Practice guideline update: Corticosteroid treatment of Duchenne muscular dystrophy

Report of the Guideline Development Subcommittee of the American Academy of Neurology

David Gloss, MD, MPH&TM[1]; Richard T. Moxley III, MD[2]; Stephen Ashwal, MD[3]; Maryam Oskoui, MD[4]

(1) Department of Neurology, Geisinger Health System, Danville, PA
(2) Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, NY
(3) Department of Neurology, Loma Linda University Medical Center, Loma Linda, CA
(4) Departments of Pediatric and Neurology/Neurosurgery, McGill University, Montréal, Québec, Canada

Correspondence to
American Academy of Neurology:
guidelines@aan.com

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AUTHOR CONTRIBUTIONS

Dr. Gloss: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision
Dr. Moxley: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content
Dr. Ashwal: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content
Dr. Oskoui: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision

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DISCLOSURE

David Gloss serves as a paid evidence-based medicine consultant for the American Academy of Neurology (AAN).

Richard T. Moxley III has served as an editorial advisory board member of the *Journal of the American Medical Association* Clinical Trials Board; has received $2,500 in honoraria for an Isis Pharmaceuticals meeting (honoraria donated to the Abrams Family Fund for myotonic dystrophy research at the University of Rochester in Rochester, NY); and was awarded a 5-year National Institute of Neurological Disorders and Stroke grant 2U54NS048843 (totaling $7,013,097), a 4-year US Food and Drug Administration grant 1R01FD003716 (totaling $1,510,125), and a National Cancer Institute contract HHSN2612012003188P (totaling $40,000).

Stephen Ashwal has served on a medical advisory board for the Tuberous Sclerosis Association; has served as an associate editor for *Pediatric Neurology*; has a patent pending for use of HRS for imaging in stroke; is a coeditor of and has received royalties for *Pediatric Neurology: Principles and Practice*, 6th edition; has received grant funding from the National Institute of Neurological Disorders and Stroke for use of advanced imaging for detecting neural stem cell migration after neonatal HII in a rat pup model; works in the Department of Pediatrics at Loma Linda University School of Medicine; and is called once yearly to act as a witness in legal proceedings as a treating physician for children with nonaccidental trauma.

Maryam Oskoui has received travel funding from the AAN and Isis Pharmaceuticals and has received research support from Isis Pharmaceuticals, Fonds de recherché Santé (Québec, Canada), NeuroDevNet, the Canadian Institutes of Health Research (Canada), and McGill University Research Institute.

ABSTRACT

Objective: To update the 2005 American Academy of Neurology (AAN) guideline on corticosteroid treatment of Duchenne muscular dystrophy (DMD). The following questions were asked: What is the efficacy of corticosteroids in DMD, what are their side effects, and what is the optimal dosing regimen? Are there useful interventions to maximize bone health in patients with DMD taking corticosteroids?

Methods: We systematically reviewed the literature from January 2004 to July 2014. We graded the relevant studies according to the AAN classification scheme for therapeutic articles and predicated recommendations on the strength of the evidence.

Results: Thirty-four studies met inclusion criteria. One was rated as Class I.

Recommendations: In children with DMD, prednisone should be offered for improving strength (Level B) and pulmonary function (Level B). Prednisone may be offered for improving timed motor function (Level C), reducing the need for scoliosis surgery (Level C), and delaying cardiomyopathy onset by 18 years of age (Level C).
Deflazacort may be offered for improving strength and timed motor function and delaying age at loss of ambulation by 1.4 to 2.5 years (Level C). Deflazacort may be offered for improving pulmonary function (Level C), reducing the need for scoliosis surgery (Level C), delaying cardiomyopathy onset (Level C), and increasing survival at 5 to 15 years of follow-up (Level C). Deflazacort and prednisone may be equivalent in improving motor function (Level C). There is insufficient evidence to establish a difference in effect on cardiac function (Level U). Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort (Level C). Deflazacort may be associated with a greater risk of cataracts than prednisone (Level C). The preferred dosing regimen of prednisone is 0.75 mg/kg/day (Level B). Over 12 months, prednisone 10 mg/kg/weekend is equally effective (Level B), with no long-term data available. Prednisone 0.75 mg/kg/day is associated with significant risk of weight gain, hirsutism, and cushingoid appearance (Level B). Prednisone 0.3 mg/kg/day may be used as an alternative dosing regimen with lesser efficacy and fewer adverse events (AEs) (Level C). Prednisone 1.5 mg/kg/day is another alternative regimen; it may be equivalent in efficacy to 0.75 mg/kg/day but may be associated with more AEs (Level C). Data are insufficient to support or refute the benefit of prednisone for survival in DMD (Level U) or a preferred dose of deflazacort in DMD (Level U). Data also are insufficient to support or refute the addition of calcifediol or bisphosphonates (alendronate) as significant interventions for improving bone health in patients with DMD who are taking prednisone (Level U), or the benefit of bisphosphonates for improving survival of patients with DMD who are taking corticosteroids (Level U).

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy in childhood, affecting 1.3–1.8:10,000 live male births.[e1] The pathogenic dystrophin gene mutations at Xp21.2-p21.1 are inherited in two-thirds of patients and occur sporadically in one-third.[e2] The natural history of DMD without intervention leads to loss of independent ambulation typically before age 12, declining pulmonary function from increasing respiratory muscle weakness, scoliosis, and chest wall abnormalities, and progressive cardiac dysfunction, with cardiomyopathy universally present by adulthood.[e3,e4] Mean age at death increased from 14.4 years in the 1960s to 25.3 years in the 1990s with interventions, including the use of corticosteroids and noninvasive ventilation.[e5,e6]

The pathologic gene in DMD was identified in the 1980s, but non–gene-based therapies remain the mainstay of treatment with a multidisciplinary approach.[e7] Corticosteroids, especially prednisone, have been shown to slow motor function decline in DMD. Deflazacort, the oxazolone derivative of prednisolone, does not have US Food and Drug Administration approval, but is used in Canada[e8] and Europe. Studies evaluating the relative potency of prednisone compared to deflazacort found it to be 1:1.3.[e9] One side effect of corticosteroids is worsened bone health, contributing to the decreased bone mineral density and increased risk of fractures in this population. Active vitamin D metabolites (e.g., calcifediol and, more frequently, bisphosphonates such as alendronate) have been used for the prevention and treatment of bone loss and fractures associated with corticosteroid use.[e8]

A 2005 American Academy of Neurology (AAN) guideline on this topic recommended prednisone or deflazacort in the treatment of DMD for short-term benefit in muscle strength and function, in association with a discussion of the potential side effects of these medications with the patient and his or her family.[e10] There are variations in practice in corticosteroid use, and various regimens are in place to optimize risk–benefit ratios.[e11] Since publication of the previous guideline, there have been new studies examining the short- and long-term benefit of corticosteroids in DMD management as well as articles examining therapeutic strategies for optimizing bone health. Studies of long-term use have observed prolonged ambulation, improved cardiopulmonary function, reduced need for scoliosis surgery, and increased survival.[e12]

This guideline update is intended to inform clinical treatment decisions for those who provide care for patients with DMD with regard to the following questions related to corticosteroid use:

1. What is the efficacy of corticosteroids with regard to DMD progression, specifically their effect on survival, quality of life (QoL), motor function, scoliosis, pulmonary function, and cardiac function?
2. What are the side effects of corticosteroid treatment in DMD?
3. How do prednisone and deflazacort compare in efficacy or side effect profile?
4. What is the optimal dosing regimen for corticosteroids in DMD?
5. Are there any useful interventions for maximizing bone health in patients with DMD taking corticosteroids?

