analysis is a form of factor analysis, which is a technique that aims to identify groups or clusters of variables. As such it is an explorative method that can be used to describe the underlying structure of (side effect) items making up a questionnaire [41]. Oblique rotation was initially chosen; because it was thought the underlying factors were related. Subsequently, however, an orthogonal rotation was also performed. Sensitivity analysis revealed the best underlying factor structure for oblique rotation. In interpreting factor loading we used Stevens [40] criterion that loadings >0.51 can be considered significant for a sample size of 100 and his suggestion to interpret factor loadings >0.40 (see Table 1). Since corticosteroids are generally started at a young age, the answers reported by parents are

Table 1

Psychometrics: short item-description of part C of the SIDECORT (original 33 side effect items) and results of principal component analyses (two factor solution) as based on parents' reports. The respective factor loadings are followed by the mean (a score of 1 meaning "no problem", a score of 4 indicating a "serious problem") and standard deviation per item

Short description of item	Factor loadings			Descriptive statistics	
	F1	F2	n	Mean	SD
I. Cognitive/Behavioural/Emotional Functioning					
1. Problems concentrating	0.84*	-0.16	105	1.68	0.95
2. Distracted easily	0.82*	-0.20	105	1.76	0.96
3. Feels restless during the day	0.79*	-0.02	105	1.56	0.84
4. Feels anxious	0.76*	0.08	103	1.71	0.94
5. Gets upset easily	0.72*	0.06	106	2.19	1.05
6. Has trouble controlling himself	0.70*	0.08	105	1.86	0.92
7. Gets into fights	0.66*	0.14	105	1.38	0.79
8. Forgets things easily	0.66*	-0.14	105	1.48	0.79
9. Feels depressed	0.58*	0.06	106	1.63	0.85
10. Feels worried	0.56*	0.35	105	1.72	0.93
11. Trouble getting to sleep	0.56*	0.17	105	1.58	0.82
12. Mind doesn't work as fast as it should	0.51*	0.00	77	1.45	0.82
II. Physical Functioning					
1. Puffy cheeks	-0.14	0.70*	106	2.15	0.93
2. Can't do things because too short	0.06	0.65*	104	1.55	0.86
3. Too short	0.02	0.61*	105	2.28	1.07
4. Gained weight	0.12	0.60*	106	2.36	1.14
5. Looks too young for his age	-0.20	0.56*	106	1.68	0.86
6. Childish face	-0.04	0.53*	77	1.52	0.79
7. Stretch marks on tummy or legs	0.03	0.52*	104	1.46	0.80
8. Teased at school	-0.00	0.45	106	1.59	0.78
9. Too much hair	0.08	0.43	106	1.42	0.68
10. Often hungry	0.26	0.43	104	1.94	0.98
11. Can't see well on sunny days	0.03	0.41	105	1.35	0.80
Items not belonging to any of the two factors					
1. Trouble sleeping through	0.38	0.38	97	1.46	0.78
2. Headaches	0.29	0.26	106	1.53	0.80
3. Dizzy	0.16	-0.00	105	1.14	0.38
4. Warts on hand/feet	0.16	0.30	103	1.25	0.64
5. Skin rash	0.15	0.09	104	1.34	0.65
6. Pimples or acne	0.10	0.28	104	1.30	0.50
7. Broken arm	0.09	0.23	106	1.27	0.79
8. Fracture of his back bone	-0.14	0.36	105	1.25	0.65
9. Broken leg	-0.25	0.22	106	1.28	0.75

F1: cognitive, behavioural and emotional functioning, F2: physical functioning. *significant (factor loading >0.5).

considered substantially more reliable. Furthermore we had to take into consideration the high prevalence of cognitive impairment in DMD patients. Therefore, only the answers provided by the parents were used for principal component analysis in order to construct the final version of the SIDECORT. The reliability of the questionnaire was calculated by using Cronbach's alpha.

Total scores were calculated by adding all scores separately for patients and parents groups belonging to the items dealing with side effects (after principal component analysis assessment). Similarly, a total [19]-score was calculated for each corresponding factor identified.

Allocated benefits and side effects as measured by the different Likert scales were compared between

parents and patients by means of a dependent (paired) *t*-test [42–44]. Additionally, Pearson's correlation was calculated to investigate a possible relation between corticosteroid treatment duration and reported side effects. For all tests a Bonferroni correction was performed. Given the two main tests performed, i.e. i) comparing benefits between parents and patients, and ii) comparing side effects between parents and patients, alpha was divided by two and set at a level of 0.025. For correlation analysis the alpha of 0.05 was maintained.

RESULTS

The data for all individual items were plotted and carefully inspected. The calculated differences

between parents and patients regarding both benefit allocations and reported side-effects (including the total sum scores) as measured by the different Likert-scales were normally distributed.

