Optimal Dosing Schedule in the Treatment of Duchenne Muscular Dystrophy

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Optimal Dosing Schedule in the Treatment of Duchenne Muscular Dystrophy

Abstract

Background: Duchenne muscular dystrophy (DMD) is a common X-linked neuromuscular disease that causes progressive muscle weakness and leads to early death. Those affected often present with muscle weakness as their primary symptom and generally develop scoliosis, respiratory, and cardiac complications as well. In the natural course of DMD, affected males lose ambulation at a mean age of 9.5 years and death generally ensues in the second or third decades of life. There is no curative treatment and corticosteroids are the only approved therapy for slowing the progression of the disease. While much research has been done assessing efficacy of corticosteroid treatment, there is still great uncertainty concerning the optimum dosing schedule.

Method: An extensive search of medical literature was conducted with Medline-OVID, CINAHL, Web of Science and MDConsult using key terms: Duchenne muscular dystrophy, corticosteroids or adrenal cortex hormones, and drug administration schedule or alternate. Studies that assessed efficacy of alternate-day dosing and intermittent dosing regimens were selected and compared to data collected on daily dosing regimens. Articles that met inclusion criteria were chosen and assessed for quality using the GRADE method.

Results: Four studies met inclusion criteria and were included in this systematic review. Two studies focused on alternate-day dosing regimens and two studies evaluated intermittent corticosteroid dosing schedules. While all regimens were found to prolong ambulation and slow progression of DMD when compared to the natural course of the disease, daily dosing seems to be most effective. Alternate-day and intermittent dosing schedules also prolong independent ambulation but not to the extent that daily corticosteroid therapy did. Lastly, significant scoliosis and declines in respiratory function were delayed in patients treated with all corticosteroid dosing regimens.

Conclusion: Corticosteroids have shown to slow progression of DMD by prolonging ambulation, postponing or preventing the development of scoliosis, and delaying respiratory function decline. Evidence suggests that daily corticosteroid therapy is most efficacious in managing DMD but with highest rates of moderate to severe side effects. A recommendation can be made for the use of alternate-day corticosteroid dosing initiated early in the disease process (age 2-4 years). More research is needed to determine whether or not alternative regimens can be as effective as daily treatment and at what age to initiate therapy.

Keywords: Duchenne muscular dystrophy, corticosteroids, dosing schedule, prolonging ambulation

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Optimal Dosing Regimen of Corticosteroids in the Treatment of Duchenne Muscular Dystrophy

Jessica Cooley

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 9, 2014

Faculty Advisor: Mary Von DHEd, PA-C, DFAAPA
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Biography

Jessica Cooley received a Bachelor of Science degree from Boise State University in 2012, with a major in Health Science and a minor in Psychology. Prior to PA school she worked as a residential-habilitation technician, helping to care for those with mental and physical disabilities. She is interested in all aspects of medicine but especially pediatrics, dermatology, and infectious disease.
Abstract

Background: Duchenne muscular dystrophy (DMD) is a common X-linked neuromuscular disease that causes progressive muscle weakness and leads to early death. Those affected often present with muscle weakness as their primary symptom and generally develop scoliosis, respiratory, and cardiac complications as well. In the natural course of DMD, affected males lose ambulation at a mean age of 9.5 years and death generally ensues in the second or third decades of life. There is no curative treatment and corticosteroids are the only approved therapy for slowing the progression of the disease. While much research has been done assessing efficacy of corticosteroid treatment, there is still great uncertainty concerning the optimum dosing schedule.

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Conclusion: Corticosteroids have shown to slow progression of DMD by prolonging ambulation, postponing or preventing the development of scoliosis, and delaying respiratory function decline. Evidence suggests that daily corticosteroid therapy is most efficacious in managing DMD but with highest rates of moderate to severe side effects. A recommendation can be made for the use of alternate-day corticosteroid dosing initiated early in the disease process (age 2-4 years). More research is needed to determine whether or not alternative regimens can be as effective as daily treatment and at what age to initiate therapy.

