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Corticosteroids for the treatment of Duchenne muscular dystrophy.

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[Intervention Review]

Corticosteroids for the treatment of Duchenne muscular dystrophy

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ABSTRACT

Background

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy of childhood. Untreated, this incurable disease, which has an X-linked recessive inheritance, is characterised by muscle wasting and loss of walking ability, leading to complete wheelchair dependence by 13 years of age. Prolongation of walking is a major aim of treatment. Evidence from randomised controlled trials (RCTs) indicates that corticosteroids significantly improve muscle strength and function in boys with DMD in the short term (six months), and strength at two years (two-year data on function are very limited). Corticosteroids, now part of care recommendations for DMD, are largely in routine use, although questions remain over their ability to prolong walking, when to start treatment, longer-term balance of benefits versus harms, and choice of corticosteroid or regimen.

We have extended the scope of this updated review to include comparisons of different corticosteroids and dosing regimens.

Objectives

To assess the effects of corticosteroids on prolongation of walking ability, muscle strength, functional ability, and quality of life in DMD; to address the question of whether benefit is maintained over the longer term (more than two years); to assess adverse events; and to compare efficacy and adverse effects of different corticosteroid preparations and regimens.

Search methods

On 16 February 2016 we searched the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, EMBASE, CINAHL Plus, and LILACS. We wrote to authors of published studies and other experts. We checked references in identified trials, handsearched journal abstracts, and searched trials registries.

Selection criteria

We considered RCTs or quasi-RCTs of corticosteroids (e.g. prednisone, prednisolone, and deflazacort) given for a minimum of three months to patients with a definite DMD diagnosis. We considered comparisons of different corticosteroids, regimens, and corticosteroids versus placebo.

Data collection and analysis

The review authors followed standard Cochrane methodology.

Main results

We identified 12 studies (667 participants) and two new ongoing studies for inclusion. Six RCTs were newly included at this update and important non-randomised cohort studies have also been published. Some important studies remain unpublished and not all published studies provide complete outcome data.

Primary outcome measure: one two-year deflazacort RCT (n = 28) used prolongation of ambulation as an outcome measure but data were not adequate for drawing conclusions.

Secondary outcome measures: meta-analyses showed that corticosteroids (0.75 mg/kg/day prednisone or prednisolone) improved muscle strength and function versus placebo over six months (moderate quality evidence from up to four RCTs). Evidence from single trials showed 0.75 mg/kg/day superior to 0.3 mg/kg/day on most strength and function measures, with little evidence of further benefit at 1.5 mg/kg/day. Improvements were seen in time taken to rise from the floor (Gowers' time), timed walk, four-stair climbing time, ability to lift weights, leg function grade, and forced vital capacity. One new RCT (n = 66), reported better strength, function and quality of life with daily 0.75 mg/kg/day prednisone at 12 months. One RCT (n = 28) showed that deflazacort stabilised muscle strength versus placebo at two years, but timed function test results were too imprecise for conclusions to be drawn.

One double-blind RCT (n = 64), largely at low risk of bias, compared daily prednisone (0.75 mg/kg/day) with weekend-only prednisone (5 mg/kg/weekend day), finding no overall difference in muscle strength and function over 12 months (moderate to low quality evidence). Two small RCTs (n = 52) compared daily prednisone 0.75 mg/kg/day with daily deflazacort 0.9 mg/kg/day, but study methods limited our ability to compare muscle strength or function.

Adverse effects: excessive weight gain, behavioural abnormalities, cushingoid appearance, and excessive hair growth were all previously shown to be more common with corticosteroids than placebo; we assessed the quality of evidence (for behavioural changes and weight gain) as moderate. Hair growth and cushingoid features were more frequent at 0.75 mg/kg/day than 0.3 mg/kg/day prednisone. Comparing daily versus weekend-only prednisone, both groups gained weight with no clear difference in body mass index (BMI) or in behavioural changes (low quality evidence for both outcomes, one study); the weekend-only group had a greater linear increase in height. Very low quality evidence suggested less weight gain with deflazacort than with prednisone at 12 months, and no difference in behavioural abnormalities. Data are insufficient to assess the risk of fractures or cataracts for any comparison.

Non-randomised studies support RCT evidence in showing improved functional benefit from corticosteroids. These studies suggest sustained benefit for up to 66 months. Adverse effects were common, although generally manageable. According to a large comparative longitudinal study of daily or intermittent (10 days on, 10 days off) corticosteroid for a mean period of four years, a daily regimen prolongs ambulation and improves functional scores over the age of seven, but with a greater frequency of side effects than an intermittent regimen.

Authors' conclusions

Moderate quality evidence from RCTs indicates that corticosteroid therapy in DMD improves muscle strength and function in the short term (twelve months), and strength up to two years. On the basis of the evidence available for strength and function outcomes, our confidence in the effect estimate for the efficacy of a 0.75 mg/kg/day dose of prednisone or above is fairly secure. There is no evidence other than from non-randomised trials to establish the effect of corticosteroids on prolongation of walking. In the short term, adverse effects were significantly more common with corticosteroids than placebo, but not clinically severe. A weekend-only prednisone regimen is as effective as daily prednisone in the short term (12 months), according to low to moderate quality evidence from a single trial, with no clear difference in BMI (low quality evidence). Very low quality evidence indicates that deflazacort causes less weight gain than prednisone after a year's treatment. We cannot evaluate long-term benefits and hazards of corticosteroid treatment or intermittent regimens from published RCTs. Non-randomised studies support the conclusions of functional benefits, but also identify clinically significant adverse effects of long-term treatment, and a possible divergence of efficacy in daily and weekend-only regimens in the longer term. These benefits and adverse effects have implications for future research and clinical practice.

PLAIN LANGUAGE SUMMARY

Corticosteroid therapy for Duchenne muscular dystrophy

Review question

Is there new evidence for benefit from corticosteroids for prolongation of walking, and improving muscle strength and functional abilities in Duchenne muscular dystrophy (DMD), particularly over the long term (more than two years)? Are different corticosteroids, or different regimens equally effective, with similar side effect profiles?

Background

DMD is an incurable disease beginning in childhood that almost exclusively affects boys. Muscle wasting and loss of walking lead to wheelchair dependence and early death. Randomised controlled trials (RCTs) have shown that corticosteroids improve muscle strength and function for up to six months and strength up to two years (evidence on function at two years is limited). Data from other study types suggest that corticosteroids produce better function over a five-year period in many patients. Overall, long-term benefit remains unclear, and has to be weighed against long-term side effects. It is also unclear whether different corticosteroids differ greatly in side effects. Earlier versions of this review found insufficient evidence to determine whether an intermittent regimen is as effective as a daily regime, or produces fewer side effects.

Study characteristics

We found 12 studies of corticosteroid treatment in DMD, involving a total of 667 randomised boys; two other studies are ongoing. Among the 12 completed studies, the treatments were: a corticosteroid versus inactive medicine (placebo) (in nine trials); daily versus weekend-only prednisone (in one trial); and deflazacort versus prednisone (in three trials). Some studies included more than one comparison; some were not fully reported or provided results that could not be analysed.

Key results and quality of the evidence

One trial, a two-year study comparing a corticosteroid (deflazacort) with placebo, assessed the effects of corticosteroids on the ability to continue walking, but the data were not suitable for analysis. Most studies did not report ability to continue walking.

At the usual 0.75 mg/kg/day dose, corticosteroids improved muscle strength and function over six months compared to placebo. These results are based on combined data (up to 152 participants) from four trials, which provided moderate quality evidence. Improvements were seen in timed tests (eg. timed walk or run, time to stand, stair climb), ability to lift weights, a leg function grade, and a measure of the strength of muscles used in breathing. Evidence from single trials showed 0.75 mg/kg/day prednisone to be superior to 0.3 mg/kg/day on most strength and function tests, with little evidence of greater benefit at 1.5 mg/kg/day. Changes in appearance and hair growth were more common at 0.75 mg/kg/day than 0.3 mg/kg/day.

One RCT (n = 66) also reported better strength, function and quality of life at 12 months with daily 0.75 mg/kg/day prednisone. The two-year RCT, which had 28 participants, showed that deflazacort stabilised muscle strength for up to two years compared to placebo. This study did not show benefit on timed tests at two years; however, these results are imprecise and at high risk of bias, with less than half the original participants contributing data.

One trial found that changes in muscle strength and function were similar with daily and weekend-only prednisone regimens over a 12-month period (low to moderate quality evidence).

Two small RCTs compared daily prednisone 0.75 mg/kg/day with daily deflazacort 0.9 mg/kg/day, but trial methods did not allow comparisons of muscle strength or function.

Previous versions of this review have found adverse events such as excessive weight gain, abnormal behaviour, changes in appearance, and abnormal hair growth to be more common with corticosteroids than with placebo. We assessed the quality of evidence for abnormal behaviour and weight gain for this review and found it to be moderate. The newer study of daily versus weekend-only prednisone showed that both groups gained weight. The body mass index (BMI; a measure of weight for height) did not show any clear difference between the regimens (low quality evidence). The weekend-only group had a greater increase in height. According to very low quality evidence from two studies, deflazacort appeared to cause less weight gain at one year than prednisone, and no significant difference in numbers with behaviour change. Data were insufficient to assess the risk of fractures or cataracts.

The evidence is up to date to February 2016.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Corticosteroids versus placebo for Duchenne muscular dystrophy

Patient or population: patients with Duchenne muscular dystrophy
Setting: outpatient
Intervention: corticosteroids
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk or score/value with placebo	Risk or score/value with corticosteroids				
Prolongation of time to loss of ambulation - not reported	See comment	See comment	Not estimable	-	-	An outcome measure in one 2-year trial (n = 28) . The trial reported a 13-month prolongation of walking with deflazacort among boys who became wheelchair-dependent, but statistical analysis was flawed as it did not take account of participants still walking at study end
Mean change in average muscle score: prednisone - daily dose regimen (0.75 mg/kg/day) Assessed with: MRC scale (higher indicates stronger) Follow-up: 6 months	The mean change in average muscle score was 4.73 units[1]	The mean change in average muscle score in the intervention group was 0.52 units more (0.33 more to 0.71 more)	-	147 (3 RCTs)[2]	⊕⊕⊕◯ **Moderate**[3]	The average muscle score (MRC scale) also showed a clear difference in favour of corticosteroid at 0.3 mg/kg/day and 1.5 mg/kg/day. For other strength outcomes see text

Nine-metre walking/running time: prednisone - daily dose regimen (0.75 mg/kg/day) Assessed with: seconds Follow-up: 6 months	The mean nine-metre walking/running time was 9.1 seconds[4]	The mean nine-metre walking/running time in the intervention group was 2.73 seconds quicker (3.97 quicker to 1.50 quicker)	-	111 (3 RCTs)[5]	⊕⊕⊕○ **Moderate**[3]	For other functional outcomes and corticosteroid doses, see text
4-stair climbing time: prednisone - daily dose regimen (0.75 mg/kg/day) Assessed with: seconds Follow-up: 6 months	The mean 4-stair climbing time was 7.40 seconds	The mean 4-stair climbing time in the intervention group was 3.09 seconds quicker (4.33 quicker to 1.85 quicker)	-	152 (4 RCTs)[6]	⊕⊕⊕○ **Moderate**[3]	For other functional outcomes and corticosteroid doses, see text
Mean % weight gain: prednisone - daily dose regimen (0.75 mg/kg/day) Follow-up: 6 months[8]	The mean %weight gain was 6.95 %	The mean % weight gain in the intervention group was 9.27% more (6.87% more to 11.68% more)	-	126 (2 RCTs)[7]	⊕⊕⊕○ **Moderate**[3]	For other prednisone doses, see text. 1. 09% more weight gain reported with deflazacort (2 mg/kg alternate days) than with placebo (mean gain 25.5%)
Behavioural changes - prednisone (0.75 mg/kg/day) Follow-up: 6 months	500 per 1000	695 per 1000 (470 to 1000)	RR 1.39 (0.94 to 2.06)	135 (2 RCTs)	⊕⊕⊕○ **Moderate**[3]	For other doses, see text
Fractures Follow-up: 6 months	1 participant receiving deflazacort had a pathological fracture of tibia. An arm fracture occurred in the placebo group of a prednisone trial and a traumatic fracture of femur occurred in the placebo phase of a cross-over prednisone trial		-	143 (3 RCTs)	-	None of the included studies measured bone densitometry. A 6-month trial is too short to adequately assess long-term side effects. Other trials did not com-

				ment on the occurrence of fractures

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **MRC**: Medical Research Council; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Mean of mean control group values.
[2]Two additional trials (6 and 12 months' duration), which could not be included in the meta-analysis, also demonstrated improvements in muscle strength over placebo with daily or intermittent prednisone 0.75 mg/kg/day - see text for details (Beenakker 2005; Hu 2015).
[3]Single downgrading for unclear risk of allocation bias and possible publication bias.
[4]Mean of the mean control group values at 6 months from Griggs 1991, Hu 2015 and Mendell 1989 (data are not provided in Rahman 2001 report).
[5]Two additional trials (6 and 12 months' duration), which could not be included in the meta-analysis, also demonstrated improvements in timed walk over placebo with daily or intermittent prednisone 0.75 mg/kg/day - see text for details (Beenakker 2005; Hu 2015).
[6]An additional 6-month trial, which could not be included in the meta-analysis, also demonstrated improvements in 4-stair climb over placebo with intermittent prednisone (0.75 mg/kg/day given for the first 10 days of every month for six months) - see text for details (Beenakker 2005; Hu 2015).
[7]Two additional trials (6 and 12 months' duration), which could not be included in the meta-analysis, monitored weight during daily or intermittent prednisone 0.75 mg/kg/day; no clear difference was present between groups at six months (intermittent dosing) or a year; however these results were imprecise - see text for details (Beenakker 2005; Hu 2015).
[8]For details of other dosages and the deflazacort versus placebo comparison see the review text.

BACKGROUND

Description of the condition

Duchenne muscular dystrophy (DMD), which has an incidence of 1 in 3500 to 1 in 5000 male live births (Emery 1991; Mendell 2012), is the most common muscular dystrophy of childhood.

Boys with DMD present in the first five years of life with abnormal gait, inability to run, and difficulty in rising from the floor. Untreated, the combination of muscle weakness and contractures of the tendo Achilles and iliotibial bands leads to loss of independent walking at a mean age of 9.5 years (range 7 to 13 years). Before corticosteroids were routinely used, once these boys become constant wheelchair users, over 50% developed scoliosis. Subclinical cardiomyopathy is very common, but this becomes symptomatic only in about 20% of patients, often in the second decade of life (Frankel 1976; Ishikawa 1995; Ishikawa 1999; Muntoni 2003). The late teen years are marked by progression of respiratory muscle weakness, nocturnal hypoventilation, respiratory failure, and death in late teens or twenties in untreated patients. No curative treatment for DMD is known, but the quality of life and comfort of the patient can be improved by symptomatic physiotherapeutic and medical treatments (Bushby 2003; Dubowitz 1995; Emery 2003; Heckmatt 1989). Provision of respiratory support, with ventilator use at the appropriate stage, can prolong survival into the fourth decade (Eagle 2002; Eagle 2007; Gomez-Merino 2002; Jeppesen 2003).

The DMD gene locus is at Xp21 and codes for a protein named dystrophin (Hoffman 1987). Depending on the type of mutation in the dystrophin gene, there may be a severe reduction or absence of dystrophin in muscle, resulting in DMD (Koenig 1989). Dystrophin localises at the cytoplasmic side of the sarcolemma and binds to a glycoprotein complex (Matsumura 1993; Matsumura 1994; Mendell 1995). This dystrophin-glycoprotein complex provides a link between the cytoskeleton of the muscle fibre and the extracellular matrix. Lack of dystrophin compromises this link and is postulated to lead to muscle fibre degeneration (Deconinck 2007; Petrof 1993; Petrof 1998).

Although DMD is not primarily an immune-mediated disease, some evidence raises the possibility that humoral and cellular immune responses contribute to the pathological processes. This includes invasion of necrotic muscle fibres by macrophages and cytotoxic T-cells (Arahata 1984), complement activation with deposition of membrane attack complexes on necrotic fibres, and expression of HLA class I antigens on the dystrophic muscle fibres (Engel 1982), making them susceptible to T-cell mediated damage. Initial empirical studies of prednisone in DMD (e.g. Drachman 1974) and the above histopathological observations led to trials of immunomodulation therapy with corticosteroids (Angelini 1994; Bäckman 1995; Biggar 2001; Bonifati 2000; Dubowitz 2002; Fenichel 1991a; Fenichel 1991b; Griggs 1991; Griggs 1993; Mendell 1989; Mesa 1991; Sansome 1993), azathioprine (Griggs 1993), and ciclosporin (Sharma 1993). Complimentary DNA (cDNA) microarray studies on the mdx mouse demonstrated a differential gene expression in affected and non-affected muscles (Porter 2003), and a "skeletal muscle molecular signature" dominated by chronic inflammatory response (Porter 2002). A study of cDNA microarray analysis of skeletal muscle from DMD patients reported a variable gene expression pattern that correlated with the severity of dystrophic changes on histological examination (Noguchi 2003). Pescatori 2007 undertook gene expression profiling of skeletal muscle from DMD patients and reported induction of genes involved in the inflammatory response, extracellular matrix remodeling and muscle regeneration, and reduced transcription of genes involved in energy metabolism. Dudley 2006 investigated the interactive effect of mechanical and oxidative stresses in pathogenesis of muscle fibre damage in dystrophin-deficient mdx mice and normal wild-type control mice. Their experiments suggested that sarcolemmal damage in dystrophin deficiency is modulated by synergistic interactions between mechanical and oxidative stresses. Taken together, these quoted studies provide further evidence that the absence of dystrophin, though necessary, is not sufficient to cause the pattern of fibrosis, inflammation, and muscle degeneration and regeneration, characteristic of DMD.