Patient characteristics

Patients with DMD between 5 and 28 years old and their parents were recruited between 2010 and 2012 from four different neuromuscular centres in the United States of America, Canada, and the Netherlands. Ethical approval was obtained from the local ethics board at Holland Bloorview Kids Rehabilitation Hospital, Alberta Children's Hospital, and Kempenhaeghe Centre of neurological learning disabilities.

Boys older than nine years old were invited to complete the questionnaire themselves with cooperation of their parents. For younger boys, only parents were asked to complete the questionnaire as literature suggests that for health-reported QoL and single-item symptom measures, the age of 5 is already considered reliable [45], with increases after the age of 7 in the general population [46]. The SIDECORT questions are however different and do not relate to quality of life, nor do they consist of a single-item. Consequently we decided to increase the age to 9 years of age, to be sure that self-report data are reliable.

In total, 217 questionnaires were returned, of which 129 were completed by parents and 88 by individuals with DMD; thereby representing a convenience sample. Four participants were excluded because of incomplete data on corticosteroid type and corticosteroid use. Of the remaining 125 participants, all were treated with corticosteroids: 68.0%, deflazacort (98.8% daily, 1.2% on a 10 days on/10 days off regime), and 29.6% prednisone (67.6% daily, 18.9% on a 10 days on/10 days off regime, 5.4% every other day, 5.4% in weekends, 2.7% a different regime), 2.4% had taken prednisone as well as deflazacort (100% daily). The starting age of corticosteroid treatment ranged from 3 to 14 years old (mean age 6.63 years, SD = 2.30 years). The duration of corticosteroid treatment ranged from 0 to 20 years with a mean of 7.84 years (SD = 4.75 years).

The participating parents and their sons lived in areas spread throughout the Netherlands ($n=13$), Canada ($n=32$) and the United States of America ($n=75$); for 5 participants the country of residence was missing. The survey was completed anonymously, and demographic information was not collected for non-responders. The mean age of the

patients was 14.5 years (SD = 5.1 years) with a minimum age of 5 years and a maximum of 28 years. The mean height was 141.2 cm (SD = 18.9 cm), with a minimum of 103 cm and a maximum of 182 cm. The mean weight was 46.1 kg (SD = 16.6), with a minimum of 17.2 kg and a maximum of 91.2 kg.

Eighteen percent of the patients over 18 years ($n=22$) reported to have general puberty changes, 32% had undergone scoliosis surgery, and 41% were night-time ventilation-dependent. Only one patient within this age-specific sample (i.e. >18 years) required daytime ventilation. Of the boys older than 14 years ($n=56$), 27% were ambulatory.

SIDECORT psychometrics

Validation analysis: Principal component analysis for side effects (as reported by parents)

We investigated the underlying factors of the questionnaire by means of principal component analysis for parents' ratings. The two, three, and four factor solutions after oblique rotation were inspected consecutively. The two-factor solution was most robust and could be interpreted with the first factor describing cognitive, emotional, and behavioural functioning (12 items; *eigenvalue*: 7.16, percentage explained variance 22.4%) and the second factor could be labelled physical functioning and complaints (11 items; *eigenvalue*: 3.38, percentage explained variance 10.6%). Nine items did not show a significant loading on the two factors and were removed from further analyses. All factor loadings can be found in Table 1.

Reliability analysis

Internal consistency of the parent report 23-item questionnaire was good with a Cronbach's alpha of 0.87. The internal consistency of the separate two subscales based on the factor-analysis was good: 0.89 for the subscale cognitive, behavioural, and emotional functioning and 0.82 for the subscale physical functioning.

Parent and patient report on steroid benefits and side effects: Is there a difference?

Possible benefit allocation

Due to data mismanagement, one of the original benefits ("delay the need for night-time ventilation") was not collected for patients and therefore excluded from the analysis. All possible benefits were rated as important (Table 2) by both parents

Table 2
Importance of possible benefits as a consequence of corticosteroid use: parents vs. DMD patients

		Not important	Moderately important	Very important
Walk longer (3–5 yr.)	Parents	0.8%	5.8%	93.3%
	Patients	7.9%	9.0%	83.1%
Keep spine straight	Parents	0%	5.9%	94.1%
	Patients	0%	12.5%	87.5%
Prevent spine operation	Parents	0%	2.5%	97.5%*
	Patients	2.3%	9.1%	88.6%
Keep arms stronger	Parents	0.8%	3.3%	95.9%
	Patients	0%	11.2%	88.8%
Keep breathing stronger	Parents	0%	0.8%	99.2%*
	Patients	0%	7.9%	92.1%
Keep heart stronger	Parents	0%	0%	100%*
	Patients	0%	5.6%	94.4%
Prevent lung infections	Parents	0%	5.8%	94.2%
	Patients	0%	9.1%	90.9%
Have better cough	Parents	1.7%	6.7%	91.7%***
	Patients	5.6%	22.5%	71.9%
Feed him-/myself	Parents	0.8%	8.3%	90.8%
	Patients	0%	13.6%	86.4%