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# Table of Contents

Biography ........................................................................................................................................... 2  
Abstract ............................................................................................................................................... 3  
Table of Contents ............................................................................................................................... 4  
List of Tables ....................................................................................................................................... 5  
List of Abbreviations .......................................................................................................................... 5  
Background ......................................................................................................................................... 6  
Methods ............................................................................................................................................... 7  
Results ................................................................................................................................................ 7  
Discussion .......................................................................................................................................... 19  
Conclusion .......................................................................................................................................... 23  
Tables ................................................................................................................................................ 25  
References .......................................................................................................................................... 27
List of Tables

Table 1: GRADE Quality of Assessment
Table 2: Merlini et al Study Data
Table 3: Side Effects of Daily vs Intermittent Dosing Regimens

Box 1: The 17 Items Included in the NorthStar Ambulatory Assessment

List of Abbreviations

DMD Duchenne muscular dystrophy
LOA Loss of ambulation
AFO Ankle-foot orthosis
FVC Forced vital capacity
LVSF% Left ventricular shortening fraction percentage
EF Ejection fraction
SD Standard deviation
BP Blood pressure
NSCN NorthStar clinical network
NSAA NorthStar Ambulatory Assessment
DEXA Dual-energy x-ray absorptiometry
BMD Bone mineral density
ADR Adverse drug reaction
NIH National Institutes of Health
HR Hazard Ratio
GRADE Grading of Recommendations, Assessment, Development and Evaluations
Optimal Dosing Regimen of Corticosteroids in the Treatment of Duchenne
Muscular Dystrophy

BACKGROUND

Duchenne muscular dystrophy (DMD) is an X-linked progressive neuromuscular disorder that affects 1 in 3600 male live births.\textsuperscript{1,2} DMD is caused by a defect in the gene responsible for producing dystrophin, which “provides reinforcement to the sarcolemma and stabilizes the glycoprotein complex, thereby shielding it from degradation.”\textsuperscript{3} Without dystrophin the glycoprotein complex is susceptible to digestion by proteases leading to degeneration and necrosis of muscle fibers and resulting in significant muscle weakness.\textsuperscript{3}

Muscle weakness is the primary symptom and onset usually occurs between the ages of two and three years.\textsuperscript{4} Clinically, weakness is generally seen in the lower extremities and in proximal muscles first. Muscle weakness often results in difficulties rising from the floor, walking, running, and climbing stairs.\textsuperscript{5} Affected children may also present with calf hypertrophy, lumbar lordosis, Gower’s sign, and a waddling gait.\textsuperscript{3}

In the natural course of DMD, independent ambulation is generally lost between the ages of 6 and 13 (mean age of 9.5 years).\textsuperscript{6} Studies show that the prevalence and severity of scoliosis is much lower in DMD patients treated with corticosteroids. King et al\textsuperscript{7} found that not only were patients treated with corticosteroids ambulant 3.3 years longer, they were also less likely to develop scoliosis (31 to 91%) when compared to untreated boys. In addition to the development of scoliosis, progressive respiratory, cardiac, and orthopedic complications are common in the second decade of life and eventually lead to premature death in late teens or twenties.\textsuperscript{6,5}
Although there is currently no curative treatment for DMD, corticosteroid therapy has been approved as the only pharmacological intervention known to slow progression of the disease and prolong independent ambulation.\textsuperscript{6,8,9} The exact mechanism is unknown but “it has been hypothesized that corticosteroids have anti-inflammatory and immunosuppressive actions, promote myoblast proliferation, and reduce muscle necrosis.”\textsuperscript{10} Furthermore, studies have shown that corticosteroids are effective in slowing the progression of DMD. There are currently several dosing regimen options (i.e., daily, alternate-day, intermittent, and weekend only) but the question remains as to which is the best and at what age to begin therapy.

**METHODS**

An extensive search of medical literature was conducted using Medline-OVID, CINAHL, Web of Science, and MDConsult. Search terms included Duchenne muscular dystrophy, corticosteroids or adrenal cortex hormones, and drug administration schedule or alternate. The search was narrowed to include English language articles on human subjects. Studies that focused on daily, alternate-day, and intermittent corticosteroid dosing treatments were included. Articles matching these criteria were evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method.\textsuperscript{11}

**RESULTS**

The initial search of medical literature yielded 19 articles available for review. The studies were examined and those found to focus on alternate-day and intermittent corticosteroid dosing regimens that met inclusion criteria were selected and compared to
data collected assessing daily corticosteroid therapy. There were two alternate-day dosing\textsuperscript{12,13} studies and two intermittent dosing\textsuperscript{14,15} studies chosen. See Table 1.