DESCRIPTION OF THE ANALYTIC PROCESS

The AAN Guideline Development Subcommittee convened a panel of experts on the treatment of DMD to develop this guideline update (appendix e-1 and e-2) following the AAN's 2004 process manual for guideline development.[e13] We searched MEDLINE for articles published from January 2004 through June 2012 using the term "Duchenne's muscular dystrophy" (see appendix e-3 for the specific search strategy used). We performed an updated search that covered July 2012 through April 2013 and a second updated search that covered May 2013 through July 2014. Similar terms were used to search the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and Science Citation Index. We conducted a secondary search of the references of selected articles and review articles to identify studies missed in our initial search.

We reviewed the titles and abstracts of the identified citations for relevance to the clinical questions and retrieved the full text of potentially relevant articles. We included both retrospective and prospective studies of patients with DMD regardless of age, clinical condition, disease severity, or comorbidities. In addition, we included all the Class I–III trials from the original guideline. We excluded trials with fewer than 10 patients in order to minimize publication bias. Two authors reviewed articles and completed data abstraction independently from each other. Discrepancies were resolved through discussion. We rated studies for their risk of bias using the AAN 4-tiered classification of evidence scheme for therapeutic studies (appendix e-4). We also rerated studies from the original guideline using the updated classification of evidence scheme. We linked the strength of practice recommendations to the strength of evidence.

Outcome measures varied between studies, and studies rated as Class III or higher were required to have either an objective outcome or a measurement that was explicitly stated as being performed by someone other than the treating provider. For example, for motor outcome, we considered age at loss of ambulation an objective measure. Functional motor measures were considered subjective unless performed by someone other than the treating provider.

ANALYSIS OF EVIDENCE

Our initial search and the 2 updated searches identified a total of 757 citations. We reviewed the full text of 121 potentially relevant articles. Sixty-three articles fulfilled the inclusion criteria, of which 24 were graded Class I–III. Some of the articles from the previous guideline were downgraded, primarily due to a lack of allocation concealment or failure to show whether baseline characteristics were equal, and we included 10 of these previous studies. Some were graded Class IV due to failure to state explicitly either objective evaluation or independent evaluation. Many articles reported some outcomes that were Class IV, such as motor outcomes for which the blinding of the examiner was unspecified, but were a higher class for objective outcomes. We were unable to create a meaningful funnel plot because of the heterogeneity of treatments and outcomes. Table e-

1 describes the selected studies on corticosteroids, and table e-2 lists the selected studies on bone health interventions in patients taking corticosteroids.

What is the efficacy of corticosteroids with regard to DMD progression, specifically their effect on survival, QoL, motor function, scoliosis, pulmonary function, and cardiac function?

Do corticosteroids have an effect on survival?

We identified 4 Class III studies addressing this question. One study did not show significant differences in survival, with mean age at death 28.1 years (SD 7.8) in the treated group (16 on prednisone, 1 on deflazacort) and 30.0 years (SD 6.5) in the nontreated group (difference in means 1.9 years, 95% confidence interval [CI] -1.53 to 5.33 years); however, the study lacked precision to detect a difference.[e14] In another study, 5% (2/40) of boys treated with deflazacort died in their second decade of life vs 35% (12/34) who were not treated (relative rate [RR] 0.14, 95% CI 0.03–0.59).[e15] In a third study, mortality was higher in the nontreated group (21% or 5/24) than in the deflazacort-treated group (3% or 1/30) after a mean follow-up period of 14.9 years and 15.5 years, respectively (RR 0.16, 95% CI 0.02–1.28).[e16] In a fourth study, mortality was higher in the nontreated group (10/23 or 43%) than in the deflazacort- or prednisone-treated group (7/63 or 11%) after a mean follow-up of 11.3 years (RR 3.91, 95% CI 1.69–9.06, only combined corticosteroid data available). Survival rates were greater at 5, 10, and 15 years of follow-up in the treated group (log rank $p = 0.0005$), with a decrease in all-cause mortality (hazard ratio [HR] 0.24, 95% CI 0.07–0.91, $p = 0.035$).[e17]

Conclusions. In patients with DMD, deflazacort possibly increases survival over 5 to 15 years of treatment (3 Class III studies). There is insufficient evidence to support or refute the benefit of prednisone on survival in patients with DMD (1 Class III study using both prednisone and deflazacort and 1 negative underpowered study).

Do corticosteroids have an effect on QoL?

One Class III study of 17 patients included a QoL measure as a secondary outcome.[e18] In this randomized controlled crossover trial, prednisone 0.75 mg/kg/day was given the first 10 days of each month. The study examined QoL as measured by the DUX-25[e19] (a 5-point scale measuring physical, emotional, social, and home functioning). QoL did not change during the 6-month treatment period compared with the 6-month placebo period. Due to the small number of patients examined, the study is underpowered to detect differences.

Conclusion. There is insufficient evidence to support or refute the benefit of corticosteroids on QoL in patients with DMD (1 Class III study).

Is there an effect on motor function with corticosteroids compared with no treatment?