* $p < 0.025$, *** $p < 0.001$.

and boys/young men. In general, patients and parents strongly agreed on the benefits. When comparing parents and patients' judgements (Table 3) it can be seen that parents consider four benefits as significantly more important than their sons, that is: 'keep heart stronger' ($p = 0.024$), 'prevent spine operation' ($p = 0.020$), 'keep breathing stronger' ($p = 0.013$), and 'have a better cough' ($p < 0.001$). Overall, when comparing the total benefit scores as based on the 9 benefit questions (Tables 2 and 3) between parents and patients, parents consider the potential (physical) benefits of steroids more important than their sons (mean difference 0.71, $t = 3.26$ $p = 0.002$). At the same time, when giving a general judgement on the overall experienced help (which here served as a validation question for the benefit

total score), parents (mean = 8.59, SD = 1.86) also reported more help from the steroids when compared to patients (mean = 8.01, SD = 2.10, $t = 2.753$, $p = 0.007$). Finally, although a trend was visible in favour of parents, patients and parents seemed to agree in recommending the use of corticosteroids for other boys with DMD ($t = 1.884$, $p = 0.063$).

Perceived Side effects

Overall-item- and subscale assessment. Due to data mismanagement three items were not collected for patients (see Table 4). The total scores of all side effects items added-up (if present), thus reflecting the overall severity, were rated statistically higher for parents (mean difference 1.98, $t = 2.622$, $p = 0.011$). Regarding the subscales cognitive/behavioural/emotional functioning and physical functioning both total scores were, again, higher for parents. However, the score on the former domain, as based on the first factor identified, was not considered statistically significant ($p = 0.09$). In contrast, compared to patients, parents reported significantly more side effects on the physical sub-scale, as based on the second factor identified (mean difference 1.18, $t = 2.52$, $p = 0.014$).

Individual-item assessment. Generally, in both groups the side effects that were perceived as most problematic were: (I) being too short, (II) gaining weight, (III) puffy cheeks, (IV) often hungry, (V) feeling worried, (VI) getting upset easily, and

Table 3

Comparison between patients and parents with regards to their perception on the potential benefits of corticosteroids: sample size, the mean and standard deviation (SD) of the paired difference (i.e. parent report- patient report), t-score and p-value are depicted in the table

	n	Mean	SD	t	p
Walk 3 to 5 years longer	86	0.105	0.595	1.632	0.106
Keep spine straight	86	0.058	0.387	1.394	0.167
Keep arms stronger	87	0.057	0.318	1.684	0.096
Keep breathing stronger	87	0.069	0.255	2.524	0.013
Prevent spine operation	86	0.093	0.364	2.371	0.020
Keep heart stronger	87	0.057	0.234	2.290	0.024
Prevent lung infections	86	0.023	0.375	0.575	0.567
Have a better cough	87	0.230	0.499	4.298	0.000
Be able to feed myself	86	0.047	0.373	1.157	0.251

Table 4

Comparison between patients and parents on the experienced and perceived side effects of corticosteroids respectively. The items are listed in descending order; the most common side effects (as reported by boys with DMD) are listed first. Paired differences are based on the parents' mean score minus the patients' mean score (as performed for all questionnaires completed by both parents and patients). Thus, negative mean results indicate patients, on average, considering the side effects as more severe

Side effect	Patients		Patients			Paired Difference (= Parent – patient)		
	Mean	SD	Mean	SD	n	Mean	SD	p
1. I am too short	2.13	1.08	2.32	1.11	69	0.19	0.97	0.11
2. Gain weight***	2.03	1.04	2.38	1.11	71	0.35	0.83	0.00
3. Puffy cheeks	1.93	0.98	2.13	0.88	70	0.20	0.81	0.04
4. Often hungry	1.85	0.89	1.81	0.94	67	-0.05	0.68	0.59
5. Feels worried	1.75	0.86	1.77	0.91	69	0.02	0.78	0.88
6. Get upset easily*	1.73	0.93	2.00	0.97	71	0.27	0.97	0.02
7. Looks to young for his age	1.73	0.88	1.87	0.91	71	0.14	0.83	0.16
8. Can't do things because short	1.65	0.96	1.65	0.94	68	0.00	0.93	1.00
9. Feel depressed	1.55	0.73	1.62	0.80	71	0.07	0.66	0.37
10. Feels anxious	1.54	0.88	1.64	0.85	67	0.10	0.86	0.32
11. Problems concentrating	1.53	0.81	1.50	0.74	70	-0.29	0.68	0.73
12. Being teased	1.52	0.84	1.68	0.81	71	0.16	0.75	0.09
13. Trouble controlling acting	1.45	0.81	1.67	0.82	69	0.22	0.84	0.04
14. Stretch marks	1.44	0.76	1.41	0.70	68	-0.03	0.73	0.74
15. Feel restless	1.40	0.67	1.41	0.69	70	0.01	0.77	0.88
16. Trouble falling asleep	1.39	0.73	1.48	0.70	69	0.09	0.59	0.22
17. Too much hair (on arms)	1.39	0.73	1.42	0.71	71	0.03	0.76	0.76
18. Forget easily	1.39	0.73	1.37	0.73	70	-0.01	0.69	0.86
19. Can't see well on sunny days	1.31	0.75	1.46	0.91	70	0.14	0.89	0.18
20. Get into many fights	1.28	0.73	1.32	0.74	69	0.04	0.76	0.63
21. Gets distracted easily	-	-	1.76	0.96	-	-	-	-
22. Childish face	-	-	1.52	0.79	-	-	-	-
23. Mind doesn't work as fast	-	-	1.45	0.82	-	-	-	-