\textbf{Yilmaz et al Study}

The observational cohort study\textsuperscript{12} compared the effectiveness of alternate-day dosing of prednisolone to untreated patients with DMD in prolonging independent ambulation, onset of scoliosis, muscle strength, 10-m walking, and ankle contractures. Of most importance to this review are age at which ambulation was lost and onset of scoliosis. For this study, authors reviewed data from 66 DMD boys who had received alternate-day prednisolone therapy and 22 DMD boys in the control group who received no treatment. Participants in the treatment group (mean age 6.8 ± 2.1 years, range 2.5-12.5 years) received oral prednisolone 0.75 mg/kg on alternate days and vitamin D 600-1200 units/day daily. Members of both the treatment and control groups received a calcium-rich diet as well. Control subjects (mean age 7.0 ± 1.3 years, range 5-9 years) were taken from an earlier cohort group so age-matching could be performed. There was no statistically significant difference between the mean ages of the treatment and control groups.\textsuperscript{12}

Each participant underwent an initial evaluation and was re-examined every 6 months. At the time of initiation, all were instructed to engage in specific strengthening and stretching exercises, posture and breathing exercises, and positioning and nighttime ankle-foot (AFO) use. Length of follow-up was 2.75 ± 0.1 years (range 1.5-5 years).\textsuperscript{12}

When evaluating treatment efficacy for DMD, the age at which ambulation is lost is commonly a primary response of interest. Participants in the therapy group of this study lost the ability to walk independently at 10.0 years ± 1.5 years (range 7-14 years).
Those in the control group lost independent ambulation at 8.6 years ± 2.6 years (range 6-11). While there were no DMD boys ambulant beyond the age of 11 years in the control group, there were 14 ambulant from the therapy group at age 12 and three boys still ambulant at the age of 13.12

In the natural course of DMD, the majority of patients develop scoliosis (often after ambulation is lost) that can have severe negative effects on respiratory function and quality of life. Authors of this study found that none of the therapy group patients had scoliotic curves greater than 24° at the end of the follow-up period, but there were seven in the control group that had curves > 45° by the mean age of 11.7 years ± 0.8 years (range 9-16 years).12

Interestingly enough, participants of the therapy group experienced increases in 10-m walking time, decreased muscle strength of upper and lower extremities after 12 months of therapy, and increased rates of ankle contractures in comparison to the control group. These results may indicate that exercises play an important role in maintaining muscle strength. Despite these deficits, patients treated with corticosteroids remained ambulant longer than those who did not receive treatment.12

Merlini et al Study

This long-term prospective observational study13 assessed the value of early administration of alternate-day corticosteroid treatment in five boys with DMD. The primary outcome of interest was prolongation of independent ambulation but authors also evaluated the ability to rise from the floor, respiratory and cardiac function, as well as significant side effects of corticosteroid treatment.13
Researchers began this study in 1996 by enrolling eight DMD patients between the ages of 2 and 4 years. The parents of five participants chose alternate-day corticosteroid treatment and three opted for no treatment. Corticosteroid therapy was prednisone 0.75 mg/kg daily for 2 weeks then 1.25 mg/kg every other day (max dose of 50 mg). This regimen continued for 3 years at which time it was switched to deflazacort to lower risk of weight gain. The alternate day deflazacort (1.5 mg/kg every other day with a max dose of 60 mg) was then progressively tapered to 0.7-1.0 mg/kg every other day around the ages of 12-14 years. Participants were also given supplemental vitamin D3 400 units and calcium 1250 mg by mouth daily. The authors hypothesized that beginning treatment at a younger age, before significant motor loss was evident, would provide more benefits due to the progressive nature of the disease.

Participant monitoring was performed every 3-6 months and researchers evaluated muscle function via several timed tests, respiratory function by forced vital capacity (FVC), and side effects of treatment through parent interviews and clinical exams. The primary outcome of interest was prolongation of independent walking. One boy in the therapy group and one in the control group were followed just until they lost independent ambulation at the ages of 10 years both. The two remaining participants in the control group were lost to follow-up when they lost the ability to rise from the floor at the ages of 8 and 9.5 years. The remaining four participants in the therapy group were followed for 14 years. At the time of the last follow-up, all four in the therapy group were fully and independently ambulatory (aged 16-18) and three were still able to climb stairs. The fourth had lost the ability to climb stairs at the age of 17 years. Two of the remaining
four boys in the therapy group had lost the ability rise from the floor at the ages of 12.5 and 15.5 years, a task that is often the first motor skill lost in the course of DMD.\textsuperscript{13,17}

Another important outcome of interest, respiratory function, was also routinely evaluated. Forced vital capacity (FVC) was ascertained with electronic spirometry. Researchers found that two of the remaining participants in the treatment group had normal FVCs and the other two had moderately reduced pulmonary function based on their FVCs at the final follow-up. A summary of FVC results can be found in Table 2. Researchers found a similar trend with respect to muscle strength in the remaining participants of the therapy group. Muscle strength in all four increased somewhat between the ages of 5 and 9-10 then began to decline. This decline was most dramatic in knee extensor muscles. Participants were also assessed by a cardiologist annually. Based on physical exam, electrocardiograms and echocardiograms, only one participant in the therapy group was found to have a mildly reduced left ventricular ejection fraction (EF) of 50%. The remaining three patients had left ventricular EFs between 57-60%. Cardiologists determined a left ventricular EF below 50% as indicative of systolic dysfunction, and <45% graded as moderate or severe dysfunction.\textsuperscript{13}