Two Class II and 14 Class III studies were identified to address this question. A Class II study compared prednisone 0.75 mg/kg/day and 1.5 mg/kg/day with placebo (table e-3).[e20] Prednisone 0.75 mg/kg/day was started in boys at an average age of 9.16 years (SD 2.95), with no significant difference in age between the 3 groups. At 6 months, muscle strength scores on a 10-point averaged muscle scale improved significantly over 34 muscle groups for both doses of prednisone vs placebo. The average difference reported was 0.43 ($p < 0.0001$, 95% CI could not be calculated). After 6 months of treatment, both treatment groups also improved in timed motor function, such as time to stand, compared with placebo (placebo 6.17 sec, prednisone 0.75 mg/kg 4.15 sec, prednisone 1.5 mg/kg 3.43 sec, mean difference 2.74 sec, $p = 0.0001$, 95% CI could not be calculated). Time to stand is an early, sensitive marker of proximal muscle weakness and disease progression in younger affected boys, and this difference could be considered clinically significant.[e21]

In a Class II randomized controlled study, prednisone 0.75 mg/kg/day was compared with prednisone 0.3 mg/kg/day and with placebo (table e-4). Prednisone 0.75mg/kg/day was started in boys at mean age 9.36 years (SD 2.86), with no significant difference in age between the 3 groups.[e22] At 6 months, average muscle strength favored the use of prednisone over placebo (0.75 mg/kg 6.00, $p = 0.0001$; 0.3 mg/kg 5.82, $p = 0.0001$; placebo 5.48). In addition, patients taking 0.75 mg/kg had significantly higher average muscle strength at 6 months than those taking 0.3 mg/kg ($p = 0.03$).

Of the 14 Class III studies, 5 using deflazacort 0.9 to 1 mg/kg/day[e15, e23–e26] and 1 using deflazacort 2 mg/day alternate-day dosing[e27] showed an improvement in motor outcome using various measures: age at loss of ambulation in 3,[e23,e24,e27] functional motor score in 5,[e15,e24–e27] and muscle strength in 1 (this last one using deflazacort 1 mg/kg/day).[e26] The average difference in mean age at loss of ambulation was between 1.4 and 2.5 years in 3 studies. Of the 6 Class III studies using prednisone or prednisolone, all showed an improvement in motor outcome using various outcome measures: age at loss of ambulation in 1,[e28] functional motor score in 4,[e18,e29–e31] and strength in 2.[e31,e32] The 2 Class III studies using both prednisone and deflazacort showed an improvement in motor function using different outcomes: age at loss of ambulation[e33] and functional motor score.[e34] One of these studies also showed a longer duration of corticosteroid use delayed the age at loss of ambulation,[e33] whereas another study did not.[e23] Because there is no standardized treatment effect for these various parameters of strength and functional scores, we are unable to make a meaningful funnel plot.

Conclusions. In patients with DMD, prednisone 0.3 to 1.5 mg/kg/day probably improves strength (2 Class II studies and several Class III studies) and possibly improves timed motor function (1 Class II study and several Class III studies). In patients with DMD, deflazacort 0.9 to 1 mg/kg/day possibly improves strength, age at loss of ambulation by 1.4 to 2.5 years, and timed motor function (several Class III studies).

Do corticosteroids decrease the need for scoliosis surgery?

Ten Class III studies addressed this question. Five studies showed that patients taking deflazacort or prednisone had less need for surgical correction by 18 years of age: 53%

(10/19) of the control group vs 11% (2/18) of the prednisone group (RR 0.21, 95% CI 0.05–0.83),[e29] 29% (13/45) of the control group vs 15% (11/75) of the prednisone- or deflazacort-treated group (RR 0.51, 95% CI 0.25–1.04),[e34] 92% (22/24) of the control group vs 20% (6/30) of the deflazacort-treated group (0.22, 95% CI 0.11–0.45),[e16] 37% (41/117) of the control group vs 14% (2/14) of the prednisone- or deflazacort-treated group (RR 0.39, 95% CI 0.11–1.44),[e14] and 54% (13/24) of the nontreated group vs 0% (0/30) of the prednisolone-treated group (RR 0.03, 95% CI 0.00–0.48).[e24] Five studies showed delayed or slowed scoliosis development.[e15,e23,e25,e35,e36] At a mean age of 13.8 years (SD 1.6), 30/34 (90%) nontreated boys had developed greater than 20 degrees of spinal curvature, compared with 4/40 (10%) boys treated with deflazacort (RR 0.11, 95% CI 0.04–0.30).[e15] In another study on deflazacort in boys 15 to 18 years of age, 76% (16/21) of untreated boys developed scoliosis vs 17% (5/29) of treated boys (RR 0.23, 95% CI 0.10–0.52).[e23] By a mean age of 10.8 years (SD 1.2), 0/66 boys treated with prednisone had developed scoliosis vs 7/22 (32%) untreated boys (RR 0.02, 95% CI 0.00–0.38).[e36] Two studies did not provide the data needed for calculation of an RR or 95% CI. The first reported that in boys older than 13 years, 90% of those not treated developed a spinal curvature of greater than 20 degrees vs 30% of boys taking deflazacort 0.6 mg/kg/day and 16% of boys taking deflazacort 0.9 mg/kg/day.[e26] The second study showed a delayed age at scoliosis onset with longer duration of prednisone treatment (r = 0.44, $p < 0.01$).[e35]

Conclusion. Corticosteroids (prednisone and deflazacort) possibly slow the development of scoliosis and reduce the need for scoliosis surgery by 18 years of age (10 Class III studies).

Do corticosteroids have an effect on pulmonary function?

Two Class II and 12 Class III studies addressed this question. A Class II study of prednisone 0.75 mg/kg/day and 1.5 mg/kg/day compared with placebo over 6 months of treatment reported significant improvement in mean forced vital capacity (FVC) (placebo 1.52 L; prednisone 0.75 mg/kg 1.68 L, $p = 0.0004$; 1.5 mg/kg 1.66 L, $p = 0.002$) and maximal expiratory pressure (MEP) (placebo 14.74 mm Hg; 0.75 mg/kg 17.32 mm Hg, $p = 0.01$; 1.5 mg/kg 18.19 mm Hg, $p = 0.001$) at 6 months. This study also showed significant improvement in maximal voluntary ventilation (MVV) with prednisone 0.75 mg/kg/day (placebo 40.64 mm Hg, prednisone 0.75 mg/kg 45.49 mm Hg, $p = 0.03$).[e20] Another Class II study noted significant improvement in FVC for both doses of prednisone (0.3 and 0.75 mg/kg/day) compared with placebo over 6 months of treatment (0.75 mg/kg 1.67 L, $p = 0.001$; 0.3 mg/kg 1.64 L, $p = 0.006$; placebo 1.48 L), but this was not seen for MEP or MVV.[e22] Neither study provided percent predicted values.

Eleven Class III studies using either deflazacort or prednisone showed a benefit in various measures of pulmonary function.[e14,e15,e23,e24,e28,e30,e32,e36–e39] Another Class III study reported improved FVC with treatment but did not report values.[e16] The outcome measure and length of treatment varied widely between studies (age requiring noninvasive ventilation, FVC, MEP), which prevented the pooling of data.

Conclusions. In patients with DMD, prednisone probably improves pulmonary function as measured by FVC (2 Class II studies, several Class III studies). In patients with DMD, deflazacort possibly improves pulmonary function (several Class III studies).