* $p < 0.025$, *** $p < 0.001$.

(VII) looking to young (although not in the same order across the two groups; see Table 4). When studying the individual items as shown in Table 4, there was a significant difference between parents and their sons in the perception of one physical side effect (i.e. gaining weight; $p = 0.001$) and one behavioural/emotional side effect (i.e. getting upset easily; $p = 0.023$), with parents reporting more problems for both items.

Correlation analysis between corticosteroid treatment duration and side effects for patients on daily regime

Correlations between treatment duration and the 23 reported side effects (as based on the principal component analysis) were examined for both the parents' and patients' groups separately by means of a Pearson's correlation analysis. This was irrespective of corticosteroid type and done for patients on a daily-regime only. Significant negative correlations were found between the duration of corticosteroid treatment and the following by-proxy reported side

effect items: getting upset easily ($r = -0.26$, $p = 0.016$, $n = 87$), distraction ($r = -0.34$, $p = 0.001$, $n = 87$), restlessness, ($r = -0.30$, $p = 0.005$, $n = 86$), trouble with self-control ($r = -0.37$, $p = 0.001$, $n = 86$), concentrating problems ($r = -0.24$, $p = 0.025$, $n = 87$), and information processing speed ($r = -0.29$, $p = 0.024$, $n = 63$). Among parental reports there were no correlations with physical side effects.

However, in contrast to the parents' reports, the following, physical correlations with treatment duration became apparent in the patient group: puffy cheeks ($r = 0.28$, $p = 0.035$, $n = 58$) and often hungry ($r = -0.28$, $p = 0.038$, $n = 56$). A trend was identified for the following: DMD patients appeared to increasingly think that corticosteroid usage was more important with longer treatment durations ($r = 0.22$, $p = 0.06$, $n = 75$), reflecting their perceived positive and beneficial role among boys and men with DMD in the long-term (among the parents a comparable trend was also visible regarding this question; $r = 0.17$, $p = 0.083$, $n = 103$). Finally, for patients and parents, the number and/or severity of the side effects (section 4) appeared not to correlate with treatment duration.

DISCUSSION

To investigate the perceived benefits and side effects of corticosteroids, both a self-report and a by-proxy questionnaire were constructed that could equally be administered to parents and boys/young men with DMD in order to quantitatively measure benefit perception and (severity of) side effects. This could furthermore enable clinicians to continuously monitor such effects during treatment. Questionnaires such as SIDECORT may thus be of great importance for research and clinical purposes, not only in DMD, but perhaps also in other diseases that are chronically treated with corticosteroids. This is to our knowledge, the first questionnaire aiming to assess these constructs simultaneously. The construction of the SIDECORT was based upon literature on side effects and benefits using a classical test theoretical approach and in accordance with an existing questionnaire on side effects of anti epileptic drugs, which are also known for their long term-treatment and side effects. The SIDECORT was aimed to be easy and quickly administrable for both parents and patients older than 9 years of age.

The questionnaire presented here, has good reliability (Cronbach's alpha of 0.87). Furthermore, its (construct) validity is confirmed by the underlying factor structure and the reliabilities for the subscales found. The two subscales based on factor analysis, i.e. cognitive/behavioural/emotional- and physical functioning, and the distinction between these could be equally important for clinical practice.

The current study is – albeit apart from a recent study by Sienko and colleagues who assessed slightly other aspects (i.e. differences in child behaviour perceptions and QoL and their differences between parents and patients) [35] – the first to assess different perceptions of parents and boys/young men on both side- and beneficial effects of corticosteroids. All potential steroid benefits were rated as very important. Thus, the SIDECORT did not differentiate between (physical) benefits that are evaluated as more important than others. However, parents rated four potential effects as more important than their sons, that is, in consecutive order: *keep heart stronger*, *prevent spine operation*, *being able to breath strong(er)*, and *being able to maintain a good/better cough*. The latter two might be attributed to the fact that parents' are well aware and concerned of the ultimate respiratory involvement in DMD [6], which contributes to it being a life limiting condition [47, 48]. Moreover, parents rate – on average – every, possible

individual steroid benefit as more important than their sons (Table 2), as has also been shown in asthma treatment [49]. Next to a different benefit allocation, parents generally also reported significantly more help from steroid treatment than their sons. Differences in parents' and sons' perceptions have also been noted in measures of QoL where parents report lower overall health related QoL when compared to their sons [50]. The differences in parent-patient perception highlight the importance of ensuring we are inquiring about both caregiver and patients perspectives with treatment interventions.