As with all pharmacological interventions, side effects are a crucial factor and should not be ignored. Researchers found that growth failure, delayed bone maturation, and delayed puberty were the most problematic side effects of corticosteroid treatment. After 1 year of treatment, all four remaining participants of the therapy group had experienced declined growth rates. At their last follow-up all had heights between 3.01 and 4.77 standard deviations (SDs) below normal and had nearly reached their final
height based on yearly left hand x-rays for bone age. According to parent reports, short stature and growth failure remained a major concern of corticosteroid treatment.¹³

Researchers explain that excessive weight gain and development of cushingoid features are the most common side effects of daily corticosteroid therapy.⁶,¹⁸ They continue by declaring that with their alternate day regimen “cushionoid features were not observed, and weight gain was limited.” Three of the four participants in the treatment group were overweight in childhood until the ages of 13-15 (indicated by BMI). Although weight gain was not a major negative finding, body fat percentages measured by DXA scan was. There was a mean total fat mass of 36.7% in the four remaining therapy participants (compared to 10.5% in healthy children) by the age of 8 that continued to increase to a mean value of 60% by the last follow-up. For these reasons, investigators argue that DXA should be used over BMI as the method of choice for assessing weight gain and obesity in DMD research.¹³

Bone age was chosen as a method of assessing degree of maturation. Bone age was delayed in all patients until puberty was reached, and the timing of onset of puberty was related to bone age more than chronologic age. Researchers clarify that onset of puberty for boys is considered normal if between the ages of 9 and 13.5 years.¹⁹ Puberty was so delayed in this participant population that by the ages of 14-15, three of the four treated participants required androgen treatment (testosterone 50 mg/monthly) to induce puberty. It was noted that at the end of androgen therapy, participants had a completely normal hormonal profile. Catch up growth during puberty is generally 25-30 cm in normal boys. However, all participants experienced less; approximately 10 cm in the three participants that required androgen therapy and around 14 cm in the patient with
spontaneous puberty. Investigators also commented that scoliosis was not detected in any participants based on clinical exam findings including the forward bend test (thus x-rays of spine were not performed). Although bone fractures were rare in this small sample of DMD patients on corticosteroids (one patient in the therapy group sustained an arm fracture during this study), low bone mineral density (BMD) and delayed bone maturation confirm the value of DXA and osteoporosis monitoring.\textsuperscript{13,20,21}

**Ricotti et al Study**

In addition to daily and alternate-day corticosteroid dosing regimens, intermittent dosing schedules (usually 10 days on and 10 days off) are another common option chosen for DMD treatment. In this prospective longitudinal observational study,\textsuperscript{14} data were collected from 17 pediatric neuromuscular centers in the UK. The 360 male participants included were between the ages of 3 and 15 with confirmed DMD. Participants were treated either with daily prednisolone or an intermittent schedule of 10 days on/10 days off. Investigators state that while daily corticosteroid therapy is believed to be the most effective, side effects are great and often a reason for noncompliance or discontinuation. For this reason other regimens have been suggested and intermittent dosing schedules are a widely used alternative in the UK. The purpose of this study was to compare the benefits and adverse effects of daily versus intermittent prednisolone schedules.\textsuperscript{14}

As mentioned, data from the 360 DMD participants were collected from 17 participating specialist pediatric neuromuscular centers in the UK and compiled into the NorthStar database. In 2003 the NorthStar clinical network for pediatric neuromuscular disease (NSCN) was established allowing researchers to uniformly and systematically collect data from the various participating centers. Participants were aged 3-15 and were
assessed biannually. Included in this study were 136 patients in the daily corticosteroid regimen group and 154 in the intermittent group as well as 70 DMD boys that switched treatment schedules sometime during the study. The “switchers” were assigned to the group in which they spent the majority of the study duration (total of 191 on intermittent and 169 on daily prednisolone) and their data were analyzed in that group. DMD was genetically confirmed in each patient and parent or guardian consent was obtained. To ensure standardized assessments across all centers, physicians and physiotherapists underwent a national training program. Primary outcomes of interest included loss of ambulation (LOA) and the NorthStar Ambulatory Assessment (NSAA) score which will be described shortly and summarized in Box 1. Researchers were also interested in evaluating severity of side effects in both therapy groups.14