Description of the intervention

Over the last three decades, many studies of the use of prednisone, prednisolone and deflazacort in DMD have been published. In the neuromuscular literature, authors often described these medications as "steroids" (e.g. Dubrovsky 1998) or "corticosteroids" (e.g. Bushby 2004 and Moxley 2005). Corticosteroids (the steroids produced by the adrenal cortex) may have a predominant glucocorticoid or mineralocorticoid activity. The relevant corticosteroids in neuromuscular practice (prednisone, prednisolone, and deflazacort) have a predominant glucocorticoid action, and their dose equivalence, toxicity and possibly, at least one mode of action relates to this glucocorticoid activity.

The commonly used corticosteroids in published trials are prednisone, prednisolone, and deflazacort. The corticosteroid dose used in various trials for prednisolone or its equivalent ranges from 0.3 mg/kg/day to 1.5 mg/kg/day, given daily or on alternate days, or in an intermittent (10 days on, 10 or 20 days off) regimen (Angelini 1994; Beenakker 2005; Escolar 2011; Griggs 1991; Mendell 1989; Dubowitz 2002).

How the intervention might work

The precise mechanism by which corticosteroids increase strength in DMD is not known, but their potential beneficial effects include inhibition of muscle proteolysis (Elia 1981; Rifai 1995), stimulation of myoblast proliferation (Bal 1980), stabilisation of muscle fibre membranes (Jacobs 1996), increase in myogenic re-

pair (Anderson 2000), anti-inflammatory or immunosuppressive effect (Kissel 1991), reduction of cytosolic calcium concentrations (Metzinger 1995; Passaquin 1998; Vandebrouck 1999), up-regulation of utrophin (Pasquini 1995), and differential regulation of genes in muscle fibres (Muntoni 2002).

Why it is important to do this review

Evaluation of the role of corticosteroids in DMD by systematic reviews, such as Wong 2002, Campbell 2003, and Moxley 2005, helped the development of clinical practice parameters (Moxley 2005), and international workshops establishing standards for use of corticosteroids in DMD (Bushby 2004). Although many observers claimed a beneficial effect on muscle strength, the long-term functional benefit remained unclear, and had to be weighed against the short-term and long-term side effects and tolerability of these drugs.

The previous version of this review examined RCT evidence that showed corticosteroid therapy in DMD improved muscle strength and function in the short term (six months), and evidence exists for benefit on strength at two years, although no conclusions can be drawn from two-year timed function data, which are very limited. The most effective prednisone regimen appeared to be 0.75 mg/kg/day given daily. In the short term, adverse effects were significantly more common with corticosteroids than placebo, but not clinically severe. Long-term benefits and hazards of corticosteroid treatment could not be evaluated from the published RCTs at that time. Since the last review, care recommendations for DMD have been published that recommend the use of corticosteroids (Bushby 2010a; Bushby 2010b). However, additional questions important to clinical practice about the choice of corticosteroid, optimal dosage regimens, long-term outcomes, and age of initiation or discontinuation of treatment remain (Bushby 2004; Bushby 2007). Updating systematic reviews such as this one is essential to answer these questions and plan further studies.

OBJECTIVES

To assess the effects of corticosteroids on prolongation of walking ability, muscle strength, functional ability, and quality of life in DMD; to address the question of whether benefit is maintained over the longer term (more than two years); to assess adverse events; and to compare efficacy and adverse effects of different corticosteroid preparations and regimens.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised or quasi-randomised trials of corticosteroids such as prednisone, prednisolone, deflazacort, or others, with a minimum treatment period of three months. (Quasi-randomised trials use a method of allocating participants to different interventions that is not truly random, such as by date of birth, day of the week, or medical record number).

Types of participants

We considered trials involving patients with a definite diagnosis of Duchenne muscular dystrophy (DMD), based on either of the following.

1. The definition of Brooke 1981.
    - Male patient with onset of proximal weakness by five years and elevated serum creatine kinase (CK), together with two of the following minor criteria:
        - muscle hypertrophy/lower limb contractures/toe walking, electrocardiogram (ECG) changes, myopathic electromyogram (EMG) changes, and dystrophic change on muscle biopsy.
2. The European Neuromuscular Centre (ENMC) DMD diagnostic criteria (Emery 1997).
    - Onset of proximal weakness by five years of age, loss of unassisted walking by 13 years, 10-fold or greater elevation of serum CK, dystrophic muscle biopsy, absent or minimal dystrophin on muscle biopsy, and/or Duchenne-type mutation in the dystrophin gene.

Types of interventions

We considered trials examining the effects of any corticosteroid, including prednisone, prednisolone, and deflazacort, compared with placebo or another corticosteroid, or comparing regimens. The minimum treatment period was three months. For placebo comparisons, to analyse the effect of corticosteroids on patients with DMD, we considered the three drugs together as a group. The corticosteroids were reviewed on the basis of their dose equivalence, which is well known (BNF 2016; Frey 1990).

Types of outcome measures

Primary outcomes

Prolongation of time to loss of ambulation (independent walking without long leg calipers) (Heckmatt 1985; Spencer 1962).

Secondary outcomes

1. Strength outcome measures (performed after an intervention period of at least three months) assessed by manual muscle strength testing using Medical Research Council (MRC)

strength scores (MRC 1976), ability to lift weights, or hand-held dynamometry (Beenakker 2001).

2. Functional outcome measures, assessed by functional rating scores such as Motor Ability Score (Scott 1982), Functional Grade (leg function grade) (Brooke 1981; Brooke 1983), and North Star Ambulatory Assessment score (Ricotti 2016; Scott 2012), or functional tests, such as timed walk, time taken to rise from the floor (Gowers' time), and four-stair climbing time (Brooke 1981; Brooke 1983; Scott 1982).

3. Pulmonary function - forced vital capacity (FVC)

4. Quality of life, assessed by a validated measure, such as the Pediatric Quality of Life Inventory (PedsQL) Neuromuscular Model (Davis 2010)

5. Adverse events (noted during treatment or up to one year after cessation of treatment), including:

- deaths;
- life-threatening infections;
- abnormal behaviour, e.g. irritability, hyperactivity, euphoria, mood lability, depression;
- cushingoid appearance;
- fractures (if data were available beyond one year after cessation of treatment they were collected);
- hyperglycaemia, glycosuria;
- hypertension;
- weight gain;
- height restriction;
- cataracts

Search methods for identification of studies

Electronic searches

On 16 February 2016, we searched for eligible trials in the Cochrane Neuromuscular Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Register of Studies Online (16 February 2016), MEDLINE (January 1966 to February 2016), EMBASE (January 1980 to February 2016), CINAHL Plus (January 1937 to February 2016), and LILACS (January 1982 to February 2016).

On 26 April 2016 we searched ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/).

The detailed search strategies are in the appendices: Appendix 1 (Cochrane Neuromuscular Specialised Register), Appendix 2 (CENTRAL), Appendix 3 (MEDLINE), Appendix 4 (EMBASE), Appendix 5 (CINAHL Plus), Appendix 6 (LILACS), and Appendix 7 (clinical trials registers).

Searching other resources

We wrote to authors of published studies and other experts in this disease to help identify other trials. We checked all references in the identified trials and contacted trial authors to identify any additional published or unpublished data, or other trials.

Data collection and analysis

Selection of studies

One review author (EM) independently screened the initial search of all the databases and reference lists to identify citations with potential relevance to the review. EM obtained the full text of selected articles (translated into English where required) and using predefined eligibility criteria, selected trials for inclusion in the review. AM and TK checked and agreed study selection. Review authors were not blinded to trial authors, journal or results. Discussion between the review authors and, if necessary, the involvement of a third party (editor in charge of the review) resolved disagreements when they occurred.

We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and 'Characteristics of excluded studies' table.

Data extraction and management

For the earlier versions of this review, one review author entered data into Review Manager 5 (RevMan) (RevMan 2014) and the then Review Group Co-ordinator checked the data entry. For this update two review authors (EM and RB) extracted data for the newly included studies and RB entered data into RevMan. EM checked the data entry.

Assessment of risk of bias in included studies

Two review authors (EM and RB) independently assessed the risk of bias in each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion. We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains

listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.
When considering treatment effects, we took into account the risk of bias for the studies that contribute to that outcome.

Measures of treatment effect

For dichotomous outcomes we reported risk ratios (RRs) with a 95% confidence interval (CI). For continuous outcomes we reported mean differences (MDs) with a corresponding 95% CI when the outcomes were measured in the same units in each trial. We reported calculations of MD and 95% CI from Review Manager 5 in preference to values given in trial reports, where different (e.g. because of rounding), for consistency of approach across the review

Unit of analysis issues

We used the generic inverse variance (GIV) method in RevMan when analyses included cross-over studies.

Dealing with missing data

We sought full reports from authors where trials were published in abstract form, presented at meetings or presented as posters, and we contacted trial authors to obtain missing or ambiguously reported data. Because a number of the published papers gave only P values and means or differences (Griggs 1991; Mendell 1989), we inferred the standard deviations (SDs) and other quantities required for the RevMan meta-analysis by inverting the P value calculations. Care was required by a statistician to obtain reasonable values from what were sometimes very small and 'rounded' P values. One study reported the difference (and P values) in responses as daily rate of change, obtained from a regression using data from a six-month follow-up period (Beenakker 2005). We scaled up the response to 24 weeks (six months) equivalent, and deduced the standard error (SE) from the P values, assuming they had been obtained using a normal (the 1.96 cut-off) rather than a t-test, because RevMan assumes normality, and any other approach would give conflicting results. However, the P values were sometimes very small and rounding errors may make the results very approximate, so results using these inferred SEs have to be interpreted cautiously.

Assessment of heterogeneity

We conducted meta-analysis only when clinically appropriate. We assessed statistical heterogeneity using the I^2 statistic (Higgins 2011). We used a random-effects meta-analysis in all cases, even when the heterogeneity was low.

Assessment of reporting biases

The review included too few trials in any one analysis to reliably assess small study effects using funnel plots. The *Cochrane Handbook for Systematic Reviews of Interventions* recommends that tests for funnel plot asymmetry are only used when at least 10 studies are included in a meta-analysis (Higgins 2011).

Data synthesis

Where appropriate, we pooled estimates from individual studies to obtain overall estimates and 95% CIs. For continuous outcome measures we did this using the MD with corresponding 95% CIs. The MD is a method of meta-analysis used to combine differences between treatment effects from different studies when the outcomes are measured in the same units in each trial. It averages the differences from the studies involved in the meta-analysis, weighting them according to precision of the effect estimate.
If any of the studies using a common outcome measure did not report the SD or we could not deduce it, we deduced the SE and pooled estimates from the individual studies using the Revman GIV facility to obtain overall estimates and 95% CIs. By this method, the weight given to each study is chosen to be the inverse of the variance of the effect estimate (i.e. one over the square of its standard error). Thus, larger studies, which have smaller SEs, receive more weight than smaller studies, which have larger SEs. This choice of weight minimises the imprecision (uncertainty) of the pooled effect estimate. For dichotomous outcomes, we used RRs with corresponding 95% CI. To include an additional study in GIV meta-analyses at this update, we entered available data into the calculator tool available in RevMan to produce a mean and SE with 95% CI.

'Summary of findings' tables

We included 'Summary of findings' tables for each main comparison. We assessed the evidence for key outcomes using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias). We graded the evidence as high, moderate, low, or very low quality using these criteria, providing a rationale for any decisions to downgrade the evidence. We included the following outcomes in these tables.

1. Prolongation of time to loss of ambulation (independent walking without long leg calipers).
2. Strength outcome measures (performed after an intervention period of at least three months).
3. Functional outcome measures: walking times, such as time taken to walk 30 feet (Brooke 1981; Brooke 1983; Scott 1982), and four-stair climbing time.
4. Adverse events:
    - weight gain;
    - fractures (if data were available beyond one year after cessation of treatment they were collected);

- abnormal behaviour such as irritability, hyperactivity, euphoria, mood lability, and depression.

Where data for several prednisolone/prednisone doses were reported, we reported the data for 0.75 mg/kg/day daily in the 'Summary of findings' tables, as this dose is most commonly used in clinical practice. We limited the adverse events reported in the 'Summary of findings' tables to those that commonly cause patients to cease treatment with corticosteroids. For efficacy outcomes, in addition to the primary outcome (prolongation of walking), we chose strength and functional outcomes that reflect daily activities most closely (speed of walking and climbing stairs).

Subgroup analysis and investigation of heterogeneity

We investigated the possibility of heterogeneity of treatment effect differences among studies with appropriate tests.

It was not possible to carry out subgroup analyses (e.g. for age at initiation of corticosteroid: less than seven years old or seven years or older) as these data were not available for individual studies.

Sensitivity analysis

We performed a sensitivity analysis removing trials assessed at high risk of bias for any domain.

RESULTS

Description of studies

Results of the search

The number of papers found by the first electronic searches for this update in April 2015 were: Cochrane Neuromuscular Specialised Register 57, CENTRAL 68, MEDLINE 221 (65 new papers), EMBASE 95 (36 new papers), CINAHL Plus 39 (16 new papers), and LILACS 3, with a further 84 references (57 after removal of duplicates) from a late search in February 2016 (Register 17, CENTRAL 18, MEDLINE 10, EMBASE 29, CINAHL 10, and LILACS 0). We identified two additional records from reference lists of included studies.

Simple searches of clinical trials registries in April 2016 revealed 13 references in ClinicalTrials.gov and 16 references in the International Clinical Trials Registry Platform. From these we identified two trial reports: CTRI/2009/091/000738, which is an ongoing trial, and ACTRN12605000075684, which did not provide enough information for eligibility to be assessed. Although listed as recruiting (as of April 2016), this trial was registered on ICTRP in 2005.

After deduplicating the new references above in the Cochrane Register of Studies software or manually, we obtained 163 new references.

For the previous version of the review, six studies met the inclusion criteria and had been published in full in peer reviewed journals (Angelini 1994; Bäckman 1995; Beenakker 2005; Griggs 1991; Mendell 1989; Rahman 2001). All six trials randomised participants to corticosteroids against placebo (five to prednisolone or prednisone for six months and one to deflazacort for two years).

In this update, we identified six additional trials for inclusion:

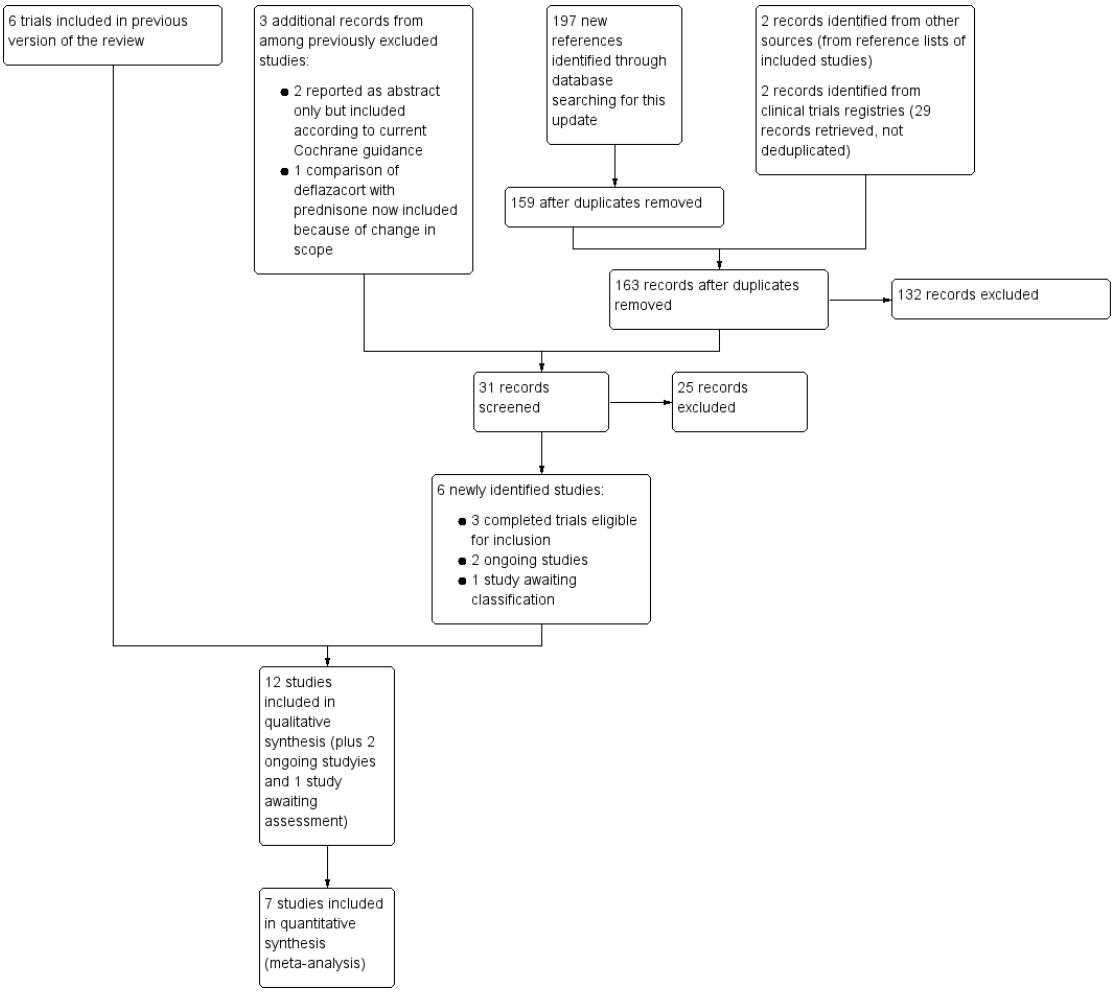
- three new randomised studies published since the last version of the review (Escolar 2011; Hu 2015; Karimzadeh 2012);
- one previously excluded study comparing deflazacort and prednisone (Bonifati 2000), now eligible because of the expanded scope of the review to evaluate evidence from comparative trials of corticosteroids;
- two previously excluded studies published only as abstracts, as this is current Cochrane practice (Brooke 1996; Todorovic 1998). However, we were unable to obtain further data from the trial authors.