Do corticosteroids have an effect on cardiac function?

Shortening fraction (SF), a measure of left ventricular function,[e40] is often used to track progression of cardiomyopathy, a condition that affects one-third of patients with DMD at age 14 and almost all by age 18.[e41] We identified 6 Class III studies addressing this question. The first study showed that by 18 years of age, boys treated with deflazacort were less likely to have cardiomyopathy (left ventricular ejection fraction [LVEF] < 45%) (4/40, 10%) than untreated boys (20/34, 59%) (RR 0.17, 95% CI 0.06–0.45).[e15] This study also showed higher mean percent SF in the treated group, reporting mean %SF of 33 (SD 7) in treated boys vs mean %SF of 21 (SD 8) in untreated boys (mean difference in %SF -12, 95% CI -15.48 to -8.52).[e15] A second study showed an improvement in LVEF with deflazacort in boys 17 to 22 years of age compared with younger nontreated boys (12 to 15 years of age), with an LVEF median of 53% (range 51%–57%) vs 48% (range 42%–51%), $p < 0.001$.[e42] A third study showed that boys treated with deflazacort or prednisone over a mean follow-up of 11.0 years (SD 4.8) were less likely to have cardiomyopathy (%SF < 28) (7/63, 11%) than untreated boys (14/23, 61%) (RR 0.18, 95% CI 0.08–0.39), with an HR for cardiomyopathy of 0.38 (95% CI 0.16–0.9) in treated boys.[e17] The study also showed a lower decline in LVEF (-0.43% vs 1.09%, $p = 0.027$) and a slower rate of decline in %SF (-0.32% vs -0.65%, $p = 0.002$). Another study defining cardiomyopathy as %SF < 28% or LVEF < 55% showed delayed onset of cardiomyopathy with treatment over a mean follow-up period of 4.1 years (SD 3.4).[e33] Of the 202 boys who developed cardiomyopathy, the mean age at onset was 15.2 years (SD 3.4) in treated boys and 13.1 years (SD 4.8) in nontreated boys (data not provided for CI calculation). Regression analysis demonstrated that for every year of corticosteroid treatment, cardiomyopathy onset was delayed by 4% (95% CI 2.6–5.4). Another study of prednisone or deflazacort vs no treatment over a mean follow-up of 3.0 years (SD 2.5) showed that the odds of nontreated boys 3 to 10 years of age developing cardiomyopathy (defined as %SF < 28%) were 4.4 times greater compared with treated boys ($p = 0.02$), and the odds were 15.2 times greater ($p = 0.01$) in boys 11 to 21 years of age.[e43] The same authors published a later study examining 9 boys taking prednisone 0.75 mg/kg/day, 5 boys taking deflazacort 0.9 mg/kg/day, and 23 boys not undergoing treatment. This study reported an HR of corticosteroid use to predict left ventricular dysfunction (%SF < 28%) of 0.16 (95% CI 0.04–0.70).[e44] When age was added to the model, the HR for corticosteroid use in prediction of left ventricular dysfunction was 0.15 (95% CI 0.03–0.74).

Conclusion. In patients with DMD, corticosteroids (deflazacort 0.9 mg/kg/day or prednisone 0.75 mg/kg/day) possibly delay the onset of cardiomyopathy (defined as %SF < 28% or LVEF < 45%) by 18 years of age (several Class III studies with various endpoints).

What are the side effects of corticosteroid treatment in DMD?

Two Class II studies and 23 Class III studies addressed this question, comparing corticosteroid side effects with those of no treatment or placebo (table e-5). A Class II study noted a significant increase in weight gain after 6 months of treatment in patients taking prednisone (37% [11/33] of 0.75 mg/kg/day group and 32% [10/34] of 1.5 mg/kg/day group vs 6% [2/36] of placebo group gained more than 20% of their baseline weight, $p < 0.0001$). Other side effects more common in patients taking prednisone than in controls included cushingoid appearance (17% [6/36] in placebo vs 55% [18/33] in 0.75 mg/kg/day dose and 73% [24/34] in 1.5 mg/kg/day dose, $p = 0.0001$) and hirsutism (22% [8/36] in placebo vs 52% in 0.75/mg/day [17/33] and 1.5 mg/kg/day doses [17/34], $p = 0.005$).[e20] There was no difference in side effect profile between the lower and higher dose of prednisone and no reported cataracts or difference in behavioral changes between treated and nontreated groups over the 6-month treatment period. Another Class II study noted that prednisone treatment groups with dosing regimens of 0.75 mg/kg and 0.3 mg/kg over 6 months had a significant increase in weight compared with the placebo group: 1/32 (3%) nontreated boys gained more than 20% of their baseline weight compared with 3/34 (11%) boys taking 0.3 mg/kg/day and 10/34 (31%) boys taking 0.75 mg/kg/day (RR prednisone 0.3 mg/kg/day vs placebo is 2.82, 95% CI 0.31–25.77, and RR of prednisone 0.75 mg/kg/day vs placebo is 9.41, 95% CI 1.28–69.42). Other side effects seen in only the prednisone 0.75 mg/kg/day group included cushingoid appearance (11/32 [35%] nontreated vs 24/34 [71%] treated, RR 2.05, 95% CI 1.21–3.47), hirsutism (4/32 [13%] nontreated vs 14/34 [41%] treated, RR 3.29, 95% CI 1.21–8.96), and increased appetite (12/32 [39%] nontreated vs 23/34 [68%] treated, RR 1.80, 95% CI 1.09–2.99).[e22] No cataracts were reported in any of the boys over this 6-month period.

Twenty-two Class III studies reported adverse events (AEs).[e14–e18,e23–e32,e34,e39,e44–e48] Three studies predominantly using deflazacort showed that treated boys were shorter and at greater risk of developing cataracts.[e15–e17] In the first study, 30 boys taking deflazacort followed for an average of 15.5 years were shorter (141 cm [SD 8] vs 158 cm [SD 8], mean difference in height 17 cm, 95% CI 12.60–21.40) and heavier (55 kg [SD 5] vs 51 kg [SD 9], mean weight difference -4 kg, 95% CI -7.88 to -0.12) than 24 nontreated boys.[e16] No difference was seen in long bone fractures, but treated boys were taking bisphosphonates. Cataracts were detected in 21/30 (70%) treated boys vs none in the nontreated group. Of the 21 boys with cataracts, 2 underwent surgery because of impairment in visual acuity. The second study had an average follow-up of 11.0 years (SD 4.8) and showed that boys treated with deflazacort were shorter than nontreated boys (149 cm [SD 4] for 63 treated boys vs 167 cm [SD 11] for 23 nontreated boys, mean difference -18 cm, 95% CI -22.68 to -13.32).[e17] However, there was no difference in mean weight between the 2 groups (54 kg [SD 16] for treated boys vs 54 kg [SD 24] for nontreated boys, mean difference 0 kg, 95% CI -8.93 to 8.93). In the third study (deflazacort 0.9 mg/kg/day but reduced to 0.5 mg/kg/day in some boys who developed side effects), 22/40 treated teenaged boys in whom cataracts were screened systematically developed cataracts after 4 months to 10 years of treatment vs 0/34 in the nontreated group (RR 38.33, 95% CI 2.41–608.94).[e15] At 10 years of age, nontreated boys were heavier than treated boys (37 kg [SD 6] in nontreated boys vs 34 kg [SD 4] in treated