Researchers remind us that the progressive nature of DMD often leads to loss of ambulation by 9.5 years of age (range 6-12 years) if untreated.5 Corticosteroids have shown to slow the deterioration of muscle function and prolong independent ambulation.22 A Cox regression model was used for this study to compare loss of ambulation between the daily and intermittent therapy groups. Loss of ambulation was reported in 39/168 boys on daily therapy and 51/184 boys on the intermittent schedule during the course of this study. There were two participants who were never ambulant and six whose ambulation statuses were never known. These eight participants were excluded from this portion of the analysis (one participant from the daily group and seven from the intermittent group). The median LOA age in the daily corticosteroid group was 14.5 years and 12 years for the intermittent group, however the authors state that the
difference in mean ages of LOA was not statistically significant (p=0.13). The hazard ratio (HR) for the intermittent vs daily therapy group was 1.57 (95% CI 0.87-2.82). In addition to LOA, investigators evaluated overall function in ambulant boys with DMD by assigning a score based on the NorthStar Ambulatory Assessment (NSAA). The NSAA consists of 17 different items that are ordered into one of three categories. If activities were carried out normally with no obvious modification 2 points were given, 1 point was given if the activity could be performed independently but with modified methods, or 0 points if the task could not be carried out. A total of 34 points were possible and the assessments were carried out in 20 minutes. The analysis of NSAA total scores illustrated a slower decline of function in the daily regimen group. Neither the daily group nor the intermittent group experienced a regression in NSAA scores before the age of 6. However, those in the intermittent regimen began demonstrating a decline in total scores by the age of 7 and the difference in NSAA scores between the two regimens increased by 1.58 points each year (95% CI 1.04 to 2.11). Researchers also compared the NSAA total scores of participants that began corticosteroid therapy before the age of 5 to those who initiated therapy after the age of 5 years. An overall trend in favor of beginning therapy before the age of 5 may exist (difference of 3.04; 95% CI 0.15 to 6.23; p=0.06).

Respiratory and cardiac outcomes did not differ between the daily and intermittent corticosteroid schedules. When the participants were analyzed as a whole, researchers were able to conclude that the mean FVC and LVSF values remained within normal limits. Despite remaining in normal limits, there was a significant progressive
decline in FVC% by 2.2% each year after the age of 10 years (p<0.001). LVSF% also declined by 1% each year after the age of 12 years (p<0.001).14

The authors of this study were very interested in comparing the severity of side effects of daily and intermittent corticosteroid regimens. They concluded that moderate and severe side effects were more frequent in the group treated with daily corticosteroids (Table 2) after evaluating biannual assessments and parental reports. There were statistically significant higher rates of cushingoid features, hyperactivity, GI symptoms, hypertension, height restriction, decreased bone mineral density, and vertebral fractures in those in the daily corticosteroid group.14

Height restriction, or growth failure, is a common side effect of long-term corticosteroid use. Participants in the daily therapy group had significantly lower mean height z-scores, the authors reported a difference in z-scores of 1.09 (95% CI 0.78 to 1.40; p<0.001) even when adjusted for length of time on corticosteroid therapy. The mean difference in baseline BMI was significantly higher in the daily treatment group as well; mean difference of 0.43 (95% CI 0.11 to 0.74; p<0.01). Researchers found BMD to be compromised in both treatment groups but, again, more so in those treated with daily corticosteroids. They observed that 8% of participants in the daily group had a BMD z-score ≤ -2.5 on dual-energy x-ray absorptiometry (DEXA) scan in comparison to only 5% in the intermittent group. Vertebral fractures, defined as vertebral wedging on lateral spine radiography by the NSCN, were reported in twice as many cases in the daily group when compared to the intermittent (8% and 4% respectively).14

Straathof et al Study
In their retrospective observational study, Straathof et al.\textsuperscript{15} analyzed data from 35 patients with DMD treated with intermittent dosing of prednisone. Participants were boys with DMD confirmed by DNA analysis whose parents consulted the De Trappenberg rehabilitation center for treatment with corticosteroids. Of the 43 boys with DMD that consulted the center between 1996 and 2005, 35 met inclusion criteria and had been treated with intermittent corticosteroid therapy and were thus included in the study. Participants had been treated with prednisone 0.75 mg/kg in an alternating schedule of 10 days on followed by 10 days off. After they lost ambulation the dose was lowered to 0.3-0.5 mg/kg still in an intermittent 10 days on then 10 days off regimen. Prednisone therapy was initiated while participants were still ambulatory at a median age of 6.5 years (range 3.5-9.7 years). Participants were assessed by the rehabilitation physician as well as a pediatrician every six months. Investigators focused their evaluations on motor skills and side effects of the corticosteroid treatment. Timed tests were performed at each evaluation including 10-m fast walk or run and time to stand from sitting position on the floor without assistance. Clinical exams were performed to monitor height, weight, and blood pressure (BP). X-rays of the spine were also performed each year to monitor any development of scoliosis and to screen patients for vertebral fractures.\textsuperscript{15}