Two additional studies are ongoing (CTRI/2009/091/000738; Guglieri 2015).

In summary therefore, we included 12 studies (667 participants) at this update (Angelini 1994; Bäckman 1995; Beenakker 2005; Bonifati 2000; Brooke 1996; Escolar 2011; Griggs 1991; Hu 2015; Karimzadeh 2012; Mendell 1989; Rahman 2001; Todorovic 1998), additionally listing CTRI/2009/091/000738 and Guglieri 2015 as ongoing.

See Figure 1 for a flow chart illustrating the study selection process.

Figure 1. Study flow diagram.



Included studies

Corticosteroids versus placebo

See Characteristics of included studies.

We included data from five randomised, parallel-group, double-blind studies of corticosteroids versus placebo (Angelini 1994; Griggs 1991; Hu 2015; Mendell 1989; Rahman 2001), and one randomised, placebo-controlled, cross-over trial (Beenakker 2005). Overall, these studies comprised 332 participants. The 315 participants in the randomised parallel-group trials involved 88 in the placebo groups and 161 in the corticosteroid treatment groups (Angelini 1994; Griggs 1991; Hu 2015; Mendell 1989; Rahman 2001). One hundred and one of the 218 participants in the control groups and 164 of the 197 in the corticosteroid groups were walking, either independently or with the help of long leg braces. The corticosteroid treatment groups included prednisone (n = 170), prednisolone (n = 10), and deflazacort (n = 17). Beenakker 2005 was a cross-over study comprising 17 boys, all walking independently, who received prednisone during the six-month active treatment period.

In three of the included studies, all lasting six months, treatment groups received prednisone or prednisolone in a daily dose regimen (Griggs 1991; Mendell 1989; Rahman 2001). These studies included a total of 144 participants in the treatment group and 77 in the placebo group. Prednisone is broken down in the body to prednisolone and they are equipotent in glucocorticoid effect (Azarnoff 1975; Frey 1990).

Beenakker 2005, used an intermittent regimen, prednisone 0.75

mg/kg/day given for the first 10 days of every month, in the active treatment phase. The participants were 17 independently ambulant boys. One study (n = 28) used deflazacort (2 mg/kg body weight on alternate days for two years) in the treatment group (Angelini 1994). This was the only study to address the primary outcome measure of prolongation of walking.

Hu 2015 was a placebo-controlled study of 66 independently ambulant boys and the only placebo-controlled corticosteroid study published since the previous update of this review. The intervention was prednisone 0.75 mg/kg/day given daily for a year.

The secondary outcome measures of this review were assessed by different parameters and assessment tools in the five prednisolone/prednisone studies that were published in full and which provided data for our secondary outcomes. However, Mendell 1989 and Griggs 1991, the two studies that comprised 80% of the participants for all the four included and analysed studies, used the same outcome measures, as described in Brooke 1981 (see Characteristics of included studies). Beenakker 2005, Hu 2015, and Rahman 2001, the other three published studies of prednisolone or prednisone, also used some of these outcome measures.

Bäckman 1995, a cross-over trial, reported efficacy as the numbers improving (improved or unchanged across two-thirds or more of the tested measures) and numbers deteriorating during treatment with prednisolone (0.35 mg/kg/day) or placebo. The participants were 37 boys with Duchenne muscular dystrophy (DMD) (22 of whom were ambulant) and four with Becker muscular dystrophy. Although outcome data were not adequate for inclusion in the review, the trial provided some adverse event data.

Todorovic 1998 was a 20-month study involving 34 boys, who received prednisone 2 mg/kg alternate days (high dose) or placebo. No results have been published.

Brooke 1996 was a 12-month randomised, double-blind comparative trial with four arms: placebo, prednisone 0.75 mg/kg, deflazacort 0.9 mg/kg, and deflazacort 1.2 mg/kg, published in abstract form. We presume, although the abstract does not specify, that these were daily doses. After three months, participants in the placebo group were randomised to one of the three active treatment arms and followed up for a further nine months. The abstract presents data for the average muscle score (the method of measurement is not defined), and for weight gain as a percentage of baseline weight. This study was large, at 196 randomised participants, but we were unable to obtain data to allow for any analysis.

Weekend-only versus daily prednisone

Only one randomised study provided data for a comparison of different prednisone dosing regimes. Escolar 2011 performed a double-blind placebo-controlled randomised study comparing daily prednisone 0.75 mg/kg/day (and weekend placebo) with weekend-only prednisone 5 mg/kg/weekend day (and daily placebo), taken over a 12-month period. The study comprised 64 eligible participants with a mean age of 7.3 years (range 4 to 10), all of whom were ambulant at the start. The study did not measure the primary outcome of this review, prolongation of time to loss of ambulation, but assessed secondary outcomes at 12 months using multiple measures, including the change from baseline of quantitative muscle testing (QMT) arm and leg scores, and mean body mass index (BMI).

Deflazacort versus prednisone

Bonifati 2000, a double-blind study, randomised 18 participants to treatment with 0.75 mg/kg/day prednisone (mean age 7.5 years, range, 5.1 to 10) or 0.9 mg/kg/day deflazacort (mean age 8.6 years, range 5.3 to 14.6) for 12 months. Investigators assessed muscle strength and function using a summed Medical Research Council (MRC) score of four muscles (two right upper limb, two right lower limb) and a summed functional score comprising several timed assessments including a 10-metre walk, rise from chair and floor, and four-stair climbing. Mean weight increase after 12 months was expressed as a percentage of initial weight. The trial authors presented outcome data for MRC scores, functional scores, and weight increase graphically, limiting full analysis. They tabulated adverse events. We requested further data but received no response from study authors.

Karimzadeh 2012 initially randomised 34 participants to either prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day. Eight early dropouts occurred, but the trial continued for 12 months with 14 participants in the deflazacort group (mean age 7.1 years, range 3.2 to 10.5) and 12 in the prednisone group (mean age 7.37 years, range 6 to 10). In total, the study ran for 18 months, but at 12 months a further four participants were excluded from the prednisone group due to unacceptable weight gain; these four also had poor motor function scores. The report presented limited outcome data at 12 and 18 months. We contacted study authors for more data but did not receive a reply.

As noted above, Brooke 1996 also studied this comparison but did not provide data for analysis.

Excluded studies

Non-randomised excluded studies

See Characteristics of excluded studies.

We excluded three RCTs. These were: a comparison of prednisone and azathioprine with no placebo group (Griggs 1993), a study of deflazacort versus prednisolone in which the high dropout rate invalidated results (Pradhan 2006), and a study of ayurvedic medicine, prednisone and placebo in which investigators modified the design mid-trial (Vasanth 1996).

We also listed non-randomised studies in the excluded studies. Thirty-eight of these were fully published (Alman 2004; Balaban 2005; Biggar 2001; Biggar 2004; Biggar 2006; Bonifati 2006;

Bothwell 2003; Brooke 1987; Connolly 2002; Daftary 2007; DeSilva 1987; Drachman 1974; Dubowitz 2002; Fenichel 1991a; Fenichel 1991b; Henricson 2013; Houde 2008; Kinali 2002; Kinali 2007; King 2007; Markham 2005; Mayhew 2013; Mazzone 2013; Merlini 2003; Mesa 1991; Parreira 2007; Reitter 1995; Ricotti 2013; Sansome 1993; Schara 2001; Schram 2013; Siegel 1974; Silva 2012; Silversides 2003; Simon 2011; Takeuchi 2013; Yilmaz 2004). Eight non-randomised studies were published in abstract format only (Ahlander 2003; Angelini 1995; Aviles 1982; de Groot 2002; Dubrovsky 1999; Pandya 2001; Resende 2001; Tunca 2001). One paper was a discussion of corticosteroid use (Griggs 2013). We identified and excluded six review articles reporting the various studies (Angelini 2007; Angelini 2012; Campbell 2003; Flanigan 2012; McAdam 2012; Wong 2002).

Ongoing studies

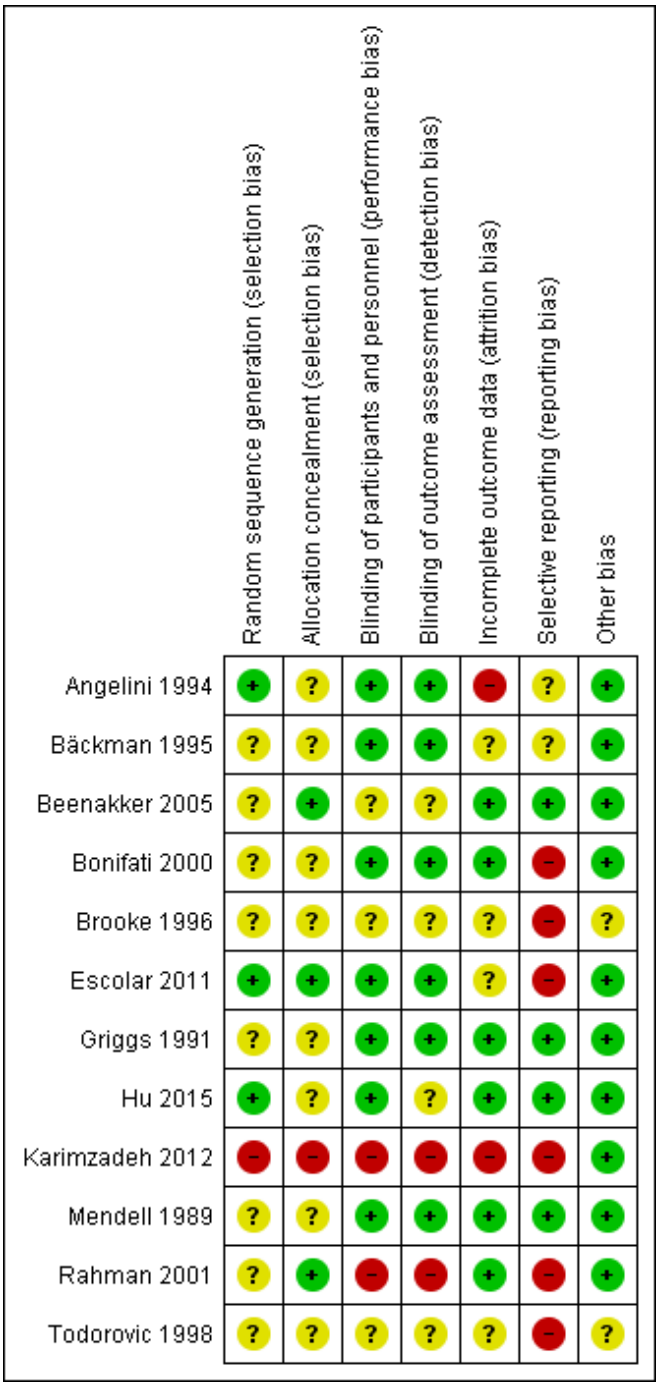
See Characteristics of ongoing studies.

Guglieri 2015 is a large ongoing randomised double-blind study taking place at 40 centres throughout the US, UK, Canada, Germany, Italy, and Spain. This study is comparing three corticosteroid regimens for efficacy and adverse events: prednisone 0.75 mg/kg/day, prednisone 0.75 mg/kg/day switching between 10 days on and 10 days off treatment, and deflazacort 0.9 mg/kg/day daily. The planned follow-up period is three to five years. No outcome data are yet available.

Risk of bias in included studies

Figure 2 illustrates the review authors' 'Risk of bias' assessments of included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Although all the studies were described as randomised, most reports did not provide enough detail to assess whether the method of randomisation was adequate. We were able to determine that three studies were at low risk of bias (Angelini 1994; Hu 2015; Escolar 2011), and one was at high risk of bias (Karimzadeh 2012). For allocation concealment, we assessed three trials at low risk of bias on the basis of information provided by the trial authors (Beenakker 2005; Escolar 2011; Rahman 2001), eight studies at unclear risk of bias, as the reports provided no information, and one study at high risk of bias (Karimzadeh 2012) (see Characteristics of included studies).

Blinding

Trial authors described eight of the 12 studies as double blind, but we considered only six of them at low risk of both performance and detection bias (Angelini 1994; Bäckman 1995; Bonifati 2000; Escolar 2011; Griggs 1991; Mendell 1989). Hu 2015 blinded participants but it is unclear whether blinding of outcome assessors or investigators was attempted. Three studies provided too little information to form a judgement (Brooke 1996; Beenakker 2005; Todorovic 1998). We judged both Rahman 2001, which used a vitamin control intervention, and Karimzadeh 2012, a single-blind study, at high risk of bias.

Incomplete outcome data

Six of the 12 studies described withdrawals and dropouts and we judged these studies at low risk of bias (Beenakker 2005; Bonifati 2000; Griggs 1991; Hu 2015; Mendell 1989; Rahman 2001). Trialists described dropouts from Griggs 1991 in a subsequent sequential study (Griggs 1993). Rahman 2001 reported one dropout and described it in response to the Cochrane authors' request.
The risk of attrition bias was unclear in four studies (Bäckman 1995; Brooke 1996; Escolar 2011; Todorovic 1998). . Karimzadeh 2012 was at high risk of attrition bias, as dropouts were those with worse outcomes. Most two-year analyses in Angelini 1994 included fewer than 50% of the randomised participants and we judged it at high risk of attrition bias.

Selective reporting

Reporting bias was difficult to assess as trial registration records and protocols are not available for earlier trials, and outcomes were rarely fully defined in methods. Our assessment of bias was 'high' for six trials and 'unclear' for two. Only Beenakker 2005, Griggs 1991, Hu 2015, and Mendell 1989 had a 'low risk' assessment.

Other potential sources of bias

Brooke 1996 and Todorovic 1998 were reported in abstracts and provided no information to assess the presence of other bias. Our assessment was 'unclear' for these trials and low risk for others.

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroids versus placebo for Duchenne muscular dystrophy; **Summary of findings 2** Weekend-only versus daily prednisone for Duchenne muscular dystrophy; **Summary of findings 3** Deflazacort versus prednisone for Duchenne muscular dystrophy

Corticosteroids versus placebo

Six studies provided data for this comparison (Angelini 1994; Beenakker 2005; Griggs 1991; Hu 2015; Mendell 1989; Rahman 2001). Bäckman 1995, a cross-over trial, reported efficacy as the numbers improving (improved or unchanged across two-thirds or more of the tested measures) and numbers deteriorating. Although these data were not adequate for inclusion in the comparison of outcome measures, the trial did provide adverse event data. The two studies reported in abstract form provided only limited information: Todorovic 1998 reported no usable results and Brooke 1996 provided some numerical data, but with insufficient detail for analysis.
See Summary of findings for the main comparison.

Primary outcome measure: prolongation of time to loss of ambulation

Only Angelini 1994 (n = 28), a two-year study, used prolongation of time to loss of ambulation as an outcome measure. The other studies were of short duration (six months or one year), and not designed to demonstrate prolongation of walking.
Angelini 1994 reported that deflazacort (2 mg/kg on alternate days) prolonged ambulation by 13 months, but the statistical technique used to infer this result was not appropriate. Four of the 17 participants in the deflazacort group became wheelchair dependent, at a mean interval of 33.2 months after randomisation, versus six of 11 placebo participants, at a mean interval of 20.5 months. The trial authors reported the difference of 13 months between these two sets of participants who lost walking ability as "mean prolongation of walking", ignoring the 13 participants in the deflazacort group and five in the placebo group who were still walking at the end of the study. The trialists did not report the age of boys who remained ambulant at the end of the study and this information was not available on contacting the lead investigator. We therefore were not able to construct Kaplan-Meier sur-

vival curves for evaluating prolongation of walking as an outcome measure.

