

Project HERCULES – Burden of steroid use in the treatment of Duchenne Muscular Dystrophy: findings from a targeted literature review and online survey

Jo Noble-Longster¹, Caleb Hariri², Luke Stainer¹, Sze Choong Wong², Emily Crossley³, Josie Godfrey⁴, Keith Tolley¹

¹Tolley Health Economics, Buxton, UK; ²School of Medicine, University of Glasgow, UK; ³Duchenne UK, London, UK; ⁴JG Zebra Consulting, London, UK

Project HERCULES is an international multi-stakeholder collaboration led by Duchenne UK that has developed disease-level tools and evidence to support HTA and access decisions for new treatments for Duchenne Muscular Dystrophy.

Background

- Duchenne Muscular Dystrophy (DMD) is an X-linked, recessive, genetic disorder caused by a mutation in the dystrophin gene, resulting in a deficiency of dystrophin protein.^{1,2}
- This deficiency causes progressive muscle-weakness, first affecting the proximal muscles in the hips and shoulders, before eventually affecting all muscles associated with movement, as well as those involved in cardiac and respiratory function.^{1,2}
- There are currently no curative treatments for DMD, and treatment is limited to progression management. Corticosteroids are often used as part of a multi-disciplinary approach, and have been shown to slow the loss of muscle strength, reduce the development of scoliosis, and delay the onset of cardiac and respiratory problems.^{2,3,4}
- Despite the benefits, there are significant adverse effects associated with the long-term use of steroids including mood changes, weight gain, cushingoid appearance, delayed puberty, and loss of bone strength/ mass.^{4,5}

Objectives

- To explore the impact of using long-term, high-dose steroids for the management of DMD on patient and parent health-related quality of life (HRQoL), personal carer burden, and health service resource use.

Methods

- A targeted literature review (TLR) was performed using the PubMed database to identify published literature pertaining to the benefits and/ or side-effects of steroid use in DMD, as well as the quantification of HRQoL and resource use impacts. Searches were run on the 9th of November 2020 (Table 1).
- Health Technology Assessment (HTA) web-searching was also conducted including National Institute for Health and Care excellence (NICE), Scottish Medicines Consortium (SMC), Gemeinsamer Bundesausschuss (G-BA), Haute Autorité de Santé (HAS), Pharmaceutical Benefits Advisory Committee (PBAC), and Canadian Agency for Drugs and Technologies in Health (CADTH).
- An anonymous online survey was circulated via patient organisations in the UK, including Duchenne UK, to determine which side-effects were of most concern to patients and their families. The survey was live between February 2021 and March 2021. Side-effects were scored on the level of concern they caused, on a scale of 0-10 (with 10 being the highest).

Table 1: TLR search strategy

Search Number	Facet	Query
#1	Population	"Muscular Dystrophy, Duchenne"[Mesh] OR "Muscular Dystrophies"[Mesh] OR "Duchenne Muscular Dystrophy"[All Fields] OR DMD[All Fields] OR Duchenne*[All Fields]
#2	Intervention	Steroids[Mesh] OR "Adrenal Cortex Hormones"[Mesh] OR steroid[All Fields] OR corticosteroid[All Fields] OR prednisone[All Fields] OR prednisolone[All Fields] OR deflazacort[All Fields] OR emflaza[All Fields] OR calcort[All Fields] OR "glucocorticoid**"[All Fields] OR "adrenal cortex hormone**"[All Fields]
#3	Population and intervention	#1 AND #2

Results

- The TLR identified 1,144 records of which 211 were deemed relevant following primary and secondary screening by two independent reviewers. No additional records were identified through HTA web-searching (Figure 1).
- Records were categorised based on content; 154 records reported response to treatment, and 149 reported side-effects associated with steroid use in DMD. Only 11 studies reported HRQoL impact, and 4 studies reported resource use and cost data associated with steroid use in DMD. Most of these studies looked at treatment response and therefore there is limited published evidence on burden (Table 2).
- A large number of side-effects associated with steroids were identified through literature (Table 3).
- A total of 33 families participated in the online survey; 32 of the respondents were parents/ guardians. The median age of the young person with DMD was 10 years (IQR = 6-13 years), and 31 of 33 (93.9%) young persons were still on steroids.
- The survey identified that fractures (vertebral and long bone), obesity, and delayed puberty were the side effects of greatest concern to parents, whereas short stature, obesity, and cushingoid features were of greatest concern to patients (Table 4).