boys), but by age 15 treated boys were heavier (58 kg [SD 6] treated vs 52 kg [SD 15] nontreated), and treated boys continued to be heavier than nontreated boys at 18 years of age (71 kg [SD 8] treated vs 53 kg [SD 12] nontreated). The number of children in each age group is not available, so RR and 95% CI cannot be calculated. The same study showed that treated boys were shorter than nontreated boys at 10 years of age (128 cm [SD 5] treated vs 135 cm [SD 6] nontreated, $p < 0.05$). By 15 years of age, treated boys continued to be shorter than nontreated boys (143 cm [SD 9] treated vs 164 cm [SD 8] nontreated, $p < 0.005$), and the same effect was preserved at 18 years of age (156 cm [SD 7] treated vs 166 cm [SD 7] nontreated, $p < 0.05$). There was no difference between groups in blood pressure, glucosuria, bruising, susceptibility to infections, fasting blood glucose, or long bone fractures.

Conclusions. In patients with DMD, corticosteroids probably have the AEs of short stature, behavioral changes, fractures, and cataracts (multiple Class II and Class III studies). Prednisone 0.75 mg/kg/day is probably associated with significant risk of weight gain, hirsutism, and cushingoid appearance (2 Class II studies). Prednisone 0.3 mg/kg/day possibly has a lower incidence of these AEs (1 Class II study). Deflazacort is inconsistently associated with weight gain, hirsutism, and cushingoid appearance (multiple Class III studies, not all consistent with each other). Deflazacort possibly increases the risk of cataracts (3 Class III studies).

How do prednisone and deflazacort compare in efficacy or side effect profile?

Is there a significant difference in efficacy between prednisone 0.75 mg/kg/day and deflazacort 0.9 mg/kg/day?

Three Class III studies directly compared these 2 corticosteroids, and all showed equivalent rates of improved strength and functional motor performance between prednisone and deflazacort.[e30,e34,e43] In a retrospective study of 18 boys treated with 0.75 mg/kg/day of prednisone, 12 boys treated with 0.9 mg/kg/day of deflazacort, and 19 nontreated boys, deflazacort and prednisone were shown to have equally beneficial effects on functional motor outcomes, pulmonary function, and development of scoliosis over 5.49 years (SD 1.98).[e30] In a randomized controlled trial (RCT) of 9 boys on prednisone 0.75 mg/kg/day, 9 boys on deflazacort 0.9 mg/kg/day, and 7 natural history controls, prednisone and deflazacort were equally effective in improving motor function and functional performance over a 12-month treatment period.[e34] A retrospective study of 29 boys on prednisone, 19 boys on deflazacort, and 63 nontreated boys reported equivalent cardiac outcome in the deflazacort- and prednisone-treated groups over a mean follow-up period of 3.0 years (SD 2.5).[e43] The odds of developing cardiomyopathy (as defined by %SF <28) were 4.4 times greater ($p = 0.02$) in nontreated boys aged 3 to 10 years, and the odds increased to 15.2 times greater ($p = 0.01$) in nontreated boys 11 to 21 years of age. Data are insufficient for further statistical analysis.

Conclusions. Prednisone and deflazacort are possibly equally effective for improving motor function in patients with DMD (2 Class III studies). There is insufficient evidence

to directly compare the effectiveness of prednisone versus deflazacort in cardiac function in patients with DMD (1 Class III study of a combined cohort).

Is there a significant difference in AEs between prednisone 0.75 mg/kg/day and deflazacort 0.9 mg/kg/day?

Two Class III studies outlined previously also addressed this question. The first retrospective study showed a difference in weight gain in the prednisone group during the first years of treatment, with no difference seen at later ages (12–15 years). At 10 years of age, their weights increased to the 75th and 90th percentiles, whereas the weights of the boys in the deflazacort group were similar to those of nontreated boys at 10 years of age, with weights between the 25th and 50th percentiles.[e30] By 12 years of age, the mean weight in the deflazacort group had increased to the 50th to 75th percentile, whereas the weights in the prednisone group remained higher, between the 75th and 90th percentiles. Two boys in the deflazacort group (2/12, 17%) developed asymptomatic cataracts, whereas no boys (0/9) in the prednisone group reported cataracts (RR 3.8, 95% CI 0.21–70.23). In the RCT of 9 boys taking prednisone and 9 boys taking deflazacort described previously, the prednisone group showed a greater weight gain in the first year of treatment than the deflazacort group.[e34] At 12 months of treatment, boys taking prednisone had a mean weight increase of 21.3%, compared with 9% in boys taking deflazacort (2.17 kg vs 5.08 kg weight increase, $p < 0.05$). An increase in body weight of more than 20% over baseline was seen in 1/9 (11%) boys taking deflazacort and in 4/8 (50%) boys taking prednisone (RR 4.5, 95% CI 0.63–32.38). Other AEs were not significantly different between the 2 groups, including behavioral changes, gastric symptoms, hypertension, glucose control, and hirsutism. One study was an interim analysis retained for reporting no difference in side effect profile but not retained for efficacy outcome.[e46]

Conclusions. Prednisone is possibly associated with greater weight gain in the first 12 months of treatment, with no significant difference in weight gain with longer-term use compared with deflazacort (2 Class III studies). Deflazacort is possibly associated with an increased risk of cataracts compared with prednisone, although most are not vision impairing (2 Class III studies).

What is the optimal dosing regimen for corticosteroids in DMD?

Is there a preferred dose of deflazacort (0.6 mg/kg/day for the first 20 days of each month vs 0.9 mg/kg/day) with regard to efficacy or AEs?