Investigators defined loss of ambulation as the inability to walk indoors unsupported. LOA was reported at a mean age of 10.9 years (median age of 10.8 years) with a 95% CI 10.0-11.8 years. The researchers explain that in similar studies those treated with daily corticosteroids lost the ability to independently ambulate at the mean ages of 11.5 and 12.5 years.\textsuperscript{15}
During the course of this study, two patients being treated with prednisone required scoliosis surgery at the ages of 13.5 and 8 years. The first patient had used prednisone for only 9 months until he required the use of wheelchair at the age of 9.9 years. The second patient had sustained a femur fracture that left him requiring the use of a wheelchair at the age of 6.5 years. While respiratory function was evaluated and no child required respiratory support during this study, it was not a focus or primary outcome of interest to this study.\textsuperscript{15}

Side effects were closely monitored and were the primary reason for discontinuation of therapy in five patients. Weight gain on the weight-to-height growth chart was observed in 46\% of participants but none of the ambulatory boys experienced weight gain $> 1.0$ SDS. Studies looking at daily corticosteroid dosing found 75\% of participants experienced weight gain $> 10\%$.\textsuperscript{23,24} This study reports that only 25\% of their intermittently treated participants experienced comparable weight gain and the greatest weight gain was in patients who had lost ambulation and required the use of a wheelchair. During corticosteroid therapy eight participants sustained a fracture; a traumatic fall was responsible in six of those eight cases and the cause of fracture was unknown in the remaining two boys. Four of the patients suffered femur fractures that left them requiring use of a wheelchair, two had forearm fractures, and the remaining two sustained lower leg fractures. The majority of patients in this study had blood pressures that remained $< 95\%$ percentile for their age and height during the follow-up period. There were 3 patients that had elevated BPs $> 95\%$ percentile on one occasion. Two of the participants were found to have decreased ejection fractions on echocardiogram and required treatment with an ace inhibitor. The first boy was 10 years old and has used prednisone
for 5 years. The second was 13 years old and had used prednisone for 7.5 years. The third participant with an elevated BP reading had stopped taking corticosteroids 3 years prior but was given digoxin by his cardiologist. Follow-up data on this participant was limited.¹⁵

**DISCUSSION**

While the medical community acknowledges corticosteroids as the mainstay of treatment for DMD, the optimal dosing regimen and age to initiate therapy has not been established. Currently, corticosteroids are “offered for boys 5 years of age or older who are no longer gaining motor skills, or whose motor skills are declining.”⁸ Based on the current research, daily corticosteroid therapy (prednisone 0.75 mg/kg or deflazacort 1.0 mg/kg) appears to be the most beneficial in prolonging ambulation and slowing progression of DMD while delaying respiratory decline and onset of scoliosis.⁶,¹² Investigators of the Ricotti et al¹⁴ study argue that there was no statistical significance in the median LOA age between those treated with daily corticosteroids when compared to those treated intermittently. However, increased ambulation of 2.5 years (median LOA for daily treatment was 14.5 years and only 12 years for those treated with intermittent dosing) is clinically meaningful to young boys with DMD as ambulation is a significant factor in quality of life. Research shows that DMD boys on long-term corticosteroid treatment have an extension of greater than 3 years’ independent ambulation in comparison to untreated patients as well as a significantly decreased risk of developing scoliosis.⁷ However noncompliance and discontinuation of therapy are not uncommon secondary to adverse effects of corticosteroid treatment especially in those treated with daily regimens.
Age at which corticosteroid therapy is initiated appears to play a significant role in delaying loss of ambulation. Ricotti et al\textsuperscript{14} found that participants who started treatment before the age of 5 had a slower decline in functional abilities, strength and mobility. Researchers were able to conclude that the NSAA total scores for the intermittent corticosteroid regimen group deteriorate faster than those on daily corticosteroids after the age of 7 at a rate of -1.58 points per year. However, participants that started therapy before the age of 5 had a slower decline in their NSAA scores than those who initiated corticosteroid therapy after 5 years of age.\textsuperscript{14} While there appears to have been little success associated with intermittent dosing schedules, Merlini et al\textsuperscript{13} had great success with prolonged ambulation in its participants that began alternate-day corticosteroid therapy between the ages of 2-4 years. At the last follow-up evaluation, the four patients treated with alternate-day prednisone initiated between the ages of 2 and 4 years were still fully ambulant (ages 16-18) and three were still able to climb stairs.\textsuperscript{13}