At the same time, parents considered the corticosteroid side effects as more severe than their sons ($p=0.011$), which may partly be in line with the finding that parents seem to underestimate their son's perception of positive aspects associated with their disease, including treatment- and side effects [50, 51]. For both subscales identified (i.e. cognitive/behavioural and physical functioning), two side effects were considered more of a problem by parents compared to their sons: *getting upset easily* and *weight gain*. Correlation analysis demonstrated a moderate to good correlation between body mass index (BMI) and the reported side-effect "gaining weight" for both patients ($r_s=0.40$, $p=0.003$) and parents ($r_s=0.57$, $p<0.001$), revealing that the concern regarding gaining weight is probably based on actual values rather than the perception of weight being an issue.

Parents and patients do not only differ in their perception on steroids, but also on the severity of specific side effects as well as on potential (respiratory) benefits. This suggests that parents may be more willing to accept a certain side effect if there is significant (concomitant) benefit. However, individual's perceptions can be influenced by many other factors. For instance, among DMD parents there can be other emotional and financial factors involved, including caregiver burnout [2]. It is important to consider such factors clinically when discussing treatment perception.

The most severe side effects subjectively reported by patients were: (I) being too short, (II) gaining weight, (III) puffy cheeks, (IV) often hungry, (V) feeling worried, (VI) getting upset easily, and (VII) looking to young. The high incidence of the first two side effects, i.e. decreased height and increased weight, is in line with the literature on side effects in DMD populations [7, 21]. It is important to note that both physical (I–IV and VII) and cognitive/behavioural/emotional (V and VI) side effects are represented in this list. This exemplifies the

importance of holistic care for the patient with DMD that includes emphasis not only on the physical, but also behavioural/emotional associations in DMD [11, 12], and is in accordance with the statement of *The Behaviour in DMD Study group*, which stated merely ten years ago that mood and behavioural side effects belonged to the most commonly reported reasons for discontinuation of corticosteroids [52]. Although we have not quantitatively determined the impact of corticosteroids on cognitive, behavioural, and emotional functioning, these findings highlight that both individuals with DMD and their parents perceive a significant impact of corticosteroid treatment on these domains, which needs to be addressed clinically. Given the prolonged life expectancy, it is furthermore essential that clinical care focuses on addressing these side effects as they can potentially impact relationships including friendships as well as the development of self-efficacy and self-determination during adolescence. These behavioural/emotional (i.e. #V and #VI) side effects, that may be brain-related, could also be related to the role corticosteroids may have in neuro-immuno modulation. Alternatively, they may be the consequence of the direct influence of steroids on GABA-receptor functioning [35, 53], which has repeatedly been shown to be impaired in DMD due to disruption of the full-length isoform (Dp427) normally clustering these receptors post-synaptically [54, 55]. Such features of brain-involvement may thus – at least partly and subjectively – not only be attributed to the corticosteroids in DMD treatment, but may also be the consequence of a lack of (certain) dystrophin (isoforms) in the CNS.

Taking into account the duration of steroids usage, correlation analyses demonstrated that the perceived side effects regarding cognitive and behavioural/emotional aspects (e.g. getting upset easily, distraction, restlessness, self-control, concentration, and information processing speed) decline the longer corticosteroids are used. Although this was based on the parent's report, this may reflect a reduction of side effects with time or adaptation to the adverse effects or the corticosteroid. It furthermore, once again, affirms that parents acknowledge these brain-related side effects as a consequence of the steroid use. Within the patient-report group no change of brain-related comorbidities was reported over time. For physical complaints, a positive correlation for puffy cheeks, illustrative of the progressive cushingoid features associated with corticosteroids was found in the patient's group.