Figure 1: PRISMA diagram of TLR

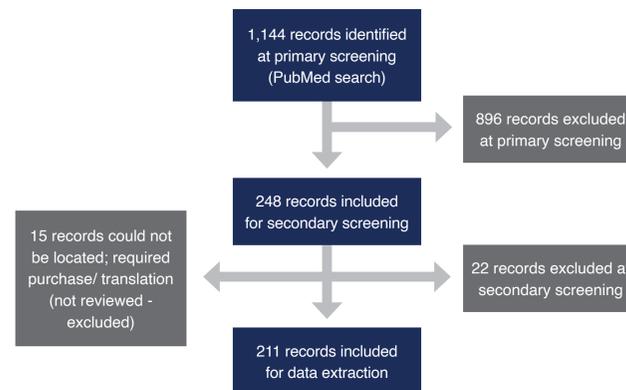


Table 2: TLR categorisation of records

Category	Number of records
Response to steroid treatment	154
Side effects of steroid treatment	149
Steroids following/ in combination with gene therapy	0
Treatment guidelines/ best practice	13
HRQoL data (patient/ carer)	11
Utility/ disutility values reported	1
Mortality as a direct consequence of long-term steroid use	0
Cost-effectiveness data	2
Cost and resource use data	4
Identification of a registry	27
COVID-19 research	1

Abbreviations: HRQoL, health-related quality of life.

Table 3: Side-effects of steroid treatment identified through TLR

Side-effects
Acne
Behavioural changes including irritability depression, anxiety, aggression, mood swings, hyperactivity, euphoria
Bruising
Cataracts
Cushingoid appearance
Delayed wound healing
Excessive hair growth (hirsutism, hypertrichosis)
GI symptoms
Glycosuria/ hyperglycaemia/ insulin resistance/ metabolic syndrome
Growth retardation
Headache
Hypokalaemia
Hypertension
Increased appetite
Life-threatening infections/ sepsis
Lipid abnormalities
Lower bone mineral density/ osteoporosis leading to increased rate of fractures/ vertebral fractures
Myoglobinuria
Nephrolithiasis
Problems with endocrine function - delayed puberty/ testosterone deficiencies, adrenal suppression
Psychosis
Skin abnormalities/ skin fragility
Sleep disturbances
Ventricular hypertrophy
Weight gain/ BMI/ increased proportion of fat tissue

Abbreviations: BMI, body mass index; GI, gastrointestinal.

Table 4: Side effects of most concern to patients and parents/ guardians identified through the online survey (n=33 families)

Side-effects of most concern to parents/ guardians	Side effects of most concern to patients
Long-bone fractures	Short stature
Vertebral fractures	Weight gain and obesity
Weight gain and obesity	Round and puffy face
Delayed puberty	

Conclusions

- Long-term corticosteroid use in the management of DMD is associated with considerable side-effects, the burden of which has not previously been explored in detail.
- The side-effects of most concern to DMD patients and their families were identified. Although most of these side-effects are addressed in previous publications, there is limited published information on delayed puberty in this population.
- The concerns of patients and their families should be discussed with clinicians prior to commencing treatment and at regular follow-ups.
- The current research is ongoing, and the findings will guide further qualitative research including conduct of a focus group on steroid burden in DMD with patient and parents, as well as healthcare professionals, in attendance. Together these qualitative research stages will allow recommendations for further research to quantify the HRQoL and resource use burden of steroid use in DMD, for HTA purposes and development of care in areas that concern the patient community the most.

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Disclosures

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