A Class III study reported a difference in motor function in patients treated with a dose of 0.6 mg/kg/day for the first 20 days of the month and none for the rest of the month compared with those treated with 0.9 mg/kg/day. Results favored the higher dose, with both groups having age-matched controls.[e25] In the higher-dose group, a difference in motor function was seen at 9, 12, and 15 years of age compared with controls. At age 15, 23% (3/13) of treated boys taking deflazacort 0.9 mg/kg/day were able to rise from the floor, compared with 0% (0/31) in the control group (RR 16.33, 95% CI 0.90–295.00),

and 77% (10/13) of treated boys were able to walk 10 m, compared with 0% (0/31) in the control group (RR 49.00, 95% CI 3.09–777.66). The boys taking deflazacort had lower weights than nontreated boys, although this difference was significant in only the lower-dose group (weighing 25% less). The boys taking deflazacort were also shorter in height than nontreated boys. This difference was seen at 9 and 12 years but not at 15 years in the lower-dose group and at all time points in the higher-dose group (by age 15, height 143 cm [SD 9] in treated boys vs 164 cm [SD 8] in nontreated boys, $p < 0.005$). Cataracts were seen in 30% (9/31) of boys on the higher-dose regimen compared with 0% (0/31) in the lower-dose or control group (RR high dose vs control 19.00, 95% CI 1.15–312.64).

Conclusion. Evidence is insufficient to determine whether there is a significant difference in efficacy between 2 different deflazacort doses (0.6 mg/kg/day for the first 20 days of each month vs 0.9 mg/kg/day) (1 Class III study). Evidence is insufficient to determine whether there is a significant difference in AEs between 2 different deflazacort doses (0.6 mg/kg/day for the first 20 days vs 0.9 mg/kg/day) (1 Class III study).

Is there a difference in efficacy or AEs between prednisone dosing regimens of 0.75 mg/kg/day and 10 mg/kg/weekend?

A Class I trial evaluated prednisone 0.75 mg/kg/day vs 10 mg/kg/weekend for the primary efficacy outcome of quantitative muscle testing (QMT) of the arm and leg. This study found similarities between groups in QMT of the arm (weekend 0.7, daily 1.3, 95% CI -1.7 to 0.6, with ±2 as the equivalent limit) and QMT of the leg (weekend 2.2, daily 2.1, 95% CI -1.8 to 2.0, with ±2 as the equivalent limit) over 12 months of treatment.[e49] There was no significant difference for the secondary outcome measures except for QMT of the elbow flexors (weekend 0.9, daily 1.3, 95% CI -1.6 to 0.9, with ±2 as the equivalent limit). For safety, equivalency was noted for the primary endpoint of body mass index (weekend 17.8, daily 19.6, $p = 0.12$). No significant difference in the secondary safety endpoints (weight, height, cataracts, lumbar spine *z* score by dual-energy x-ray absorptiometry, behavior) between the 2 study groups was noted, although there was a greater degree of linear growth in the weekend group than in the daily group.

Conclusions. Prednisone dosing regimens of 0.75 mg/kg/day and 10 mg/kg/weekend probably provide equivalent benefit to patients with DMD at 12 months (1 Class I study). Prednisone dosing regimens of 0.75 mg/kg/day and 10 mg/kg/weekend probably have similar AE profiles over 12 months (1 Class I study). There is insufficient evidence to compare the long-term efficacy or AE profile of these 2 regimens.

Is there a difference in efficacy or AEs between prednisone dosing regimens of 0.75 mg/kg/day and 1.5 mg/kg/day?

A Class II study compared both prednisone 0.75 mg/kg/day and prednisone 1.5 mg/kg/day with controls and found no significant difference between the 2 groups with regard to strength or functional benefit at 6 months.[e20] No difference in AEs was seen between prednisone 0.75 mg/kg/day and 1.5 mg/kg/day.

Conclusions. Prednisone dosing regimens of 0.75 mg/kg/day and 1.5 mg/kg/day possibly provide equivalent benefit to patients with DMD, although smaller differences cannot be excluded (1 Class II study). Prednisone dosing regimens of 0.75 mg/kg/day and 1.5 mg/kg/day possibly have similar AE profiles (1 Class II study).

Is there a difference in efficacy or AEs between prednisone dosing regimens of 0.3 mg/kg/day and 0.75 mg/kg/day?

A previously discussed Class II study evaluated 0.3 mg/kg/day of prednisone relative to 0.75 mg/kg/day and found a significant improvement in the group taking 0.75 mg/kg/day at 6 months (table e-4).[e22] A Class III study that was an extension of the previously mentioned study found that the group taking 0.75 mg/kg/day was significantly faster at climbing 4 stairs than those taking the lower dose.[e31]

A Class II study showed an increase in the rate of cushingoid appearance and hirsutism at the 0.75 mg/kg/day dose compared with the 0.3 mg/kg/day dose (cushingoid: 24/34 of the higher-dose group vs 13/33 of the lower-dose group, RR 1.79, 95% CI 1.11–2.88; hirsutism: 14/34 of the higher-dose group vs 3/33 of the lower-dose group, RR 4.53, 95% CI 1.43–14.32).[e22] The Class III extension study aiming to explore longer-term effects over an additional 12 months of follow-up showed a greater risk of hirsutism in the higher-dose group than in the lower-dose group (20/34 in the higher-dose group vs 4/30 in the lower-dose group, RR 4.42, 95% CI 1.70–11.46), with no significant difference in other AEs such as behavioral changes, cataracts, cushingoid appearance, and increased appetite.[e31]

Conclusions. A prednisone dosing regimen of 0.75 mg/kg/day is possibly more efficacious than a regimen of 0.3 mg/kg/day (1 Class II study and 1 Class III study). A prednisone dosing regimen of 0.75 mg/kg/day possibly has a greater rate of AEs than a regimen of 0.3 mg/kg/day (1 Class II study and 1 Class III study).

Is there a difference in efficacy or AEs between daily and alternate-day dosing of prednisone?

A Class III study compared alternate-day dosing of 1.25 mg/kg and 2.5 mg/kg with the daily dose and placebo groups from an earlier study and found a significant difference in strength and functional scores that favored daily dosing.[e50] The authors noted no significant difference in AEs between the daily dose and the alternate-day dose.

Conclusion. Evidence is insufficient to determine whether there is a significant difference in efficacy or AE rates between daily and alternate-day regimens for prednisone dosing (1 Class III study).

Is there a difference in efficacy or AEs between daily and intermittent dosing of prednisolone?

A Class III study compared daily prednisolone treatment with intermittent treatment (10 days on, 10 days off).[e47] The study found an earlier age at loss of ambulation in the intermittent group (HR 1.57, 95% CI 0.87–2.8) and a faster decline in motor function scale performance. There was no reported difference in pulmonary function between the 2 treatment regimens. There were more reported AEs with the daily regimen than with intermittent dosing, including cushingoid appearance, behavioral changes, hypertension, and short stature.

Conclusion. Evidence is insufficient to determine whether there is a significant difference in efficacy or AE rates between daily and intermittent regimens for prednisolone dosing (1 Class III study).