Secondary outcome measures

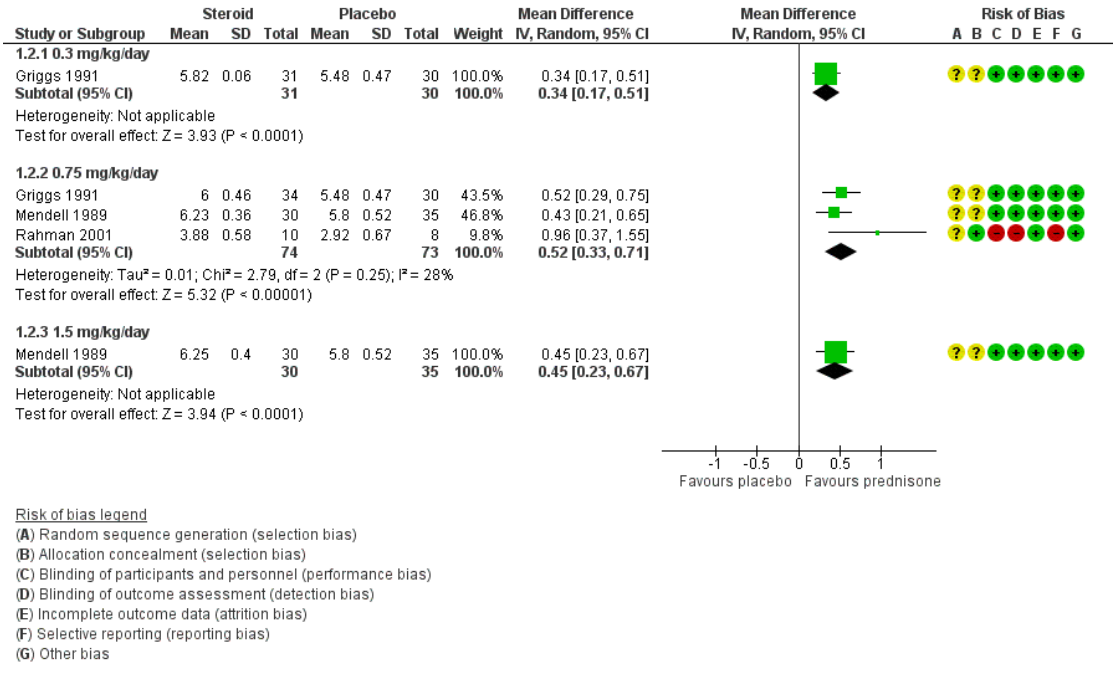
(1) Muscle strength

(a) Average muscle score

Griggs 1991, Mendell 1989 and Rahman 2001 reported muscle strength as an average muscle score (as described in Brooke 1981 and Brooke 1983). The two large studies had one placebo arm and two treatment arms (Griggs 1991; Mendell 1989). Mendell 1989 studied two prednisone dose regimens (0.75 mg/kg/day and 1.5 mg/kg/day), comparing them with a placebo group. Griggs 1991 compared 0.3 mg/kg/day and 0.75 mg/kg/day prednisone regimens with placebo. Hu 2015 studied a 0.75 mg/kg daily prednisone regimen, reporting scores for lower limb muscle strength (right hip flexion and right knee extension) according to the MRC scale expanded to a 10-point scale, at six and 12 months. These data were not suitable for meta-analysis with Griggs 1991, Mendell 1989 and Rahman 2001. Bäckman 1995 evaluated muscle strength in three ways: (a) average muscle strength from 26 muscle groups on the MRC zero to five grading system and the performance scores were added and divided by the number of muscle groups to get the average muscle strength; (b) isometric muscle strength, measured in 24 muscle groups with a Penny and Giles myometer; and (c) hand-grip strength measured bilaterally with a strain gauge. The publication did not report data, nor could the review authors obtain data from the surviving study author. Angelini 1994 measured muscle strength in two ways: (a) MRC index calculated by assessing four limb muscle groups using the MRC scale; and (b) myometry (but the number of muscle groups tested and the myometer used were not described). Beenakker 2005 assessed changes in muscle force in nine muscle groups with hand-held dynamometry (Beenakker 2001; Beenakker 2005b). Brooke 1996 was a four-way comparison of two doses of deflazacort (0.9 mg/kg and 1.2 mg/kg), prednisone (0.75 mg/kg), and placebo, which reported average change in muscle strength at three months ("based on a standardised method used in several previous trials").

Analysis of pooled data from three trials (n = 147) demonstrated a statistically significant improvement in average muscle score in the prednisone 0.75 mg/kg/day group versus placebo, with a mean difference (MD) of 0.52 (95% confidence interval (CI) 0.33 to 0.71) after six months of treatment; moderate quality evidence (Griggs 1991; Mendell 1989; Rahman 2001) (see Analysis 1.2; Figure 3; Summary of findings for the main comparison). Removal of Rahman 2001, the trial at high risk of bias, had no substantial effect on the result (MD 0.47, 95% CI 0.32 to 0.63).

Figure 3. Forest plot of comparison: 1 Glucocorticoid corticosteroids versus placebo, outcome: 1.1 MRC - Average muscle score after 6 months of treatment - prednisone.



Griggs 1991 (n = 61) also compared prednisone 0.3 mg/kg/day with placebo and after six months of treatment there was statistically significant improvement in average muscle score in favour of the prednisone group, with a MD of 0.34 (95% CI 0.17 to 0.51) (see Analysis 1.2).

Mendell 1989 (n = 65) also compared prednisone 1.5 mg/kg/day with placebo and after six months of treatment there was a statistically significant improvement in average muscle score in the prednisone group, with a MD of 0.45 (95% CI 0.23 to 0.67) (see Analysis 1.2).

Beenakker 2005 (n = 16), a cross-over study, compared an intermittent regimen of prednisone (0.75 mg/kg/day given for the first 10 days of every month for six months) with placebo. There was a statistically significant difference in the muscle force during the prednisone phase compared to the placebo phase. Using the standard errors (SEs) inferred from the quoted P values, the RevMan GIV facility gave a difference in favour of prednisone of 99.2 N (95% CI 15.63 to 182.81) (see Analysis 1.20).

Brooke 1996 (n = 196) reported an average change in muscle strength ("based on a standardised method used in several previous trials") after three months. Reported changes were -0.1 with placebo, +0.27 with prednisone 0.75 mg/kg, +0.8 with deflazacort 0.9 mg/kg, and +0.26 with deflazacort 1.2 mg/kg. For all comparisons versus placebo, P < 0.0001. The abstract provided no participant numbers for intervention groups, or standard deviation (SD).

Hu 2015 reported that lower limb muscle strength grade "remained stable" in the prednisone group, whereas it declined in the placebo group. The MD between groups favoured prednisone over placebo for both hip flexion and knee extension at six months (MD 0.64, 95% CI 0.20 to 1.08 and MD 0.71, 95% CI 0.27 to 1.15, respectively; n = 63) and at 12 months (MD 1.27, 95% CI 0.74 to 1.80 and MD 1.23, 95% CI 0.71 to 1.75, respectively; n = 58) (Analysis 1.4; Analysis 1.5).

Angelini 1994 was a 24-month trial comparing deflazacort (2 mg/kg administered on alternate days) with placebo. Treatment continued until the participants became wheelchair dependent. After six months, the MD for change in MRC index (%) was similar in the deflazacort and placebo groups (MD 1.97, 95% CI -1.79 to 5.73, n = 26); after 24 months the difference favoured deflazacort (MD 6.60, 95% CI -3.79 to 16.99, n = 13) (Analysis 1.3).

(b) Ability to lift weights

Ability to lift standardised weights (as described in Brooke 1981) was assessed and reported in two studies (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a statistically significant improvement in lifting weights in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo, with a MD of 0.75 (95% CI 0.50 to 0.99, n = 94) (see Analysis 1.15).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo, and after six months of treatment there was a statistically significant improvement in lifting weights in the prednisone group, with a MD of 0.38 (95% CI 0.13 to 0.63, n = 39) (see Analysis 1.15).

Mendell 1989 compared prednisone 1.5 mg/kg/day with placebo and after six months of treatment there was a statistically significant improvement in lifting weights in the prednisone group, with a MD of 0.96 (95% CI 0.52 to 1.40, n = 57) (see Analysis 1.15).

(2) Functional outcome measures

(a) Time taken to rise from the floor (Gowers' time)

Five studies provided six-month data on time taken to rise to the standing position (as described in Brooke 1981) (Beenakker 2005; Griggs 1991; Hu 2015; Mendell 1989; Rahman 2001). A decrease in Gowers' time indicates better ability to rise from the floor, representing improvement.

Beenakker 2005, a cross-over study in which 16 participants were analysed (17 randomised), compared an intermittent regimen of prednisone (0.75 mg/kg/day given for the first 10 days of every month, for six months) with placebo. There was a statistically significant difference in the time taken to rise from the floor during the prednisone phase compared to the rising time in the placebo phase. Using the SEs inferred from the quoted P values, the RevMan GIV facility gave a difference in favour of prednisone of -1.08 seconds (95% CI -2.51 to 0.35) (see Analysis 1.6).

Analysis of pooled data from Griggs 1991, Mendell 1989, Hu 2015, and Rahman 2001 demonstrated statistically significant improvement in the prednisone 0.75 mg/kg/day group compared with placebo after six months of treatment. Using the SEs inferred from the quoted P values for the older studies, or derived using the RevMan calculator function from the Hu 2015 group means, SD and N, the RevMan GIV facility gave a difference in favour of prednisone of -2.28 seconds (95% CI -3.12 to -1.44) (see Analysis 1.6). Removal of Rahman 2001 had no substantial effect on the result (MD -2.22, 95% CI -3.17 to -1.26),

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. The GIV analysis showed that after six months of treatment, there was a difference in favour of prednisone of -1.59 seconds (95% CI -3.75 to 0.57) (see Analysis 1.6).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with

placebo. The GIV analysis showed that after six months of treatment, there was a difference in favour of prednisone of -2.74 seconds (95% CI -3.98 to -1.50) (see Analysis 1.6).

Hu 2015 compared the effects of daily 12-month treatment with 0.75 mg/kg/day prednisone to placebo (n = 60). The results indicated a MD in Gowers' time post treatment in favour of prednisone of -2.21 seconds (95% CI -3.88 to -0.54) (see Analysis 1.6).

Angelini 1994 reported change in Gowers' time (units assumed to be seconds) with no significant difference between deflazacort (2 mg/kg alternate days) and placebo at 6 months (MD -2.06, 95% CI -6.70 to 2.58, n = 19) or 24 months (MD -4.86, 95% CI -11.01 to 1.29, n = 10) (Analysis 1.7; Analysis 1.9).

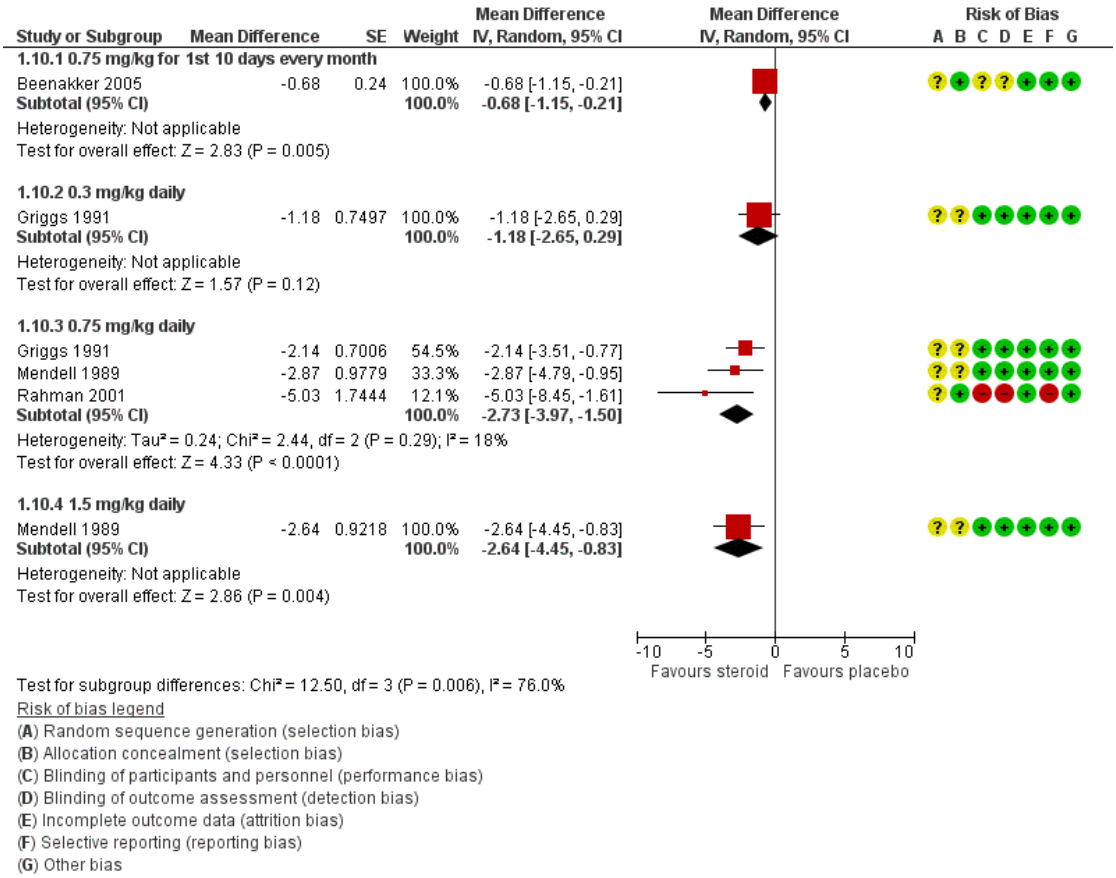
(b) Timed walk

The time taken to walk nine metres (as described in Brooke 1981) was reported in four studies (Beenakker 2005; Griggs 1991; Mendell 1989; Rahman 2001). A decrease in walking time indicates ability to walk faster, representing improvement.

Beenakker 2005 compared an intermittent regimen of prednisone (0.75 mg/kg/day given for the first 10 days of every month, for six months) with placebo, in a cross-over design study. There was a statistically significant difference in nine metres running time during the prednisone phase compared to the running time in the placebo phase. Using the SEs inferred from the quoted P values, the RevMan GIV facility gave a difference in favour of prednisone of -0.68 seconds (95% CI -1.15 to -0.21, n = 16) (see Analysis 1.10).

Analysis of pooled data from Griggs 1991, Mendell 1989, and Rahman 2001 demonstrated a statistically significant improvement in nine-metre walking time in the prednisone 0.75 mg/kg/day group after six months of treatment. Using the SEs inferred from the quoted P values, the RevMan GIV facility gave a difference in favour of prednisone of -2.73 seconds (95% CI -3.97 to -1.50, n = 111; moderate quality evidence) (see Analysis 1.10; Figure 4; Summary of findings for the main comparison). Removal of Rahman 2001 had no substantial effect on the result (MD -2.39 seconds, 95% CI -3.50 to -1.27).

Figure 4. Forest plot of comparison: 1 Glucocorticoid corticosteroids versus placebo, outcome: 1.7 Nine-metre walking/running time after 6 months of treatment - prednisone.



Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. The GIV analysis showed that after six months of treatment, there was a difference in favour of prednisone of -1.18 (95% CI -2.65 to 0.29, n = 40) (see Analysis 1.10).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo. The GIV analysis showed that after six months of treatment, there was a difference in favour of prednisone of -2.64 seconds (95% CI -4.45 to -0.83, n = 57) (see Analysis 1.10).

Hu 2015 reported time to walk 10 metres, which prevented inclusion of data in the meta-analysis. The trial reported a post treatment MD (seconds) in favour of daily prednisone 0.75 mg/kg/day over placebo; at six months, the MD was -0.94 (95% CI -1.73 to -0.15, n = 63), and at one year -1.71 seconds (95% CI -2.74 to -0.68, n = 58) (see Analysis 1.12; Analysis 1.13.

Angelini 1994 reported change in timed walk (we assume in seconds); the MD favoured deflazacort (2 mg/kg alternate days) at six months (MD -3.01, 95% CI -4.76 to -1.26, n = 23), but no clear difference was present at 24 months (MD -0.67, 95% CI -2.37 to 1.03, n = 12) (see Analysis 1.11; Analysis 1.14).