All these studies\textsuperscript{12-15} provide evidence for the benefits of corticosteroids in treatment of DMD, yet all have limitations. There are few RCT studies comparing efficacy of various corticosteroid regimens or initiation age of therapy. Loss of follow-up, small sample sizes, subjective measurements of end points, and the observational nature of studies are common limitations associated with the current studies assessing efficacy of corticosteroids in treatment of DMD. The four studies included in this review were retrospective observational in nature, thus lowering their overall quality with respect to the GRADE criteria. Although the Merlini et al study\textsuperscript{13} had a complete and lengthy follow-up, the entire control group was lost during that time and researchers were unable to compare results of the treatment group to a control group resulting in a serious
limitation of the study. Three of the four studies\textsuperscript{12,13,15} had imprecision issues secondary to small sample sizes, a common inadequacy of many studies assessing efficacy of various corticosteroid regimens in DMD patients. While the Ricotti study\textsuperscript{14} incorporated a decently sized sample population, the authors allowed participants to switch therapy groups during the course of the study. The researchers analyzed the participants in the therapy group in which they spent the majority of the study duration; however the inappropriate handling of participants switching between treatment and therapy groups created an inconsistency limitation that further downgraded the quality of this study. All data collected for the Straathof et al study\textsuperscript{15} was collected from one rehabilitation center thus increasing the risk of bias. The subjective measurement and collection of outcomes and data was a limitation of several studies. Researchers of the Merlini et al study\textsuperscript{13} monitored patients for scoliosis with clinical exams and forward bending tests but no objective screening modalities were used. Similarly, authors of the Ricotti et al study\textsuperscript{14} admit that their study faced challenges associated with subjective collection of data and parental reports. When assessing study quality with respect to prolonged ambulation, normal respiratory function, and delayed onset of scoliosis, all studies\textsuperscript{12-15} included in this review received an overall quality rating of very low because of the various limitations previously discussed.

More subtle limitations are identified in these studies. Researchers of the Yilmaz et al study\textsuperscript{12} found that muscle strength was lower in the therapy group but question whether or not the decreased muscle strength in the therapy group was a result of neglected stretches rather than a detrimental effects of corticosteroid treatment. This confounder could very well explain the difference in muscle strength between the two
Researchers continue searching for the optimal dosing schedule. A recent randomized blinded trial of weekend vs daily prednisone in 64 DMD boys illustrates a possible new option for treatment. Participants in this study were treated with either daily prednisone (0.75 mg/kg/day) or weekend prednisone (5 mg/kg Saturday and Sunday) for 12 months. Weekend dosing appeared to be equally beneficial in preserving muscle strength when compared to the daily therapy. The two regimens were equally tolerated with respect to side effects; however, those in the weekend dosing group had significantly greater linear growth.²⁵

Before a definitive answer can be given as to which regimen is best and what age to initiate therapy, a long-term randomized clinical trial comparing several dosing regimens beginning at various ages should be performed. Future studies require internationally standardized endpoints that can be objectively measured. For example, it is both difficult and non-standardized when objectively defining non-ambulatory status, measuring cushingoid features, calculating reduction in height potential, and quantifying behavioral problems. An international clinical trial comparing various corticosteroid regimens in young corticosteroid naïve patients in a randomized controlled trial is currently underway (funded by NIH) and will hopefully shed light on the questions that remain.²⁶
CONCLUSION

Corticosteroids play a significant role in prolonging ambulation, slowing progression of DMD, and delaying onset of scoliosis as well as respiratory decline. “The age at which ambulation is lost is a clinical meaningful endpoint for evaluating the efficacy of treatment in DMD patient.” Current research confirms corticosteroids prolong independent ambulation beyond the mean age of 9.5 years associated with the natural course of DMD. Daily corticosteroid therapy (prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day) has demonstrated to be the most effective dosing regimen for prolonging independent ambulation and slowing the progression of DMD. While evidence supports daily therapy to be most effective, moderate to severe adverse effects were more frequent in those treated daily corticosteroids. Alternative dosing schedules (including alternate-day, intermittent, or weekend dosing regimens) are an option that many parents are choosing for their boys with DMD. These alternative options also prolong ambulation and decelerate progression of DMD but not to the extent that daily corticosteroid therapy does. Parents often choose or switch to these regimens as they are associated with less severe side effects. It is important to consider ADRs when choosing a treatment regimen but prolonged ambulation and quality of life are the most important factors to consider in patients with this disorder as early death will ensue. Allsop and Ziter explain that the important thing to consider when discussing DMD treatment is the ability of children to preserve functioning and performing activities (1981).