The current pilot study has several important limitations such as (a) limited representativeness of study sample in a cross sectional design; (b) one-time assessment with a newly developed questionnaire without features to distinguish between the origin of the symptoms (i.e. are the reported effects indeed the consequence of steroids usage, or perhaps a side effect of other medication, or even a pre-existent or new comorbidity); (c) lack of relevant medical history and psychological data to address in the study; (d) lack of insights in response rates due to the collection of a convenience sample; and (e) the influence of cognitive impairment on the data as reported by DMD patients, although the magnitude of this problem is unknown. Consequently, more research on the underlying structure and the interpretation of the scores is needed. The fact that this is a retrospective study conducted on a single time point is important, as the perceived importance of most of the SIDECORT benefits and side effects will vary with age. Furthermore, the consequence of the substantial range between the youngest subject (5 years of age) and the eldest subject (28 years of age) is that their answers cannot be readily compared. However, the latter could also be considered a strength because it surveys and relates to a wide age-range. We decided not to evaluate differences per age groups (e.g. between adults and boys) as we expected this to result in a loss of power. Finally it should be noted that the principal component analysis was based on the answers given by parents because of the relatively young age of the sample and the expected higher prevalence of cognitive deficits in boys with DMD. However, parents are known to be very alert to side effects, as also partly revealed by the differences in scores between parents and patients in this study. Therefore, their answers, on which the final version of the SIDECORT is based, may (also) contain a bias.

We believe that the data of this pilot study are promising and that the 23-item SIDECORT as constructed on the basis of this study constitutes a useful and potentially promising tool for both research- and clinical purposes. The current pilot study provided information on the face validity and reliability of the questionnaire. Further research is needed using (a) objective, physical parameters to validate the perceived effects, not least when considering the diverse factors that could have attributed to the differences found here (e.g. a difference in understanding the question between parents and their sons); (b) repeated assessment of side effects in order to assess specificity of the items but also to attain information on the

developmental profile of side effects, which can change over time; (c) implementation of the SIDECORT in a corticosteroid using non-DMD population to differentiate between illness specific and medication specific effects of corticosteroids; (d) determination of cut-off scores in order to interpret the calculated scores in clinical routine; (e) subjecting the SIDECORT to modern psychometric approaches in larger samples, using the Rasch measurement model to measure latent traits; (f) comparison of DMD patients using corticosteroids and patients who are not using these drugs in order to determine which events can most likely be regarded as side effects; and finally (g) evaluation of differences with regards to benefit allocation and report of side effect severity between patients using deflazacort and prednisone (e.g. by making use of SIDECORT), not least since this has been extensively studied in literature, yet without attaining straightforward consensus. Unfortunately, the latter was not possible in this pilot study due to the discrepancy between deflazacort and prednisone with regards to the different regimes clinically used (i.e. deflazacort is mostly used daily whereas prednisone is not, see patient characteristics), making correction for the regime impossible due to the limited sample size in the prednisone group.

CONCLUSION

This study reports on corticosteroid benefits and side effects in an international cohort of DMD patients as assessed by means of a newly developed self- and by-proxy report questionnaire (SIDECORT) with good validity and internal consistency. It confirms that physical side effects are common and parents generally report more problems with side effects than their sons. At the same time, however, they regard the potential benefits as more important than their sons. This study furthermore shows that parents and patients acknowledge the cognitive, behavioural, and emotional features, or even comorbidities, associated with DMD, which can additionally – albeit subjectively – be considered the consequence of corticosteroid usage. In contrast to patients, parents consider especially some cognitive, behavioural, and emotional side effects to decrease with longer treatment durations. Future research on the perceived side effects of corticosteroid treatment utilizing SIDECORT is necessary to confirm the psychometric characteristics and perceived side effect profile over time.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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APPENDIX A: THE RATIONALE FOR ALL INCLUDED BENEFIT ITEMS

Corticosteroids have impacted the natural history of DMD; please refer to the introduction for full details. The following items were chosen as corticosteroids have influenced these clinical areas.

Item	Rationale
1. Walk 3–5 years longer	Loss of ambulation is a significant marker in the progression of DMD.
2. Keep spine straight	Approximately 90% of the boys with DMD develop scoliosis without corticosteroid treatment.
3. Keep arms stronger	The progressive muscle weakness that eventually affects the arms in all DMD boys is slowed with corticosteroid treatment.
4. Keep breathing stronger	Respiratory muscle weakness is part of the progression of DMD.
5. Prevent spine operation	The abovementioned scoliosis often requires surgery; this question serves as a validation for benefit #2 (i.e. respondents are expected to answer in similar directions).
6. Keep heart stronger	Similar to respiratory muscle weakness, cardiologic involvement contributes to DMD being a life-limited disorder.
7. Prevent lung infections	Due to respiratory muscle weakness, boys with DMD are more prone to develop chest infections, which can put them greatly at risk for respiratory complications.
8. Have a better cough	Having a strong cough may prevent the development of lung infections to some extent and, in turn, pulmonary deterioration; this item serves as a validation for benefit #7 and #4.
9. Being able to feed himself	This aims to give more insight in the importance of self-reliance. This item also serves as a validation for benefit #3

APPENDIX B: THE RATIONALE FOR ALL INCLUDED SIDE EFFECT ITEMS

Corticosteroid product monographs provide an extensive list of side effects, however, understanding the side effect profile of corticosteroids in children with DMD has not been thoroughly investigated. It is important to understand the impact of corticosteroids within the context of the neurodevelopmental profile in DMD. The clinical experience of the authors, together with the literature – as partly summed up in the introduction-, was utilized to identify side effects that have been noted to be significant in this patient population, and were subsequently focussed on in the construction of SIDECORT. Multiple questions were generated and some were related to serve as a validation tool, as they were expected to be reported in the same direction (i.e. “feels worried about many things” and “feels anxious too often”).