(c) Four-stair climbing time

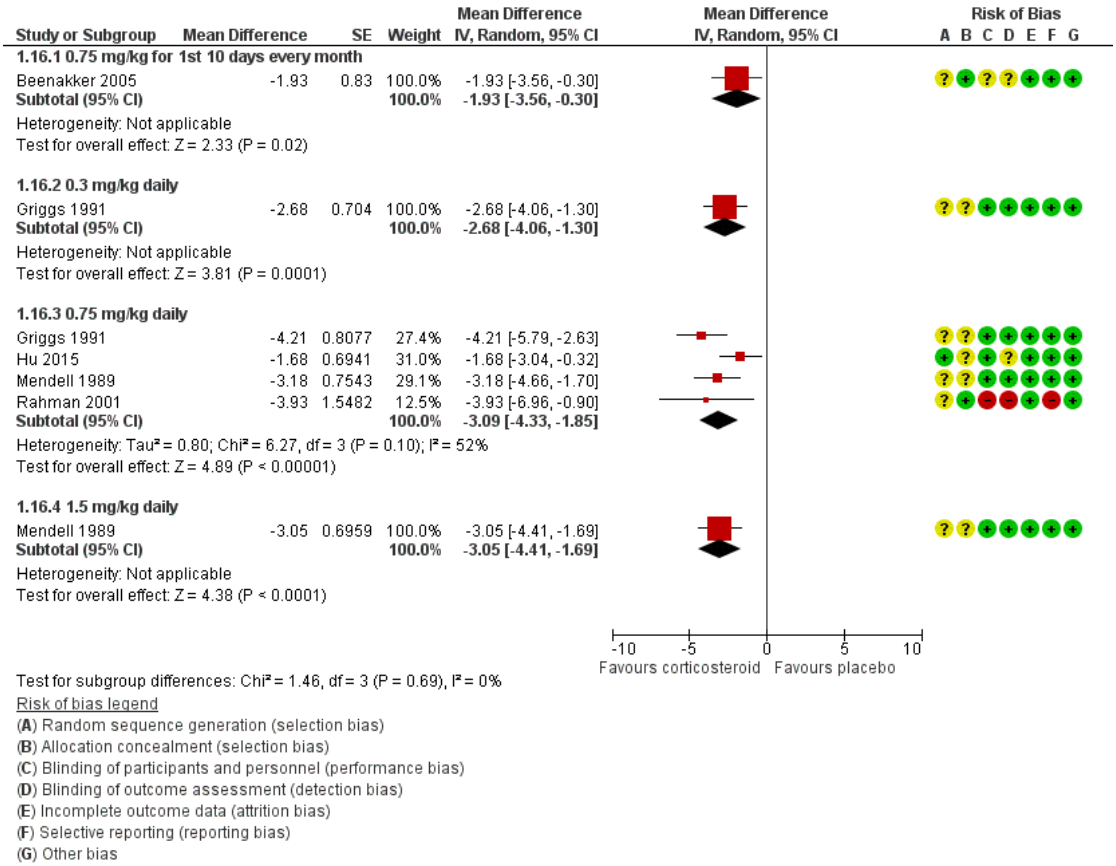
Five studies reported the time taken to climb four standardised stairs (as described in Brooke 1981) at six months (Beenakker 2005; Griggs 1991; Hu 2015; Mendell 1989; Rahman 2001). A decrease in four-stair climbing time indicates ability to ascend stairs faster, representing improvement.

Beenakker 2005 compared an intermittent regimen of prednisone (0.75 mg/kg/day given for the first 10 days of every month for six months) with placebo, in a cross-over design study. There was a statistically significant difference in four-stair climbing time during the prednisone phase compared to the placebo phase. Using the SEs inferred from the quoted P values the RevMan GIV facility gave a difference in favour of prednisone of -1.93 seconds (95% CI -3.56 to -0.30, n = 16) at 6 months (see Analysis 1.16). Analysis of pooled data from Griggs 1991, Mendell 1989, Hu

2015, and Rahman 2001 demonstrated a statistically significant benefit over placebo in four-stair climbing time in the prednisone 0.75 mg/kg/day group after six months of treatment. Using the SEs inferred from the quoted P values for the older studies, and using the RevMan calculator tool to derive SE from the Hu 2015 (final values) data, the RevMan GIV facility gave a difference in favour of prednisone of -3.09 seconds (95% CI -4.33 to -1.85, n = 135; moderate quality evidence) (see Analysis 1.16; Summary of findings for the main comparison). Removal of Rahman 2001 had no substantial effect on the result (MD -2.98, 95% CI -4.43 to -1.53), and increased heterogeneity (I^2 = 66%).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. The GIV analysis showed that after six months of treatment, there was a difference in favour of prednisone of -2.68 seconds (95% CI -4.06 to -1.30, n = 32) (see Analysis 1.16; Figure 5).

Figure 5. Forest plot of comparison: 1 Glucocorticoid corticosteroids versus placebo, outcome: 1.11 Four-stair climbing time after 6 months of treatment - prednisone.



Mendell 1989 compared prednisone 1.5 mg/kg/day with placebo. The GIV analysis showed that after six months of treatment, there was a difference in favour of prednisone of -3.05 seconds (95% CI - 4.41 to -1.69, n = 42) (see Analysis 1.16).

Hu 2015 compared daily prednisone 0.75 mg/kg/day with placebo. After a year of treatment, the mean difference in four-stair climb time favoured prednisone, at -1.63 seconds (95% CI -3.07 to -0.19, n = 52) (see Analysis 1.18).

Angelini 1994 reported change in "time, stairs" (not further specified), comparing deflazacort (2 mg/kg alternate days) and placebo. The results (we assume in seconds) were imprecise, allowing for the possibility of effects in either direction, MD -2.96, 95% CI -

7.02 to 1.10, n = 23 at six months, and MD 0.63, 95% CI -4.29 to 5.55, n = 11 at 24 months (see Analysis 1.17; Analysis 1.19).

(d) Leg function grade

Leg function grade (as described in Brooke 1981 and Brooke 1983) was assessed in two studies (Griggs 1991; Mendell 1989). The leg function grade is assessed on a 10-point scale: grade 1 representing ability to walk and climb stairs without assistance; and grade 10 representing confinement to bed. Analysis of pooled data from these studies demonstrated a statistically significant improvement in the prednisone 0.75 mg/kg/day group versus placebo after six months of treatment, with a MD of -0.41 points (95% CI -0.73 to -0.09, n = 129) (see Analysis 1.21).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment the mean improvement in leg function grade was 0.39 points (95% CI 0.01 to 0.79, n = 58) less than in the placebo group (see Analysis 1.21).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo and after six months of treatment the mean improvement in the prednisone group was 0.49 points (95% CI 0.05 to 0.93, n = 68) less than in the placebo group (see Analysis 1.21).

(3) Pulmonary function - forced vital capacity (FVC)

FVC (as described in Brooke 1981) was measured in two studies (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a mean improvement in FVC in the prednisone 0.75 mg/kg/day group, after six months of treatment of 0.17 L more than in the placebo group (95% CI 0.10 to 0.24, n = 127) (see Analysis 1.22).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment the improvement in FVC in the prednisone group was 0.16 L (95% CI 0.05 to 0.27, n = 59) more than in the placebo group (see Analysis 1.22).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo. After six months of treatment the mean improvement in FVC in the prednisone group was 0.14 L (95% CI 0.05 to 0.23, n = 62) more than in the placebo group (see Analysis 1.22).

(4) Quality of life (QoL)

Measured in Beenakker 2005 and Hu 2015.

Beenakker 2005 measured QoL with the DUX-25 at the start and end of both six-month trial periods. This questionnaire covers four domains: physical, emotional, social, and home functioning. The items are scored using a five-point scale. The raw data or statistical analysis of QoL were not available. The QoL did not change significantly during the prednisone period. With every new measurement, however, participants reported a slightly higher QoL, irrespective of the medication given, resulting in a significant improvement in the last measurement on two scales (emotional functioning and the total scale); Beenakker et al considered this to be possibly related to the attention of being involved in a trial.

Hu 2015 assessed child self reported and parent proxy reported quality of life using the Chinese version of PedsQTLM 3.0 NMM (total score). Items are rated on a five-point scale, and transformed linearly to a zero to 100 scale. "Scores were computed as the sum of items divided by the number of items answered." Higher scores indicated better quality of life.

Twenty-nine boys were too young to complete the questionnaire at baseline, being under seven years old. Clear differences in favour of prednisone 0.75 mg/kg/day were present at six and 12 months in self reported and proxy reported quality of life. At six months, the MD for the self reported questionnaire was 10.87, 95% CI 0.64 to 21.10, n = 38 and 9.97, 95% CI 1.96 to 17.98, n = 63, for the proxy reported measure. At 12 months, corresponding values were MD 16.05, 6.46 to 25.64, n = 41 and MD 14.42, 95% CI 5.85 to 22.99, n = 58 (Analysis 1.23; Analysis 1.24).

(5) Adverse events

Adverse events were evaluated by the different investigators as follows.

Mendell 1989 examined the participants for adverse effects in an area separate from that of clinical evaluation at baseline and at one, two, three, and six months after the start of prednisone treatment. Trialists reported data for both treatment and placebo groups.

Griggs 1991 examined the participants and interviewed the parents for adverse effects at baseline and at one, two, three, and six months of treatment. Trialists reported data for both treatment and placebo groups.

Rahman 2001 did not report adverse effect data.

Hu 2015 measured and reported body weight, height, body mass index (BMI) and diastolic blood pressure in prednisone (0.75 mg/kg/day) and control groups at six and 12 months. The report did not provide data on the incidence of other adverse effects for the placebo group; adverse effects occurred in 16 of the 31 children receiving prednisone who completed the 12-month study.

Angelini 1994 monitored the participants every two months of the study for adverse effects. Trialists reported weight gain data for treatment (deflazacort) and placebo groups, but incidence of the other adverse effects only for the deflazacort group.

Bäckman 1995 asked the parents of participants at the end of the study to report any signs or symptoms that could possibly be related to the treatment.

Beenakker 2005 evaluated the adverse effects at each visit by using a standard list that described the corticosteroid-related adverse effects. This included patient and parent interview for symptoms and examination for physical signs relating to adverse effects.

(a) Weight gain

Mendell 1989 and Griggs 1991 reported this adverse event as per

cent weight gain at last visit above baseline (first visit), on the presumption of six months of treatment. As per cent weight gain was only available as the number of participants in each of a set of intervals on the per cent weight gain scale, we derived the mean and SD for each group assuming each individual had the mid-value of the interval in which they fell. The review authors did not use Sheppard's correction for bias in variances obtained using grouped data because the interval widths were variable and the magnitude of the correction for bias in the SDs was found to be less than 2%. Analysis of pooled data from Mendell 1989 and Griggs 1991 demonstrated a statistically significant weight gain in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo, with a MD of 9.27% (95% CI 6.87% to 11.68%, n = 126; moderate quality evidence) (see Analysis 1.25; Summary of findings for the main comparison).

Hu 2015 reported that one participant in the prednisone (0.75 mg/kg/day) group showed obvious weight gain at 12 months (placebo group not reported). However, no clear difference in weight was present between the prednisone and placebo groups at six and 12 months, with wide CIs (Analysis 1.28; Analysis 1.29). Similarly, BMI (kg/m^2) showed no clear difference at six or 12 months, with wide CIs (Analysis 1.30; Analysis 1.31).

Beenakker 2005 compared an intermittent regimen of prednisone (0.75 mg/kg/day given for the first 10 days of every month, for six months) with placebo, in a cross-over design study. They reported the difference and P value in weight as daily rate of change, obtained from a regression using data from a six-month follow-up period. We scaled up the response to 24 weeks (six months) equivalent, and deduced the standard error (SE) from the P values. The mean weight gain during the prednisone phase (2.37 kg) was greater than in the placebo phase (1.47 kg), but the analysis using the SEs inferred from the quoted P values and the RevMan GIV facility showed that the difference, 0.84 kg (95% CI -0.04 to 1.72), did not quite reach statistical significance (see Analysis 1.26).

Angelini 1994 compared deflazacort with placebo and presented weight gain data for 11 deflazacort and five placebo patients as per cent weight change. As per cent weight change was only reported as the number of participants in each of a set of intervals on the per cent weight gain scale, the mean and SD for each group were derived as described above for Mendell 1989 and Griggs 1991. After two years of treatment, the degree of weight gain in the deflazacort group was slightly greater than that in the placebo group, but as CIs include the possibility of large effects in either direction (MD 1.09%, 95% CI -13.92 to 16.10, n = 16) (see Analysis 1.27), we can draw no conclusions.

(b) Behavioural changes

Three studies reported the number of patients with behavioural changes in treatment and placebo groups (Beenakker 2005; Griggs 1991; Mendell 1989).

Analysis of pooled data from these studies demonstrated a statistically non-significant risk of behavioural changes in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo, with a RR of 1.39 (95% CI 0.94 to 2.06; moderate quality evidence) (see Analysis 1.33; Summary of findings for the main comparison).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment there was no statistically significant difference in behavioural changes in the prednisone and placebo groups, with a RR of 1.02 (95% CI 0.67 to 1.56) (see Analysis 1.33).

Mendell 1989 compared prednisone 1.5 mg/kg/day with placebo. After six months of treatment there was a trend to increased risk of behavioural changes in the prednisone group but this was not statistically significant, with a RR of 1.43 (95% CI 0.92 to 2.24) (see Analysis 1.33).

Beenakker 2005 compared an intermittent regimen of prednisone (0.75 mg/kg/day given for the first 10 days of every month, for six months) with placebo, in a cross-over design study. The study reported the number of patients with behavioural side effects (hyperactivity, irritability, euphoria) in prednisone-treated and placebo-treated participants, but data on occurrence of these adverse effects during all four phases of the cross-over trial were not presented or available, and because of this, the review authors could not undertake appropriate statistical analysis.

Angelini 1994 reported behavioural changes in six of 11 participants in the deflazacort group at six months but did not report the data for the placebo group.

(c) Cushingoid appearance

Three studies reported the number of participants with cushingoid appearance in treatment and placebo groups (Beenakker 2005; Griggs 1991; Mendell 1989).

Beenakker 2005 compared an intermittent regimen of prednisone (0.75 mg/kg/day given for the first 10 days of every month, for six months) with placebo, in a cross-over design study. Four participants were noted to have cushingoid appearance during the prednisone treatment period as compared to one in the placebo period. Data on occurrence of this adverse effect during all four phases of the cross-over trial were not presented or available, and because of this, we could not undertake appropriate statistical analysis.

Analysis of pooled data from Griggs 1991 and Mendell 1989 demonstrated a significant risk of cushingoid appearance in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo, with a RR of 2.37 (95% CI 1.53 to 3.67) (see Analysis 1.34).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment there was no significant difference in cushingoid appearance in the prednisone and placebo groups, with a RR of 1.15 (95% CI 0.60 to 2.17) (see Analysis 1.34).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo, and after six months of treatment there was a significant risk of cushingoid appearance in the prednisone group, with a RR of 4.36 (95% CI 2.04 to 9.33) (see Analysis 1.34).
Angelini 1994 reported a cushingoid appearance in two of 11 participants in the deflazacort group at six months but did not report data for the placebo group.
Hu 2015 reported a cushingoid appearance in three of 31 participants in the prednisone (0.75 mg/kg/day) group at 12 months but did not report data for the placebo group.

(d) Excessive hair growth (hirsutism)

Two studies reported the number of participants with excessive hair growth in treatment and placebo groups (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a statistically significant risk of excessive hair growth in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to the placebo group, with a RR of 2.60 (95% CI 1.47 to 4.60) (see Analysis 1.32).
Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment there was no significant difference in excessive hair growth in the prednisone and placebo groups, with a RR of 0.73 (95% CI 0.18 to 3.0) (see Analysis 1.32).
Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo, and after six months of treatment there was a significant increase in the number of boys with excessive hair growth in the prednisone group, with a RR of 2.32 (95% CI 1.16 to 4.64) (see Analysis 1.32).
Angelini 1994 reported excessive hair growth in none of the 11 participants at six months and in three out of eight patients at two years in the deflazacort group, but did not report data for the placebo group.
Hu 2015 reported hair growth in two of 31 participants in the prednisone group at 12 months, but did not report data for the placebo group.

(e) Acne

Two studies reported the number of participants with acne in treatment and placebo groups (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a trend to develop acne in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo but this was not statistically significant, with a RR of 1.78 (95% CI 0.96 to 3.32) (see Analysis 1.35).
Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo and after six months of treatment there was no significant difference in acne in the prednisone and placebo groups, with a RR of 0.73 (95% CI 0.18 to 3.0) (see Analysis 1.35).
Mendell 1989 compared prednisone 1.5 mg/kg/day with placebo and after six months of treatment there was a trend to develop acne in the prednisone group, but this was not statistically significant, with a RR of 1.77 (95% CI 0.84 to 3.73) (see Analysis 1.35).
Hu 2015 reported acne in two of 31 participants in the prednisone group at 12 months, but did not report data for the placebo group.

(f) Osteoporosis, fractures

None of the included studies performed bone densitometry studies. Two studies instructed the participants in the study to take 0.3 g calcium carbonate with each meal (Griggs 1991; Mendell 1989). Two of the included studies commented upon fractures (Angelini 1994; Beenakker 2005). Angelini 1994 reported pathological fracture of the tibia in one participant in the deflazacort-treated group. There was no description of the timing of the fracture in relation to duration of deflazacort treatment, circumstances leading to the fracture, or results of any bone density studies. One participant, randomised to the placebo group in the first phase of Beenakker 2005, developed a traumatic fracture of the femur 10 days into the study and dropped out. One participant in the placebo treatment group in Griggs 1991 dropped out of the study because of an arm fracture; Griggs 1993 subsequently reported this incident.

(g) Hyperglycemia/glycosuria

Angelini 1994 and Bäckman 1995 checked blood glucose, and another two studies checked urine dipstix (Griggs 1991; Mendell 1989). Griggs 1991 reported glycosuria in one participant, who was on prednisone 0.75 mg/kg/day. The report did not state the severity of glycosuria and its impact.