Evidence may suggest that even more important than dosing schedule is the age at which therapy is initiated. “As long-term corticosteroid treatment is effective in prolonging function but not in recovering lost function, its early use seems appropriate.”
There is not enough data currently and too few randomized controlled trials to definitively reach a conclusion, but beginning treatment before significant deficits in motor function are detected (ages 2-4) seems to offer superior functional benefit. The overall combined quality of these studies is very low based on the GRADE criteria, primarily because of the observational nature of all studies and small sample sizes. There is a need for further randomized controlled studies that compare all dosing regimens head-to-head as well as different ages at which therapy is initiated.
TABLE 1 Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>GRADE Quality Assessment</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Inconsistency</td>
<td>Publication bias likely</td>
</tr>
<tr>
<td>Prolonged Ambulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Observation</td>
<td>Serious limitationsa</td>
<td>No serious indirectness</td>
<td>Very serious imprecisionb</td>
<td>Serious inconsistenciesc</td>
<td>Possible publication bias</td>
</tr>
<tr>
<td>Normal Respiratory Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Observation</td>
<td>Serious limitationsa</td>
<td>No serious indirectness</td>
<td>Serious imprecisionb</td>
<td>Serious inconsistenciesc</td>
<td>No bias likely</td>
</tr>
<tr>
<td>Delayed Onset of Scoliosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Observation</td>
<td>Serious limitationsa</td>
<td>No serious indirectness</td>
<td>Very serious imprecisionb</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
</tr>
</tbody>
</table>


a Control group lost to follow-up in the Merlini et al study; b Study is lacking objective measurement of scoliosis.

c Yilmaz et al study, d Merlini et al study, e and Straathof et al study f consisted of a small sample sizes.

d Ricotti et al study; e allowed for inconsistent handling of switching between treatment and control groups.

e Data collected for the Straathof et al study was gathered from only one rehabilitation center (increasing risk of bias).

Table 2. Merlini et al Study Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset of treatment (years)</th>
<th>Age at last follow-up (years)</th>
<th>Age at rising from floor unable (years)</th>
<th>Age at climbing stairs unable (years)</th>
<th>10-m walk speed at follow-up (m/s)</th>
<th>FVC (ml) and % of predicted at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.9</td>
<td>18.5</td>
<td>15.5</td>
<td>NA</td>
<td>1.25</td>
<td>2470 (73%)</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>18.6</td>
<td>12.5</td>
<td>17.0</td>
<td>1.11</td>
<td>2130 (65%)</td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
<td>16.1</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
<td>2610 (107%)</td>
</tr>
<tr>
<td>4</td>
<td>3.3</td>
<td>17.0</td>
<td>NA</td>
<td>NA</td>
<td>1.01</td>
<td>2250 (96%)</td>
</tr>
<tr>
<td>Mean</td>
<td>3.4</td>
<td>17.6</td>
<td>1.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Table 3.** Side Effects of Daily vs Intermittent Dosing Regimens

<table>
<thead>
<tr>
<th></th>
<th>Daily</th>
<th>Intermittent</th>
<th>$X^2$ p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushingoid Features</td>
<td>33%</td>
<td>15%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>23%</td>
<td>15%</td>
<td>0.05</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>14%</td>
<td>6%</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22%</td>
<td>5%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Temper Tantrums</td>
<td>40%</td>
<td>28%</td>
<td>0.02</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11%</td>
<td>4%</td>
<td>0.01</td>
</tr>
<tr>
<td>Mood swings</td>
<td>38%</td>
<td>29%</td>
<td>0.08</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>29%</td>
<td>21%</td>
<td>0.09</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>8%</td>
<td>4%</td>
<td>0.1</td>
</tr>
<tr>
<td>BMD z-score $\leq$ -2.5</td>
<td>8%</td>
<td>5%</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**Box 1**  The 17 Items Included in the NorthStar Ambulatory Assessment

<table>
<thead>
<tr>
<th>Activity</th>
<th>Daily Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stand</td>
<td>Gets to sitting</td>
</tr>
<tr>
<td>Walk</td>
<td>Rise from the floor</td>
</tr>
<tr>
<td>Stand up from chair</td>
<td>Lift head</td>
</tr>
<tr>
<td>Stand on right leg</td>
<td>Stand on heels</td>
</tr>
<tr>
<td>Stand on left leg</td>
<td>Jump</td>
</tr>
<tr>
<td>Climb box step – right leg</td>
<td>Hop – right leg</td>
</tr>
<tr>
<td>Climb box step – left leg</td>
<td>Hop – left leg</td>
</tr>
<tr>
<td>Descend box step – right leg</td>
<td>(Run 10 m)</td>
</tr>
<tr>
<td>Descend box step – left leg</td>
<td></td>
</tr>
</tbody>
</table>
References