APPENDIX C: SIDECORT-P (VERSION FOR PARENTS)

Participant Study ID#

SIDECORT-P: questionnaire about the effects of steroids (Parent version)

With this questionnaire we want to learn how boys with Duchenne feel about the effects of steroids. The questionnaire has four parts: Part 1 is general information about your son. Part 2 has questions about the possible benefits your son might have from the steroids. Part 3 has questions about possible side effects your son might have. In part 4, we ask you to give your overall impression about the benefits and side effects of taking steroids.

PART 1: General information.

Please answer the following questions by writing down your answer or marking the appropriate circle (0). For some questions, you also have to fill in a date as the month and year

This questionnaire was completed by	<input type="radio"/> Mother	<input type="radio"/> Father	<input type="radio"/> other:	
Date of your son's birth:		Month:	Year:	
City where your son lives:				
How tall is your son? Inches.....Centimetres			
How much does he weigh?Pounds Kilograms			
Which steroid does he take?	<input type="radio"/> prednisone	<input type="radio"/> deflazacort	Other:	
What age did your son start using steroids?	(fill in year)			
What schedule is your son on?	<input type="radio"/> daily	<input type="radio"/> 10 days on/off	<input type="radio"/> very other day	Other:
Is your son still walking?	<input type="radio"/> NO	<input type="radio"/> YES		
Is your son going through puberty?	<input type="radio"/> NO	<input type="radio"/> YES	If yes, since when	
Did your son have scoliosis surgery?	<input type="radio"/> NO	<input type="radio"/> YES	When was this?	
Does your son take growth hormone?	<input type="radio"/> NO	<input type="radio"/> YES	If yes, since when	
Does your son take ritalin/methylphenidate?	<input type="radio"/> NO	<input type="radio"/> YES	If yes, Since when	

Participant Study ID#

Is your son's blood sugar high (diabetes)?	0 NO	0 YES	If yes, Since when
Does your son take medicine for high blood sugar?	0 NO	0 YES	
Has your son had a stomach ulcer?	0 NO	0 YES	If yes, Since when
Does your son have heartburn?	0 NO	0 YES	If yes, Since when
Is your son on night time ventilation (BiPAP)?	0 NO	0 YES	If yes, since when
Is your son on ventilation during the day?	0 NO	0 YES	Is yes, since when
Did your son have a chest infection requiring antibiotics in the last year?	0 NO	0 YES	

PART 2: Possible Benefits from steroids.

Steroids may have benefits. Can you tell us how important each of the benefits listed below are for your son? Please mark the column either "not important", "moderately important" or "very important".

	Not important	Moderately important	Very important
Walk 3 to 5 years longer			
Keep his spine straight			
Keep his arms stronger			
Keep his breathing stronger			
Prevent a spine operation			
Keep his heart stronger			
Prevent lung infections			
Have a better cough			
Delay the need for night-time BiPAP			
Be able to feed himself			
Other benefits we did not mention:			

Participant Study ID#

PART 3: Possible Side-effects from steroids

Below is a list of complaints and side-effects that some boys have with steroids. Did your son have any of the problems listed below which you think **were caused by the steroids?**

For this part of the questionnaire first please mark whether the item is a problem for your son. If it is **not** a problem for him please mark the box in the left column and go to the next item.

When the item **is** a problem for your son, then rate how serious this problem is: mark the box for mild, moderate or severe. Finally, answer how long has this been a problem for your son: you can either mark "since a few weeks", "several months" or "half year and longer".

		How serious is this problem?				For how long has this been a problem?		
	BECAUSE OF STEROIDS, MY SON:	No problem	mild problem	moderate problem	serious problem	Since a few weeks	Several months	Half a year or longer
1	has puffy cheeks							
2	has been teased by others							
3	has too much hair on his arms							
4	gets upset more easily							
5	has had a broken arm							
6	has trouble sleeping through all the night							
7	has gained more weight							
8	can't see well on sunny days (has cataracts)							
9	has had a broken leg							
10	looks too young for his age							
11	gets distracted more easily							
12	feels restless during the day							
13	easily forgets things							
14	has problems concentrating on things he is doing							
15	has more headaches							
16	feels depressed or sad more often							
17	feels dizzy							

Participant Study ID#

	BECAUSE OF STEROIDS, MY SON:	No problem	mild problem	moderate problem	serious problem	Since a few weeks	Several months	Half a year or longer
18	has trouble getting to sleep							
19	is too short							
20	feels worried about many things							
21	gets into too many fights							
22	has trouble controlling the way he reacts							
23	has back pain riding on the school bus or car							
24	is often hungry							
25	has a childish face (without hair)							
26	feels anxious too often							
27	mind doesn't work as fast as it should							
28	can't do some things because he is too short							
29	has warts on his hands or feet							
30	has skin rashes							
31	has pimples or acne							
32	has stretch marks on tummy or legs							
33	Others:							

PART 4: Overall Impression

On a scale from 0 to 10, with 0 being "not at all" and 10 being "very much": Please circle the number that applies.