(h) Hypokalemia

Only Angelini 1994 and Bäckman 1995 performed blood tests for electrolyte surveillance. Angelini 1994 reported "mild hypokalemia" in three of 11 deflazacort-treated participants but this was "easily correctable" with oral potassium supplements.

(i) Hypertension

Griggs 1991 reported hypertension with a blood pressure of 130/110 in one participant taking prednisone 0.75 mg/kg/day.
Hu 2015 did not report any hypertension. Monitoring of diastolic blood pressure revealed no statistically significant differences at six or 12 months between the group treated with prednisone 0.75 mg/kg/day and the group receiving placebo.

(j) Gastrointestinal side effects

Gastrointestinal side effects were defined differently and inconsistently in the included studies.

Mendell 1989 grouped increased appetite, nausea and stomach discomfort under the umbrella of gastrointestinal symptoms; these, as a whole, were not significantly different between the placebo and prednisone treatment groups. Griggs 1991 reported increased appetite as a separate side effect and this was significantly more frequent in the prednisone 0.75 mg/kg/day group as compared to the placebo group (P = 0.02). Angelini 1994 reported that in their two-year study, none of the participants developed gastrointestinal disturbances on deflazacort 2 mg/kg on alternate days; they had, however, treated all the children with antacids (drug name not specified). Parents of the participants in Bäckman 1995, the study of prednisolone 0.35 mg/kg/day, did not report gastrointestinal side effects.

(k) Increased appetite

Two studies reported the number of participants with increased appetite in treatment and placebo groups or phases (Beenakker 2005; Griggs 1991).

Beenakker 2005 compared an intermittent regimen of prednisone (0.75 mg/kg/day given for the first 10 days of every month, for six months) with placebo, in a cross-over design study. Four of the 16 participants were noted to have increased appetite during the prednisone treatment period as compared to one out of 16 in the placebo period. Data on occurrence of this adverse effect during all four phases of the cross-over trial were not presented or available, and because of this, review authors could not undertake appropriate statistical analysis.

Griggs 1991 compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment, there was no significant difference in the prednisone and placebo groups with a RR of 1.54 (95% CI 0.90 to 2.62) (see Analysis 1.36).

Griggs 1991 also compared prednisone 0.75 mg/kg/day with placebo. After six months of treatment, there was no significant difference in the prednisone and placebo groups, with a RR of 1.80 (95% CI 1.09 to 2.99) (see Analysis 1.36).

Hu 2015 reported increased appetite in six of 31 participants in the prednisone (0.75 mg/kg/day) group at 12 months, but did not report data for the placebo group.

(l) Cataracts

The participants were evaluated for cataracts in four of the six included studies (Angelini 1994; Beenakker 2005; Griggs 1991; Mendell 1989), but the studies did not describe the precise examination (slit lamp or red reflex) performed for detection of cataracts. No cataracts were reported.

(m) Death

Bäckman 1995 reported two deaths during the study. A 16-year-old boy died of pneumonia and a four-year-old died during an appendectomy. The authors did not report whether the deaths occurred during the prednisolone or the placebo phases.

(n) Life-threatening infections

Two studies described specific monitoring to document episodes of intercurrent infection (Griggs 1991; Mendell 1989). None of the studies described the treatment strategy for exposure to chicken pox (varicella zoster). Apart from the 16-year-old boy who died of pneumonia described above (Bäckman 1995), the trials reported no other episodes of infection.

(o) Height restriction

Griggs 1991 and Mendell 1989 stated that they measured height, but presented no data. Bäckman 1995, Beenakker 2005, and Rahman 2001 did not describe height measurement.

Hu 2015 measured height (cm) at 6 and 12 months, reporting no clear difference in height between prednisone-treated and placebo-treated boys, although the results were imprecise, and allowed for effects in either direction (MD -0.88, 95 CI -6.89 to 5.13, n = 63 at 6 months and MD -2.62, 95% CI -8.66 to 3.42; n = 58, at 12 months) (see Analysis 1.37; Analysis 1.38).

Angelini 1994 monitored height every 2 months. By two years, growth was 11.4 ± 2.7 cm in the treated group and 11.2 ± 2.2 cm in the placebo group; however, the report does not state the numbers of boys measured at this time point.

Observations on prednisone dose-response relationship and adverse events

A full investigation of the prednisone dose-response relationship to identify the optimum dose would need individual patient data within-study analyses, and the included studies reported no such analyses. We consider this further in the Discussion.

Two studies made direct comparisons of prednisone doses (Griggs 1991; Mendell 1989).

Griggs 1991 compared 0.3 mg/kg/day prednisone to 0.75 mg/kg/day prednisone, finding statistically significant differences in favour of the higher dose in average muscle strength scores (5.82 versus 6.00, P = 0.026, n = 65), time (seconds) to climb stairs (5.76 versus 4.23, P = 0.0014, n = 37), time (seconds) to stand (6.64 versus 4.56, P = 0.004, n = 33), and lifting weights (kg) (1.64 versus 2.04, P = 0.0006, n = 43), but no statistically significant differences in leg function grade (4.07 versus 4.19, P = 0.53, n = 63), time (seconds) to travel nine metres (7.33 versus 6.37, P = 0.127, n = 44), or measures of pulmonary function.

Mendell 1989 compared 0.75 mg/kg/day prednisone with 1.5 mg/kg/day prednisone, finding no statistically significant differences in strength or functional outcomes between the two doses: muscle

strength score (6.23 versus 6.5, P = 0.84, n = 60), leg function grade (3.25 versus 3.36, P = 0.67, n = 64), time (seconds) to climb stairs (3.87 versus 4.00, P = 0.74, n = 47), time (seconds) to travel nine metres (6.81 versus 7.04, P = 0.77, n = 55), time (seconds) to stand (4.15 versus 3.43, P = 0.055, n = 34), lifting weights (1.88 versus 2.13, P = 0.06, n = 55), or in measures of pulmonary function.

From the forest plots showing studies grouped by dosage of prednisone on several outcome variables, the confidence in effect estimates for the efficacy of prednisone doses of 0.75 mg/kg/day or above appears fairly secure. There was no evidence from Mendell 1989 of further benefit at 1.5 mg/kg/day.

Comparing adverse event rates at the 0.3 mg/kg/day (n = 33) and 0.75 mg/kg/day (n = 34) prednisone doses, the only statistically significant differences between groups were in numbers reporting hair growth (9% versus 41%, P = 0.006) and cushingoid features (41% versus 71%, P = 0.02) (Griggs 1991). The between-group difference in number of participants with over 20% weight gain (11% versus 31%) was not statistically significant (P = 0.18), and this was also the case for differences in ankle oedema (3% versus 6%, P = 0.60), acne (9% versus 26%, P = 0.08), insomnia (9% versus 18%, P = 0.33), anorexia (3% versus 3%, P = 0.97), hyperactivity (16% versus 26%, P = 0.42), irritability (34% versus 50%, P = 0.20), increased appetite (59% versus 68%, P = 0.49), and glycosuria (0% versus 3%, P = 0.71). No cataracts occurred.

Mendell 1989 reported no statistically significant differences in rates of individual adverse events between a 0.75 mg/kg/day daily prednisone dose (n = 33) and a 1.5 mg/kg/day daily dose (n = 33). Adverse events reported were: behavioural change (48% versus 64%, P = 0.22), cushingoid appearance (55% versus 73%, P = 0.13), gastrointestinal symptoms (55% versus 61%, P = 0.62), excessive hair growth (52% versus 52%, P = 1.0), acne (36% versus 39%, P = 0.80), and easy bruising (3% versus 6%, P = 0.56). No participants had glycosuria or cataracts.

Weekend-only versus daily prednisone

Studied in Escolar 2011. See Summary of findings 2.

Primary outcome measure: prolongation of time to loss of ambulation

Not reported.

Secondary outcome measures

(1) Muscle strength

Analysis 2.1.

(a) Average muscle score

Escolar 2011 measured upper and lower extremity muscle strength using QMT scores ("the summation of maximal isometric voluntary contraction force of flexors and extensors of elbow and knee") as primary outcomes. The trialists also conducted manual muscle testing (MMT) using the modified MRC scale.

The mean change from baseline to month 12 in the MMT score (SD) in 54 participants was 4 (24.3) in the weekend-only dosing group and -0.6 (23.2) in the daily dose group, with a MD of 4.60 (95% CI -8.07 to 17.27); low quality evidence. The trial authors defined an 'equivalence limit' for MMT as one point on the 10-point scale for each of the 34 muscles tested, which was ± 17 points; by this test, the upper CI just allows for the possibility of a difference between weekend-only and daily dosing.

Results for QMT scores all included data from 57 participants. For the QMT arm score and QMT leg score, the trial authors reported an equivalent improvement in the two groups (with equivalence defined as approximately 1 SD of the baseline distribution, which was ± 2 lb for all muscle strength tests). The mean change in QMT arm score from baseline (SD) was 0.70 lb (1.7) in the weekend-only dosing group and 1.3 lb (2.4) in the daily dose group. This was a MD of -0.60 lb (95% CI -1.67 to 0.47); moderate quality evidence (Summary of findings 2). The change in QMT leg score was 2.2 lb (3.7) in the weekend-only dosing group and 2.10 lb (3.4) in the daily dosing group, with a MD of 0.10 (95% CI -1.75 to 1.95; moderate quality evidence; Summary of findings 2).

QMT scores for elbow flexors (MD -0.4, 95% CI -1.60 to 0.80) and elbow extensors (MD -0.9, 95% CI -2.00 to 0.20) also met the test for equivalence. However, knee flexors (MD 1.40, 95% CI -0.50 to 3.30), knee extensors (MD -1.20, 95% CI -3.52 to 1.12), and grip score (MD -1.70, 95% CI -3.22 to -0.18) did not, with the CIs allowing for the possibility of a difference between groups.

(b) Ability to lift weights

Not reported.

(2) Functional outcome measures

Analysis 2.2.

In Escolar 2011, the trial authors defined an 'equivalence limit' for timed functional tests of ± 0.4 seconds.

(a) Time taken to rise from the floor (Gowers' time)

Using the trial authors' definition of equivalence, we found no evidence of difference between weekend-only and daily prednisone in change in mean Gowers' time (seconds) at 12 months (MD 0.15, 95% CI -0.02 to 0.32, n = 46).

(b) Timed walk

Using the trial authors' definition of equivalence, we found no evidence of a difference between weekend-only and daily prednisone on change in the 10-metre walking time (seconds) between weekend-only and daily prednisone groups (MD 0.00, 95% CI -0.21 to 0.21, n = 56; moderate quality evidence; Summary of findings 2).

(c) Four-stair climbing time

Using the trial authors' definition of equivalence, we found no evidence of a difference between weekend-only and daily prednisone on change in mean four-stair climbing time (seconds) (MD 0.0, 95% CI -0.22 to 0.22, n = 55; moderate quality evidence; Summary of findings 2).

(d) Leg function grade

Analysis 2.3.

We found no difference between weekend-only and daily prednisone in change on the Vignos scale (MD 0.04, 95% CI -0.7 to 0.8, n = 58). This is a 10-point lower extremity mobility function scale, grade 1 representing ability to walk and climb stairs without assistance and grade 10 representing confinement to bed. The trial authors defined equivalence as ± 0.6, so the results are too imprecise to rule out difference on this measure.

(e) Arm function grade

Analysis 2.4.

We found no significant difference in arm function grade measured using the Brooke scale, a six-point scale in which grade 1 represents full straight arm abduction (to touch above the head) and grade 6 represents no useful function of the hands (MD 0.10, 95% CI -0.62 to 0.82). The trial authors defined equivalence as ± 0.3, so the results are too imprecise to rule out a difference on this measure.

(3) Pulmonary function - forced vital capacity (FVC), forced expiratory volume in one second (FEV_1)

Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8.

In 31 participants, the FVC% and the FEV_1% (n = 31) predicted showed no clear difference between the two treatments (MD 4.4%, 95% CI -9.79 to 18.59, and MD 6.0%, 95% CI -9.15 to 21.15, respectively). For pulmonary function tests the authors defined equivalence as ± 10% of the per cent predicted. The CIs therefore do not rule out the possibility of a difference between the groups. Maximal voluntary ventilation (MVV) was measured in 27 participants. There was not a clear difference between weekend-only and daily prednisone (MD 4.00, 95% CI -1.68 to 9.68).

Maximal inspiratory pressure (MIP) was measured in 42 people. We did not find evidence of a difference between the two treatments in this comparison (MD 0.00, 95% CI -7.63 to 7.63).

(4) Quality of life (QoL)

Not assessed.

(5) Adverse events

(a) Weight gain

Analysis 2.9; Analysis 2.10.

We found no clear evidence of a difference in mean body mass index (BMI) (mg/m^2) with weekend-only versus daily dosing at 12 months (MD -1.8 kg/m^2, 95% CI -3.74 to 0.14, n = 58). Weight in kg after 12 months of treatment showed no clear difference between the groups (MD -2.5 kg, 95% CI -7.54 to 2.54, n = 58; low quality evidence; Summary of findings 2).

Dosage reductions because of BMI increases were necessary in three participants in the daily group and one participant in the weekend-only group.

(b) Behavioural changes

Analysis 2.11; Analysis 2.12; Analysis 2.13; Analysis 2.14; Analysis 2.15; Analysis 2.16; Analysis 2.17; Analysis 2.18.

Escolar 2011 measured behavioural changes using the Child Behavior Checklist, a rating scale on which higher scores indicate more severe behavioural changes. There was no clear difference between weekend-only and daily prednisone on any of the scales: total problems (MD 1.00, 95% CI -4.34 to 6.34, n = 54; low quality evidence; Summary of findings 2), internalising (MD 4.0, 95% CI -0.8 to 8.8, n = 54), externalising (MD -1.0, 95% CI -6.62 to 4.62, n = 54), anxious/depressed (MD -1.0, 95% CI -4.99 to 2.99, n = 55), somatic complaints (MD 2.0, 95% CI -2.24 to 6.24, n = 55), withdrawn/depressed (MD 4.0, 95% CI -0.3 to 8.3, n = 55), attention problems (MD 2.0, 95% CI -2.4 to 6.4, n = 56), or aggressive behaviour (MD 1.0, 95% CI -3.52 to 5.52, n = 55).

One participant in the daily group had a dosage reduction because of behaviour problems, but there were no withdrawals.

(c) Cushingoid appearance

One participant on weekend-only dosing had dosage reduction for the development of cushingoid features.

(d) Excessive hair growth (hirsutism)

Not reported.

(e) Acne

Not reported.

(f) Osteoporosis, fractures

Analysis 2.19.

In 53 participants, there was no significant difference between groups in lumbar spine Z scores (SD) at 12 months: weekend-only dose -0.88 (0.85); daily dose -1.33 (0.91), P = 0.06. However, the change in Z score from baseline to 12 months favoured weekend-only dosing, with a small increase in the weekend-only dosing group (change of +0.26), compared with a small decline with daily prednisone (change of -0.30), P = 0.001.

(g) Hyperglycemia/glycosuria

Not reported.

(h) Hypokalemia

Not reported.

(i) Hypertension

Not reported.

(j) Gastrointestinal side effects

One participant in the weekend-only group withdrew from the study because of severe vomiting.

(k) Increased appetite

Not reported.

(l) Cataracts

Not reported.

(m) Death

Not reported.

(n) Life-threatening infections

One participant in the weekend-only group had a severe case of flu and fever and one participant in the daily group had acute appendicitis necessitating discontinuation (events graded by the trialists as 3 or 4 on the National Cancer Institute (NCI) Common Toxicity Criteria).

(o) Height restriction

Analysis 2.20; Analysis 2.21.

At 12 months, height was measured in 58 participants in Escolar 2011 and was not significantly different in the weekend-only dosing group than the daily dosing group (MD 1.00 cm, 95% CI -4.67 to 6.67). The trial authors report a "significant increase in linear growth in the weekend-only compared to the daily dosing group (mean change 6.6 cm versus 4.1 cm, P = 0.002). We calculated SD (assuming they were the same in each group) of 2.93, producing a MD of 2.5 cm (95% CI 0.99 to 4.01), favouring weekend-only dosing.

Deflazacort versus prednisone

Studied in Brooke 1996, Bonifati 2000 and Karimzadeh 2012. See Summary of findings 3.

Bonifati 2000 was a one-year study of 18 randomised participants with DMD.

Although Karimzadeh 2012 was an 18-month study that initially randomised 34 participants to deflazacort or prednisone, we discarded the 18-month data as invalid; at one year the investigators excluded four prednisone participants from the study because of uncontrollable weight gain, and these participants also had a reduction in motor function.

Brooke 1996 was a larger trial involving 196 participants, reported only in an abstract. The only reported efficacy outcome was average change in strength at three months.

Primary outcome: prolongation of time to loss of ambulation

Not measured.

Secondary outcome measures

(1) Muscle strength

(a) Average muscle score

Bonifati 2000 measured muscle strength using the MRC scale in four muscles: right deltoid, triceps, iliopsoas, and quadriceps femoris. The authors compared the differences in summed MRC scores at 3, 6, 9, and 12 months compared to baseline. The results were presented graphically without measures of variability and are not suitable for analysis. The authors reported that there were no between-group differences in MRC score at one year, and measures at 3, 6, and 9 months were "similar" between groups.