Are there any useful interventions for maximizing bone health in patients with DMD taking corticosteroids?

Are there any useful interventions for maximizing bone health?

A Class III study prospectively followed boys with DMD taking prednisone alone for 1 year and then taking prednisone and calcifediol 0.8 μg/kg/day for 2 years with optimization of calcium intake and found a significant improvement in bone mineral content and density.[e51] A retrospective Class III study showed a trend for improved bone density in boys with DMD taking alendronate with or without corticosteroids, but the study may have been underpowered for detecting a difference.[e52]

Conclusion. Evidence is insufficient to determine whether the addition of an active vitamin D metabolite (calcifediol) or a bisphosphonate (alendronate) improves bone health in patients with DMD who are taking prednisone (2 Class III studies).

Clinical context. Although data are insufficient to determine whether vitamin D supplementation or alendronate improves bone health, calcium and vitamin D supplementation with optimization of dietary calcium may be of benefit in patients with DMD taking corticosteroids.

Does treating bone health have an impact on survival?

A Class III retrospective case-control study examined 28 boys who were taking corticosteroids (either prednisone or deflazacort) for at least 1 year and compared them with 16 boys taking corticosteroids and a bisphosphonate for at least 1 year.[e53] Survival analysis revealed that the survival rate of patients taking bisphosphonates was greater than that of patients who were taking corticosteroids alone ($p = 0.005$) (at age 22 years, no patients without bisphosphonate treatment survived, whereas 75% of the patients with bisphosphonate treatment survived). The authors also analyzed the duration of bisphosphonate treatment and found that patients who were taking bisphosphonates for >6.5 years had a greater survival rate than those taking bisphosphonates for <6.5 years ($p = 0.007$), suggesting a significant therapy-duration effect.

Conclusion. It is unknown whether bisphosphonates improve survival in patients with DMD who are taking corticosteroids (1 Class III study).

PRACTICE RECOMMENDATIONS

Clinical context.

Prednisone 0.75 mg/kg/day has significant benefit in DMD management and should be considered the optimal prednisone dose at this point. Prednisone 10 mg/kg/weekend is equally effective over a 12-month period, although long-term outcomes of this alternate regimen remain to be seen. The ideal time to start and stop therapy is not currently known. The expectation of significant AEs (e.g., short stature, behavioral changes, cataracts, cushingoid appearance, weight gain, hirsutism, fractures) and their nature should be discussed with patients and their families prior to therapy initiation and should be managed proactively. Calcium and vitamin D intake are optimized and encouraged in clinical practice, as these children have several risk factors for low bone density and fractures, such as chronic corticosteroid use and decreased weight-bearing activities. The American College of Rheumatology Task Force osteoporosis guideline recommends calcium and vitamin D supplementation for patients taking corticosteroids (any dose with an anticipated duration of ≥3 months) in order to maintain a total calcium intake of 1,200 mg/day and vitamin D intake of 800 IU/day through dietary sources, supplementation, or both.[e54]

If a significant number of AEs develop, reducing the prednisone dose to 0.3 mg/kg/day may reduce the AE burden, albeit with a lesser degree of efficacy.

Deflazacort and prednisone show slightly different AE profiles in studies where each drug was compared with no treatment or the drugs were compared with each other. Weight gain and cushingoid appearance may occur more frequently with prednisone than deflazacort, but cataracts are more frequently reported with deflazacort. Deflazacort and prednisone require proper informed consent from the patient's family prior to initiation due to their AE risk.

Recommendations.

Prednisone, offered as an intervention for patients with DMD

- should be used to improve strength (Level B) and may be used to improve timed motor function (Level C)
- should be used to improve pulmonary function (Level B)
- may be used to reduce the need for scoliosis surgery (Level C)
- may be used to delay the onset of cardiomyopathy by 18 years of age (Level C)

Deflazacort, offered as an intervention for patients with DMD

- may be used to improve strength and timed motor function and delay the age at loss of ambulation by 1.4 to 2.5 years (Level C)
- may be used to improve pulmonary function (Level C)

- may be used to reduce the need for scoliosis surgery (Level C)
- may be used to delay the onset of cardiomyopathy by 18 years of age (Level C)
- may be used to increase survival at 5 and 15 years of follow-up (Level C)

Deflazacort and prednisone may be equivalent in improving motor function (Level C). There is insufficient evidence to establish a difference in effect on cardiac function (Level U). Prednisone may be associated with increased weight gain in the first years of treatment compared with deflazacort (Level C). Deflazacort may be associated with increased risk of cataracts compared with prednisone (Level C).

If patients with DMD are treated with prednisone, prednisone 0.75 mg/kg/day should be the preferred dosing regimen (Level B). Prednisone 10 mg/kg/weekend is equally effective over 12 months, but long-term outcome is not yet established. Prednisone 0.75 mg/kg/day is probably associated with significant risk of weight gain, hirsutism, and cushingoid appearance (Level B), with equal side effect profile seen over 12 months with the 10 mg/kg/weekend dosing. Prednisone 0.3 mg/kg/day may be used as an alternative dosing regimen with lesser efficacy and fewer AEs (Level C). Prednisone 1.5 mg/kg/day is another alternative regimen; it may be equivalent to 0.75 mg/kg/day but may be associated with more AEs (Level C).

Data are insufficient to support or refute the following (all Level U):
- the addition of calcifediol and bisphosphonates (alendronate) as significant interventions for improving bone health in patients with DMD taking prednisone
- a benefit of bisphosphonates for improving survival in patients with DMD taking corticosteroids
- a benefit of prednisone for survival in patients with DMD
- a significant difference in efficacy or AE rates between daily, alternate-day, and intermittent regimens for prednisone or prednisolone dosing
- a preferred dose of deflazacort in DMD
- an effect of corticosteroids on QoL in patients with DMD

Suggestions for counseling.

The following suggestions for counseling are not predicated on studies. They are the opinion of the authors and extend from logical conclusions of our recommendations.
- Patients with DMD and their families should have a voice in the choice of the corticosteroid used, noting that the various corticosteroids differ in evidence supporting use, cost, availability, and AE profiles. When a corticosteroid has been agreed upon, a focused discussion of the risks particular to that corticosteroid should take place if they were not discussed when the choice was made.
- All patients with DMD taking corticosteroids and their families should be informed of the risks and benefits of adding a bisphosphonate until better evidence supporting efficacy and safety is made available.