	Give a rating from 0 (not at all) to 10 (very much)										
How much do steroids help your son?	0	1	2	3	4	5	6	7	8	9	10
How many side-effects does your son have from using the steroids?	0	1	2	3	4	5	6	7	8	9	10
Given your son's experience, would you recommend steroids to other boys?	0 NO			0 YES				0 Don't know			

Thank you very much for your help.

APPENDIX D: SIDECORT-CY (VERSION FOR CHILDREN/YOUTH)

Participant Study ID#

SIDECORT-CY: Questionnaire about the effects of steroids (Children/Youth version)

We want to learn how you feel about the effects of taking steroids for your muscles. The questionnaire has four parts: Part 1 is general information about you. Part 2 has some questions about the possible benefits you may have from taking the steroids. Part 3 has some questions about possible side effects you may have. In part 4, we ask you to give your overall impression of the benefits and side effects.

PART 1: General information and functioning

Please answer the following questions by writing down your answer or marking the appropriate circle (0). For some questions, you also have to fill in a date as the month and year.

Date of your birth:		Month:	Year:
City where you live:			
What age did you start using steroids?	(fill in year)		
Are you still walking?	0 NO	0 YES	
Are you going through puberty changes?	0 NO	0 YES	If yes, since when
Did you have an operation on your back?	0 NO	0 YES	When was this?
Do you have a lot of headaches?	0 NO	0 YES	If yes, Since when
Do you have heartburn?	0 NO	0 YES	If yes, Since when

Participant Study ID#

PART 2: Possible Benefits from steroids

Steroids may have benefits. Some benefits are listed in the next part. Can you tell us how important each of these is for you? Please mark the column either "not important", "sort of important" or "very important".

	Not important	Sort of important	Very important
Walk 3 to 5 years longer			
Keep my spine straight			
Keep my arms stronger			
Keep my breathing stronger			
Prevent a back operation			
Keep my heart stronger			
Prevent lung infections			
Have a better cough			
Delay the need of night time ventilation			
Be able to feed myself			
Other benefits we did not mention:			

Participant Study ID#

PART 3: Possible side-effects from steroids

Below is a list of complaints and side-effects that some boys have from taking steroids. Have you had any of the problems listed below which you think were caused by the steroids?

For this part first please mark whether the item is a problem for you. If it is not a problem for you, please mark the "no problem" box in the left column and go to the next item.

When the item is a problem for you, then rate how serious this problem is: mark the box for mild, moderate or severe. Finally, answer how long has this been a problem: you can either mark "since a few weeks", "several months" or "half year and longer".

		How serious is this problem?				How long has this been a problem?		
	BECAUSE OF STEROIDS, I:	No problem	mild problem	moderate problem	serious problem	Since a few weeks	Several months	Half a year or longer
1	have puffy cheeks							
2	have been teased by others							
3	have too much hair on my arms/body							
4	get upset more easily							
5	had a broken arm							
6	have trouble sleeping through all the night							
7	gained too much weight							
8	can't see well on sunny days							
9	had a broken leg							
10	look too young for my age							
11	get distracted easily							
12	feel restless during the day							
13	forget things easily							
14	have problems concentrating on things I am doing							
15	have headaches							
16	feel depressed or sad more often							
17	feel dizzy							

Participant Study ID#

	BECAUSE OF STEROIDS, I:	No problem	mild problem	moderate problem	serious problem	Since a few weeks	Several months	Half a year or longer
18	have trouble getting to sleep							
19	am too short							
20	feel worried about many things							
21	get into too many fights							
22	have trouble controlling the way I act							
23	have back pain riding on the school bus or car							
24	am often hungry							
25	have a childish face (without hair)							
26	feel anxious too often							
27	fall too much							
28	can not work as fast as I should							
29	can't do some things because I am too short							
30	have warts on my hands or feet							
31	have a skin rash							
32	have pimples or acne							
33	have stretch marks on tummy or legs							
34	Other:							

PART 4: Overall rating of steroids

On a scale from 0 to 10, with 0 being "not at all" and 10 being "very much ": Please circle the number that applies.

		Give a rating from 0 (not at all) to 10 (very much)	
How much do steroids help your muscles?		0 1 2 3 4 5 6 7 8 9 10	
How bad are your side-effects from the steroids?		0 1 2 3 4 5 6 7 8 9 10	
Do you think it was a good idea for you to take steroids?	0 NO	0 YES	0 Don't know