Karimzadeh 2012 did not measure muscle strength.

Brooke 1996 reported an average change in muscle strength ("based on a standardised method used in several previous trials") after three months of +0.8 with deflazacort 0.9 mg/kg, +0.26 with deflazacort 1.2 mg/kg, and +0.27 with prednisone, but the abstract provided no participant numbers, SD or P values for comparisons.

(b) Ability to lift weights

Not measured in Bonifati 2000 or Karimzadeh 2012. Brooke 1996 provided no information.

(2) Functional outcome measures

Bonifati 2000 reported a composite score that was a sum of the grades in functional scores (10-metre walk, rising from a chair and from the floor, and four-stair climb) and also measured the time taken to perform each test. The report did not provide data from each individual test. We contacted the trial authors for details, but received no response.

Karimzadeh 2012 measured movement function every three months using the same three modalities as in Bonifati 2000, grading each modality in three levels (performed without assistance, performed with assistance, or not able to perform the task) at 3, 6, 9, 12, and 18 months. We were unable to reliably interpret the data because of inconsistencies between text and tables in the trial report.

Brooke 1996 provided no information.

(a) Leg function grade

Not measured in Bonifati 2000 or Karimzadeh 2012. Brooke 1996 provided no information.

(3) Pulmonary function - forced vital capacity (FVC)

Not measured in Bonifati 2000. Karimzadeh 2012 reported that none of the groups had an abnormal vital respiratory capacity (less than 80% normal based on age and gender) during the study, and that there were no between-group differences, without providing numerical data.

Brooke 1996 provided no information on pulmonary function.

(4) Quality of life (QoL)

Not measured in Bonifati 2000, Karimzadeh 2012, or Brooke 1996.

(5) Adverse events

(a) Weight gain

Data for 3-, 6- and 9-month time points were not provided by Karimzadeh 2012, and were presented graphically in Bonifati 2000, without any measures of variability. For Bonifati 2000, we read the data from the graph using the ruler method, and figures are therefore very approximate. The percentage body weight increase in the deflazacort and prednisone groups respectively were 2.5% and 6% at three months, 3% and 10% at six months, and 5.8% and 18% at nine months. The reported P value for the difference between groups was < 0.05 at six months and "the difference remained statistically significant at 9 and 12 months".

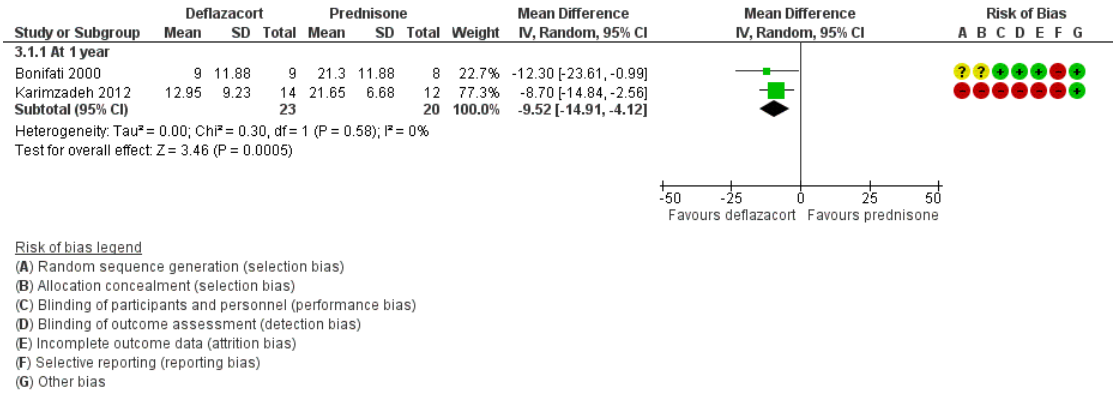
Bonifati 2000 reported the mean increase from initial weight at 12 months to be 9% (2.17 kg) in the deflazacort group (n = 9) and 21.3% (5.08 kg) in the prednisone group (n = 8) without providing SD. This was reported as a significant difference at an assumed significance threshold of P < 0.05 (the stated significance threshold for the difference at 6 months). Using the most conservative value of P = 0.05 for the between-group difference at one year, and assuming that the SD of outcome measurements were the same in each group, the estimated SD was 11.88. This gave a MD of -12.30% (95% CI -23.61 to -0.99) (Analysis 3.1).

Karimzadeh 2012 did not clearly report the numbers in which weight gain was measured at 12 months. However, authors state that the study was continued after early dropouts with 14 patients taking deflazacort, and 12 using prednisone. The MD between groups assuming these sample sizes was -8.70% (95% CI -14.84 to -2.56) (Analysis 3.1).

This trial reported a mean change of weight of 12.95% (SD 9.23, 95% CI 7.6 to 18.3) in the deflazacort group (n = 14) and 21.65% (SD 6.68, 95% CI 16.1 to 27.2) in the prednisone group (n = 12).

Combining the one-year weight gain data from Bonifati 2000 and Karimzadeh 2012 (n = 43), the MD was -9.52% (95% CI -14.91 to -4.12; very low quality evidence) in favour of deflazacort (see Figure 6; Analysis 3.1; Summary of findings 3). These data must be interpreted with caution.

Figure 6. Forest plot of comparison: 3 Deflazacort versus prednisone, outcome: 3.1 Weight gain (%).



The Brooke 1996 abstract reported weight gain as a percentage of baseline weight at 12 months as follows: deflazacort 0.9 mg/kg = 16.8%, deflazacort 1.2 mg/kg = 18.3%, and prednisone = 26.7%; P < 0.1 for comparisons of deflazacort versus prednisone. The abstract did not give the number of participants in each group or SD. Brooke 1996 also reported the percentage of participants with moderate or severe obesity: 24% in the deflazacort 0.9 mg/kg group, 11% in the deflazacort 1.2 mg/kg group, and 41% in the prednisone group; without sufficient detail for analysis.
Bonifati 2000 reported the number of participants with an increase in body weight of over 20% at one year. This was 1/9 (11%) in the deflazacort group and 4/8 (50%) in the prednisone group.

(b) Behavioural changes

The number of children with behavioural changes in Bonifati 2000 was four participants (44%) in the deflazacort group and four participants (50%) in the prednisone group at six months (RR 0.89, 95% CI 0.32 to 2.43; Analysis 3.2), and six participants (66%) in the deflazacort group and five participants (62%) in the prednisone group at one year (RR 1.07, 95% CI 0.53 to 2.17; very low quality evidence; Analysis 3.3; Summary of findings 3). The changes were reportedly "slight".Karimzadeh 2012 and Brooke 1996 provided no information on behavioural changes.

(c) Cushingoid appearance

The number of children with Cushingoid appearance in Bonifati 2000 was two (22%) in the deflazacort group and five (55%) in the prednisone group at six months (RR 0.59; 95% CI 0.13 to 2.70; Analysis 3.2) and five (55%) in the deflazacort group and four (50%) in the prednisone group at one year (RR 1.11; 95% CI 0.45 to 2.75; Analysis 3.3). These changes were also reported as "slight". Cushingoid appearance was not evaluated in Karimzadeh 2012.

Brooke 1996 reported the percentage of participants with moderate or severe moon face: 36% in the deflazacort 0.9 mg/kg group, 32% in the deflazacort 1.2 mg/kg group, and 43% in the prednisone group. The report did not give SD or the numbers of participants in each group.

(d) Excessive hair growth (hirsutism)

In Bonifati 2000, hirsutism occurred in five participants (55%) in the deflazacort group and four participants (50%) in the prednisone group at six months (RR 1.11, 95% CI 0.45 to 2.75; Analysis 3.2), and five participants (55%) in the deflazacort group and three participants (37%) in the prednisone group at one year (RR 1.48, 95% CI 0.51 to 4.31; Analysis 3.3). Karimzadeh 2012 did not report on the presence of hirsutism. Brooke 1996 provided no information.

(e) Acne

Bonifati 2000 reported that no case of acne occurred. Karimzadeh 2012 did not report on the presence of acne. Brooke 1996 provided no information.

(f) Osteoporosis, fractures

Participants in Bonifati 2000 underwent an x-ray of the hand at baseline and after one year of corticosteroid treatment. The authors do not report the results other than that during the year of treatment, bone age was similar in the two groups. One boy

in the deflazacort group had a traumatic bone fracture after four months of treatment.
Karimzadeh 2012 and Brooke 1996 did not report the occurrence of fractures or osteoporosis.

(g) Hyperglycemia/glycosuria

Bonifati 2000 measured glucose. The trial authors reported no significant change in laboratory parameters, without providing further details. Karimzadeh 2012 reported that no glucosuria was detected in either treatment group "in the 3-month evaluation" - we thought this likely to mean at the three-monthly evaluations. Brooke 1996 provided no information on this adverse event.

(h) Hypokalaemia

Bonifati 2000 measured electrolytes. The trial authors reported no significant change in laboratory parameters, without providing further details. Karimzadeh 2012 and Brooke 1996 did not report on the presence of hypokalaemia.

(i) Hypertension

No study reported blood pressure data in detail. In Karimzadeh 2012 blood pressure was measured every three months, with no increase in either group according to the age-specific standard curve. Bonifati 2000 reported that no case of hypertension occurred. Brooke 1996 provided no information on this adverse event.

(j) Gastrointestinal side effects

Bonifati 2000 reported 'Gastric symptoms' in one participant (11%) in the deflazacort group and two participants (25%) in the prednisone group at six months (RR 0.44, 95% CI 0.05 to 4.02; Analysis 3.2), and one participant (11%) in the deflazacort group and one participant (12%) in the prednisone group at one year (RR 0.89, 95% CI 0.07 to 12.00; Analysis 3.3). Antacid treatment produced complete resolution of pain. Karimzadeh 2012 and Brooke 1996 did not report on gastrointestinal effects.

(k) Increased appetite

In Bonifati 2000, appetite increase occurred in two participants (22%) in the deflazacort group and six participants (75%) in the prednisone group at six months (RR 0.30, 95% CI 0.08 to 1.07; Analysis 3.2) and three participants (33%) in the deflazacort group and six participants (75%) in the prednisone group at one year (RR 0.44, 95% CI 0.16 to 1.22; Analysis 3.3). The trial authors reported the change in appetite as "slight". Karimzadeh 2012 and Brooke 1996 did not report on appetite change.

(l) Cataracts

Participants in Bonifati 2000 underwent a slit lamp examination of the eye at baseline and after one year of corticosteroid treatment; a "slight cataract" was found in two boys in the deflazacort group and one in the prednisone group. Karimzadeh 2012 reported no cataracts at the one-year evaluation. Brooke 1996 provided no information.

(m) Death

None reported in Bonifati 2000, Brooke 1996 or Karimzadeh 2012.

(n) Life-threatening infections

The occurrence of sepsis was not reported in Bonifati 2000, Brooke 1996, or Karimzadeh 2012.

(o) Height restriction

Bonifati 2000 monitored height but did not provide any information on it in the results. Karimzadeh 2012 reported height and growth "at the end of the study" (18 months), but we discarded these data for reasons given above. Brooke 1996 did not report height data.

(p) Others

Bonifati 2000 reported that adverse event monitoring identified no ankle oedema, insomnia, or anorexia.
Karimzadeh 2012 reported no cardiomyopathy (measured by decrease in ejection fraction at one year). One participant had scoliosis at the start of the study and was treated with a brace, and had no increase in scoliosis at one-year follow-up. No scoliosis was otherwise detected.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Weekend-only versus daily prednisone for Duchenne muscular dystrophy

Patient or population: patients with Duchenne muscular dystrophy
Setting: outpatient
Intervention: weekend prednisone
Comparison: daily prednisone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Score/value with daily prednisone	Score/value with weekend-only prednisone				
Prolongation of time to loss of ambulation - not reported	-	-	-	-	-	Not an outcome in the single included study for this comparison
Change in muscle strength - QMT arm score (lb) follow-up: 12 months (higher indicates stronger)	The mean change in QMT arm score in the control group was 1.3 lb	The mean change in QMT arm score in the intervention group was 0.6 lb lower (1.67 lower to 0.47 higher)	-	57 (1 RCT)	⊕⊕◯◯ **Moderate** [1]	-
Change in muscle strength - QMT leg score (lb) follow-up: 12 months (higher indicates stronger)	The mean change in QMT leg score in the control group was 3.4 lb	The mean change in QMT leg score in the intervention group was 0.1 lb more (1.75 lower to 1.95 higher)	-	57 (1 RCT)	⊕⊕◯◯ **Moderate** [1]	-
Change in muscle strength - MMT score Follow-up: 12 months (higher indicates stronger)	The mean change in MMT score in the control group was -0.6	The mean change in MMT score in the intervention group was 4.6 higher (8.07 lower to 17.27 higher)	-	54 (1 RCT)	⊕⊕◯◯ **Low** [2]	-

Change in 10-metre walking time Follow-up: 12 months	The mean change in 10-metre walking time in the control group was 0.1 seconds	The mean change in 10-metre walking time in the intervention group was 0 (0.21 quicker to 0.21 slower)	-	56 (1 RCT)	⊕⊕◯◯ **Moderate**[3]	-
Change in 4-stair climbing time Follow-up: 12 months	The mean change in 4-stair climbing time in the control group was -0.06 seconds	The mean change in 4-stair climbing time in the intervention group was 0 (0.22 quicker to 0.22 slower)	-	55 (1 RCT)	⊕⊕◯◯ **Moderate**[3]	-
BMI (kg/m^2) at end of study Follow-up: 12 months	The mean BMI (kg/m^2) in the control group was 19.6	The mean BMI kg/m^2 in the intervention group was 1.8 lower (3.74 lower to 0.14 higher)	-	58 (1 RCT)	⊕⊕◯◯ **Low**[4]	Mean % weight gain not reported. Mean difference in weight (kg) did not show a clear difference at 12 months, being 2.5 kg lower; 7.54 lower to 2.54 higher with weekend-only dosing
Behavioural changes assessed with Child Behaviour Checklist total problems (higher scores indicate more severe behavioural changes) Follow-up: 12 months	The mean behavioural change score in the control group was 48	The mean behavioural change score in the intervention group was 1 higher (4.34 lower to 6.34 higher)	-	54 (1 RCT)	⊕⊕◯◯ **Low**[4]	-
Fractures - not reported	See comment	See comment	Not estimable	53 (1 RCT)	-	No fractures reported. Change in lumbar spine Z scores favoured weekend-only dosing (increase in the week-

				end group +0.26, compared with -0.30 decline with daily prednisolone

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
BMI: body mass index; **CI:** confidence interval; **MMT**: manual muscle testing; **QMT**: quantitative muscle testing; **RCT**: randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Trial authors defined equivalence limits (limits within which the regimens can be considered of equivalent efficacy) of ± 2 lb for QMT. We downgraded once as although serious imprecision is present, the CIs fall within the equivalence limits.
[2]We downgraded the quality of evidence twice for serious imprecision due to small sample size; trial authors defined equivalence limits (limits within which the regimens can be considered of equivalent efficacy) of ± 17 points and the CIs allow for the possibility of non-equivalence.
[3]Trial authors defined equivalence limits (limits within which the regimens can be considered of equivalent efficacy) of ± 0.4 seconds for timed tests. We downgraded once; although serious imprecision is present, the CIs fall within the equivalence limits.
[4] We downgraded the evidence for very serious imprecision (due to small sample sizes, plus the CI includes appreciable differences in favour of either intervention).

Deflazacort versus prednisone for Duchenne muscular dystrophy

Patient or population: patients with Duchenne muscular dystrophy
Setting: outpatient
Intervention: deflazacort
Comparison: prednisone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk or score/value with prednisone or prednisolone	Risk or score/value with deflazacort				
Prolongation of time to loss of ambulation - not reported	See comment	See comment	Not estimable	-	-	None of the studies investigating this comparison assessed prolongation of time to loss of ambulation
Muscle strength - not reported	See comment	See comment	-	-	-	One study measured summed MRC scores from 4 muscles at 3, 6, 9, and 12 months, but presented data graphically without measures of variability
Change in 10-metre walking time Follow-up: 12 months	-	-		-	-	Two studies (n = 43) reported composite scores of timed function tests, but did not report the scores for each test separately

Change in 4-stair climbing time Follow-up: 12 months	-	-	-	-	-	Two studies (n = 43) reported composite scores of timed function tests, but did not report the scores for each test separately
Weight gain (%) Follow-up: 12 months	The mean weight gain (%) was 21.48%	The mean weight gain (%) in the intervention group was 9.52% lower (14.91 lower to 4.12 lower)	-	43 (2 RCTs)	⊕◯◯◯ **Very low** [1,2,3]	-
Behavioural changes Follow-up: 12 months	500 per 1000	445 per 1000 (160 to 1000)	RR 1.07 (0.53 to 2.17)	17 (1 RCT)	⊕◯◯◯ **Very low** [1,2,4]	-
Fractures Follow-up: 12 months	1 traumatic fracture occurred after 4 months' deflazacort treatment in one study (n = 26). No other fractures reported		Not estimable	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **MRC**: Medical Research Council; **RCT**: randomised controlled trial; **RR:** risk ratio; **SD**: standard deviation

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]We downgraded the quality of evidence twice for a high risk of bias in most domains.
[2]We downgraded the quality of evidence once for possible publication bias - a large study remains unpublished (Brooke 1996).
[3]Analysis involved some statistical assumptions in calculating SD.
[4]CIs include the possibility of both a large effect and a clinically unimportant effect (i.e. imprecision).