RECOMMENDATIONS FOR FUTURE RESEARCH

- There is currently a paucity of high-quality data on the long-term efficacy of both prednisone and deflazacort. Too many questions remain unanswered, including the following: When should treatment be initiated?[e55] How long should patients remain on oral corticosteroid therapy? Is daily therapy more or less effective for long-term treatment than intermittent dosing? Is there an indication for switching from one therapy to another? Is one therapy more or less effective than another? Is there an optimal dosing regimen, and does the dosing change when patients lose ambulation or become ventilator dependent?[e12] There are anecdotal examples of patients with DMD who received treatment with corticosteroids from an early age remaining ambulatory.[e56,e57]
- Low-quality studies suggest that long-term corticosteroid use might beneficially affect the following 6 outcomes: (1) prolongation of ambulation, (2) reduction in risk of spinal stabilization deficits, (3) improvement of cardiopulmonary function, (4) delay in need for supported ventilation, (5) improved mortality, and (6) improved QoL.[e12,e58] Moreover, corticosteroid use may have an impact on the development of cardiomyopathy[e59] and on intelligence.[e60] These suggestions from low-quality studies should be verified with well-designed long-term trials.[e61] If sufficiently powered with a large number of participants, a single trial may suffice for obtaining answers to multiple questions. In designing such a trial, care would have to be taken to avoid biased designs, such as use of MRI as a measurement, which some researchers advocate.[e62] There is a risk for such measurements to be very selective because such measurement technologies may be unavailable to many patients.[e63] This selectivity would lead to a downgrade of the data and may result in difficulty in recruitment. Moreover, standards have been developed.[e64–e66] It would be helpful to use these standards when describing the effectiveness of intervention. Such a trial would require multicenter collaboration and careful consideration of power analysis of the primary and secondary outcomes, including Bonferroni correction.
- Targeted treatment for optimization of bone health has suggested a survival benefit for patients with DMD on corticosteroids, but the evidence needs to be verified. An RCT meeting current standards for high-level medical evidence would be very important for strengthening this finding and would help to establish the efficacy of this potential therapy. Parallel studies of standardized markers of bone health during the trial are also recommended, as there is a suggestion that the negative impact of corticosteroids on bone health may be apparent only when patients lose ambulation.[e67]
- Other treatments for complications of long-term corticosteroid use in patients with DMD on corticosteroids should be pursued.
- The effect of prednisone on survival has not been studied in trials with higher than Class IV evidence. An RCT randomizing participants to deflazacort or prednisone (or both) could be performed to show the survival benefits of prednisone.
- The optimal deflazacort dose remains unclear, and further study using well-designed prospective RCTs would help to clarify this.
- Some evidence suggests that corticosteroids may have a protective effect on cardiac function. Continued studies would be helpful to know whether this translates into a meaningful reduction of cardiac-related mortality later in adulthood.

- Studies addressing treatment with corticosteroids earlier in life (as opposed to treatment after a plateau or loss of motor function) are needed to determine the best timing for initiating therapy. Continued clinical studies that address this question are recommended.
- Effects of gene subtypes could be considered as subgroups when any of the above analyses are performed.[e68] Interactions between growth hormone and corticosteroids may occur,[e69] and such interactions may be a fruitful secondary endpoint for a trial.
- The mechanism by which corticosteroids benefit patients is still unknown. Clarification of this mechanism, or at least identification of the most relevant mechanism, may enable use of more targeted therapy that could result in a reduction of AEs.
- Validated QoL instruments should be included as part of future trials of corticosteroids in DMD treatment.
- Studies that have molecular inclusion criteria for diagnosing patients with DMD may help eliminate the possibly of inclusion of patients with Becker muscular dystrophy.
- As discussed previously, there are a plethora of avenues for future research. We recommend that the Grading of Recommendations Assessment, Development and Evaluation process be used when new studies are incorporated into DMD guidelines in the future.[e70]
- There is a trial (NCT01603407), which is currently recruiting patients; we hope it will be able to answer some of these questions.

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews, and other guidance published by the American Academy of Neurology (AAN) and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information (1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); (3) addresses only the question(s) specifically identified; (4) does not mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. The AAN provides this information on an "as is" basis and makes no warranty, expressed or implied, regarding the information. The AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. The AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

CONFLICT OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.[e13]

Appendix e-1. 2011–2013 GDS Subcommittee members

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-chair); Melissa Armstrong, MD; Eric J. Ashman, MD; Misha-Miroslav Backonja, MD; Richard L. Barbano, MD, PhD; Diane Donley, MD; Terry Fife, MD; David Gloss, MD; John J. Halperin, MD; Cheryl Jaigobin, MD; Andres M. Kanner, MD; Jason Lazarou, MD; David Michelson, MD; Pushpa Narayanaswami, MBBS, DM; Anne Louise Oaklander, MD, PhD; Tamara Pringsheim, MD; Alexander Rae-Grant, MD; Michael Shevell, MD; Kelly Sullivan, PhD; Theresa A Zesiewicz, MD; Jonathan P. Hosey, MD (Ex-Officio); Stephen Ashwal, MD (Ex-Officio); Deborah Hirtz, MD (Ex-Officio); Jacqueline French, MD (AAN Guideline Historian, Ex-Officio, Voting)

Appendix e-2. Mission statement of GDS

The mission of the GDS is to prioritize, develop, and publish evidence-based guidelines related to the diagnosis, treatment, and prognosis of neurologic disorders.
The GDS is committed to using the most rigorous methods available within our budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-3. Search strategy

("humans"[MeSH Terms] OR "humans"[All Fields]) AND ("muscular dystrophy, duchenne"[MeSH Terms] OR "duchenne"[All Fields]) AND ((steroid*[Text Word] OR prednisone[Text Word] OR deflazacort[Text Word] OR glucocorticoids[Text Word] OR prednisolone[Text Word] OR corticosteroid[Text Word] OR bone[Text Word]) OR (exp steroid/ OR exp prednisone/ OR exp deflazacort/ OR exp glucocorticoid/ OR exp prednisolone/ OR exp corticosteroid/ OR exp bone/), set with limits 1/1/2004 to 12/31/2012.

Appendix e-4 AAN classification of evidence scheme for therapeutic studies

Class I
- Randomized, controlled clinical trial (RCT) in a representative population
- Masked or objective outcome assessment
- Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences
- Also required:
a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment
    4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

Class II
- Cohort study meeting criteria a–e above or an RCT that lacks one or two criteria b–e
- All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences
- Masked or objective outcome assessment

Class III
- Controlled studies (including studies with external controls such as well-defined natural history controls)
- A description of major confounding differences between treatment groups that could affect outcome**
- Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team

Class IV
- Did not include patients with the disease
- Did not include patients receiving different interventions
- Undefined or unaccepted interventions or outcome measures

- No measures of effectiveness or statistical precision presented or calculable
*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III
**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

Appendix e-5: Classification of recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*
B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)
C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.
*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

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