DISCUSSION

Summary of main results

We identified 50 studies of corticosteroids in Duchenne muscular dystrophy (DMD) conducted over the last four decades. From these, 12 randomised controlled trials (RCTs), with a total of 667 participants, were eligible for inclusion in this review based on our predefined criteria.

Among these studies, six (n = 332) were RCTs comparing corticosteroids against placebo; five studied prednisolone or prednisone and one studied deflazacort. With regard to ambulatory status, 282 participants were walking, either independently or with the help of long leg braces. Two large studies contributed the majority of the patients (202 of 332) to the corticosteroid versus placebo comparison (Griggs 1991; Mendell 1989). The treatment groups within this comparison included prednisone (n = 217), prednisolone (n = 10) and deflazacort (n = 17). Unfortunately, two large studies of deflazacort in DMD comprising 206 participants in total have not been published beyond abstract form and their final data are not available (Brooke 1996; Reitter 1995).

We identified one RCT of daily prednisone versus weekend-only prednisone in 64 ambulant boys and two RCTs (n = 52) of prednisone versus deflazacort. A further large multicentre international RCT comparing daily prednisolone (0.75 mg/kg/day), daily deflazacort (0.9 mg/kg.day), and intermittent prednisolone (0.75 mg/kg/day 10 days on, 10 days off) is of major interest, but still in progress at the time of this review (Guglieri 2015). A further potentially eligible RCT is in progress in India, comparing daily prednisolone 0.75 mg/kg/day given for 10 consecutive days per month versus daily dosing (CTRI/2009/091/000738).

Corticosteroids versus placebo

Primary outcome measure: prolongation of time to loss of ambulation

Loss of ambulation is the key milestone in the natural history of DMD, and is of maximal functional significance. Prevention or postponement of this event is the key aim of therapeutic interventions in the first decade of life, and a desired outcome measure. Prolongation of time to loss of ambulation was not the stated primary outcome measure of most RCTs, probably because to achieve sufficient power to demonstrate this effect, studies would require a large sample size and long duration (Muntoni 2002). As progressive muscle weakness is the major contributor to loss of walking, trialists have used measurements of muscle strength as a surrogate marker, enabling clinical trials to be completed in as little as six months. These short-term studies do not demonstrate prolongation of time to loss of ambulation or allow evaluation of adverse effects that develop after long-term use of corticosteroids (Griggs 1991; Mendell 1989; Rahman 2001).

Although Angelini 1994 assessed our primary outcome measure, the data available did not allow us to create survival curves for prolongation of walking. Some disparities that cannot be readily explained further highlight the need for appropriate statistical analysis. Deflazacort and placebo groups were evenly matched at randomisation, and among participants who lost ambulation during the study, the mean age at which boys became wheelchair-dependent was very similar in the two groups (deflazacort group, 108 months; and placebo group, 104 months). Comparing these groups, the significance of the difference of 13 months in duration of walking between randomisation and becoming wheelchair-dependent cannot be ascertained without knowing the ages of the ambulant children at the end of the study.

Secondary outcome measures

Strength

Strength parameters in the corticosteroid treatment groups demonstrated statistically significant improvement compared with placebo. All seven of the included studies measured muscle strength using MRC-based scores (Angelini 1994; Bäckman 1995; Griggs 1991; Hu 2015; Mendell 1989; Rahman 2001; Todorovic 1998).

Pooled data from Griggs 1991, Mendell 1989, and Rahman 2001 demonstrated a statistically significant improvement in muscle strength over six months (reported as muscle strength score) with prednisone/prednisolone treatment versus placebo. Beenakker 2005 reported data on muscle strength as muscle force assessed by hand-held dynamometry, which could not be pooled with data from the above three studies; nevertheless, this trial demonstrated improvement in muscle force during the six-month prednisolone treatment phase over the placebo phase. The improvement in muscle strength or force occurred with all four treatment regimens (0.75 mg/kg/day for the first ten days of every month, 0.3 mg/kg daily, 0.75 mg/kg daily and 1.5 mg/kg daily). Data from the other trials were lacking or not suitable for analysis.

Hu 2015 was a 12-month study and demonstrated improvements in lower limb muscle strength at both six and 12 months. We could not include the data in meta-analysis because although investigators used MRC-based scores, they tested two muscles and did not combine results into a single score.

The two-year study of deflazacort (2 mg/kg on alternate days) versus placebo measured change in MRC index (%) over the initial score, demonstrating a difference in favour of deflazacort at 24 months, but not at 6 months (Angelini 1994).

Function

Functional parameters showed statistically significant improvement over the short term (up to a year) in corticosteroid-treated groups. The functional parameters showing improvement included time taken to rise from the floor, time taken to walk nine

metres, time taken to climb four stairs, and the leg functional grade. It is, however, important to note that none of the included studies reported any non-ambulant (wheelchair-dependent) participants regaining the ability to walk on treatment with prednisone.

Data from Beenakker 2005, Griggs 1991, Hu 2015, Mendell 1989, and Rahman 2001 demonstrated a statistically significant improvement in time taken to rise from the floor in the prednisone/prednisolone treatment groups on all dose regimens (0.3 mg/kg/day, 0.75 mg/kg/day, and 1.5 mg/kg/day in daily dose regimens or 0.75 mg/kg/day on the first 10 days of every month, in an intermittent regimen). The muscle weakness in DMD leads to increasing difficulty in rising from the floor at around five years of age, with loss of this ability towards the end of the first decade of life.

Time taken to walk nine (or ten) metres showed a statistically significant improvement in all prednisone/prednisolone treatment groups versus placebo in five trials (Beenakker 2005; Griggs 1991; Hu 2015; Mendell 1989; Rahman 2001). Leg function grades also showed a statistically significant improvement in all prednisone/prednisolone treatment groups versus placebo in three trials (Griggs 1991; Mendell 1989; Rahman 2001).

Angelini 1994, a comparison of alternate day deflazacort (2 mg/kg) versus placebo, demonstrated a difference in favour of deflazacort in timed gait at six months. but no significance difference on our analyses in other functional parameters at the six-month or two-year time points. The study measured outcomes until participants became wheelchair dependent and had a high dropout rate at two years.

Pulmonary function

One of the desired effects of any successful treatment in DMD is the preservation of respiratory muscle strength, thereby preserving pulmonary function and postponing or removing the risk of nocturnal hyperventilation and respiratory failure. A good marker of respiratory reserve is forced vital capacity (FVC) and two of the large included studies measured this outcome (Griggs 1991; Mendell 1989). A statistically significant improvement in the FVC in all prednisone treatment groups versus placebo was present after six months of treatment. Parallel results are available from non-randomised cohort studies (Biggar 2001; Biggar 2004; Biggar 2006; Silversides 2003), which showed strength improvement and stabilisation of FVC over the long term in deflazacort-treated patients (see below).

Quality of life

Two trials measured quality of life (Beenakker 2005; Hu 2015), with only Hu 2015 providing numerical data. Self reported and proxy reported quality of life measures were better with prednisone 0.75 mg/kg/day than with placebo.

Adverse events

Caution is required in extrapolating the adverse effects of corticosteroid therapy reported in these included studies to circumstances of long-term clinical use. Five of the seven included studies used daily doses of prednisone/prednisolone over a six-month period; one used a daily dose for a year. The longest included study, of two years' duration, used deflazacort 2 mg/kg on alternate days (Angelini 1994). We would expect the side effects observed during these studies to be much less than those likely to occur during five years or longer use, as may be anticipated in clinical practice. These short-term studies would be unlikely to detect long-term adverse effects, especially loss of bone mineral density, increased bone fracture incidence, cataracts, and growth failure with short stature.

The propensity for excessive weight gain on corticosteroid treatment was clear. This did not appear to adversely affect strength or function in these short-term studies, except for one participant (in the prednisone 0.3 mg/kg/day group), who at the end of the six months of the Griggs 1991 study refused to continue to another subsequent study of prednisone versus azathioprine (Griggs 1993). Behavioural changes and cushingoid side effects were statistically significant in the corticosteroid treatment groups, but were not considered important enough for treatment to be discontinued in these short-term studies.

Participants treated with prednisone 0.75 mg/kg/day over the six-month period were at significant risk of excessive hair growth. Participants and their families appear to have tolerated this side effect, which caused no participants to drop out of the study.

Combined data from Mendell 1989 and Griggs 1991 demonstrated more acne in the prednisone 0.75 mg/kg/day group during the six months of treatment compared to six months of placebo, but this difference was not statistically significant.

As the intermittent corticosteroid regimens are postulated to have a better adverse effect profile, we wanted to compare the daily dose regimen (studied in Mendell 1989, Griggs 1991, and Rahman 2001) with the intermittent regimen (studied in Beenakker 2005). We were not able to make a comparison, as adverse effects data from the only RCT of intermittent prednisone were not available in a format that would allow statistical analysis (Beenakker 2005). In this six-month randomised, controlled, cross-over trial of intermittent prednisone (0.75 mg/kg/day for the first 10 days each month), increased appetite and behavioural side effects occurred more frequently during the prednisone period than during the placebo period, but these effects appear to have been mild, as they required no dose adjustment or drug discontinuation.

Only one included study reported a pathological fracture (of the tibia) while on corticosteroid (deflazacort 2 mg/per kg on alternate days) (Angelini 1994). The report did not describe the duration of treatment prior to the occurrence of fracture or the circumstances of the fracture. One participant in the placebo treatment group in Griggs 1991 dropped out of the study because of an arm fracture (reported in Griggs 1993).

None of the studies assessed bone mineral density by dual energy x-ray absorptiometry (DEXA) scans. This relates to the age of most of the studies and their short-term nature. However, in view of the benefit of corticosteroid therapy in DMD, the treatment regimen is routinely continued in these patients over a decade or longer. In these circumstances, the development of osteoporosis is a major risk, and future studies should consider bone health assessment and systematic DEXA scanning in their protocol for adverse event monitoring (Biggar 2005; Quinlivan 2005).

Corticosteroid dose-response relationship

Clinically, it is important to use the minimum effective dose of corticosteroid. To answer the question of what this may be, we reviewed the forest plots showing studies grouped according to dosage of prednisone/prednisolone. On the basis of the evidence available for analysis, our confidence in the effect estimate for prednisone/prednisolone at doses of 0.75 mg/kg/day is fairly secure. There is little evidence of an increase in benefit when the dose is further increased from 0.75 to 1.5 mg/kg daily (Mendell 1989). This suggests that the daily dose regimen of 0.75 mg/kg/day is adequate to achieve what benefit prednisone can provide.

Differences in the proportion of boys experiencing hair growth and cushingoid features was significantly greater on a daily prednisone dose of 0.75 mg/kg/day than on 0.3 mg/kg/day, but the higher dose did not significantly increase rates of other common adverse events (Griggs 1991). Mendell 1989 found no statistically significant increases in frequency of any adverse event when comparing 1.5 mg/kg/day with 0.75 mg/kg/day prednisone.

A proper investigation of the prednisone dose-response relationship to identify the optimum dose would need individual patient data within study analyses. We recommend that future studies make arrangements for provision of individual patient data for these analyses.

Co-interventions

The co-interventions identified included daily calcium carbonate (Griggs 1991; Mendell 1989), antacids given routinely to all participants (Angelini 1994), and dietetic advice to avoid weight gain (Angelini 1994; Griggs 1991; Mendell 1989). In Hu 2015, concomitant interventions included a calcium-rich diet, medications (vitamin D, calcium, ranitidine, over-the-counter antacid), a high protein, low carbohydrate, low fat diet, and respiratory, cardiac, and rehabilitative interventions (Hu 2015). These co-interventions, however, are clinically extremely unlikely to be responsible for the benefits observed. None of the studies assessed physical activity levels as a potentially confounding factor.

Weekend-only versus daily prednisone

Escolar 2011 was the only published RCT of weekend-only versus daily prednisone. No appreciable difference was present in the primary outcomes of upper and lower limb strength or the safety outcome of body mass index (BMI) between the two groups at 12 months. We did find a difference with faster times to rise from the floor in the daily group, but no clear differences were seen for any other functional outcomes measured. The trial identified no clear difference in weight gain, as the result had wide confidence intervals that include the possibility of no benefit from weekend-only over daily treatment. The weekend-only treatment group had a larger increase in linear height.

Deflazacort versus prednisone

Of the three RCTs of deflazacort versus prednisone, only Bonifati 2000 and Karimzadeh 2012 have been published in detail, while Brooke 1996 (n = 106) has been published only as an abstract. Bonifati 2000 was a study with only 18 participants, comparing the adverse effects of prednisone with those of deflazacort, both given in a daily dose regimen over one year. The trialists did not present power calculations. The two corticosteroids demonstrated similar benefit on strength and functional tests, but the difference in weight gain was statistically significant, being more marked in the prednisone treatment group. One of the nine participants in the deflazacort group, in comparison to four of the nine in the prednisone group, experienced a weight gain of more than 20% over baseline. Karimzadeh 2012 randomised 34 participants to either daily prednisone 0.75 mg/kg/day or daily deflazacort 0.9 mg/kg/day. After early dropouts the trial continued for 12 months with 26 participants. At 12 months there was no appreciable difference in motor function scores between the two drug regimens. There was a clear difference in weight gain combining data from the two trials, with the greatest gain seen in the prednisone group, although this evidence is very low quality.

Brooke 1996 and Reitter 1995 (which is not stated to be randomised) are of major clinical interest because they involved a large number of participants. These trials compared prednisone with deflazacort and, in addition, compared prednisone and deflazacort with a contemporaneous placebo control group. The review authors contacted the authors of these studies for an earlier version of this review, but data were not available. Campbell 2003 reported similar difficulties in obtaining these data for their systematic review of deflazacort in DMD.

Evidence from excluded randomised studies

Pradhan 2006 explored the possibility that daily prednisolone initiated in the late ambulant phase of DMD would delay loss of ambulation, while also aiming to shorten the period of corticosteroid exposure and thereby diminish adverse effects. The investigators calculated the power of this study to detect a significant difference between the control and treatment groups, not on the basis of time to loss of ambulation, but on muscle power. This open, controlled trial assessed the effect of prednisolone 0.75 mg/kg daily, started at a stage when the participants had started falling several times in

a day. The investigators randomly allocated 67 serially seen boys into a prednisolone treatment group (44 participants, mean age 8.83 ± 1.25 years) or control group (23 participants, mean age 8.18 ± 0.64 years). Both groups also received vitamin E. The trialists followed up participants for two years, and thereafter until the boys reached a "chair bound stage". Of the 44 participants in the prednisolone treatment group, 24 dropped out because of adverse effects and treatment was stopped in a further five because of no improvement in power. Fifteen of the remaining 19 in the treatment group could be followed up regularly for two years, and then up to "chair bound stage"; only data from these 15 participants were used for comparison with the control group. Pradhan 2006 reported that in this subgroup of 15, the mean age of becoming wheelchair-dependent was 169 ± 9 months compared to 132 ± 8 months in the control group. As the statistical analysis was based only on the 15 participants who responded without significant adverse effects, and does not take into account dropouts or non-responders in the prednisolone treatment group, we did not include Pradhan 2006 in the review.

Though the trialists did not analyse the data in this study on an intention-to-treat basis, the results may be of clinical significance, as there appears to be a subgroup of boys with DMD who achieved prolongation of time to loss of ambulation by three years, without significant adverse effects. Caution is required in interpretation of these results as they cannot be generalised to the whole population of boys affected by DMD.

The variability in response to corticosteroid treatment amongst individuals affected by DMD in this and other studies, remains unexplained and is likely to be multifactorial. Bonifati 2006 suggested glucocorticoid receptor polymorphisms to be one of the possible factors modulating the long-term response to corticosteroids.

Evidence from non-randomised studies

Though non-randomised, these studies listed in Table 1 still constitute an important body of evidence.

The initial studies

Early, open studies aiming to document some benefit of corticosteroid therapy in DMD used prednisone in high doses ranging from 1.5 mg/kg/day to 5 mg/kg on alternate days (Brooke 1987; DeSilva 1987; Drachman 1974; Siegel 1974). DeSilva 1987, an open study, used loss of ambulation as its primary endpoint and reported prolongation of walking by approximately two years. The adverse effects of corticosteroid treatment in this study were significant and included excessive weight gain, which occurred in the majority of the participants, and hyperactivity, cataracts, hypertension, and stress fractures. These initial studies led to RCTs and further open cohort studies to assess efficacy, and to find optimal dose regimens to minimise adverse effects (Griggs 1991; Mendell 1989).

Alternate day prednisone therapy

Fenichel 1991a compared alternate-day dosing regimens of prednisone 1.25 mg/kg or 2.5 mg/kg over a six-month period. The study recruited the same 103 patients who had just completed the Mendell 1989 randomised study. The placebo group from Mendell 1989 received prednisone 1.25 mg/kg on alternate days; they improved in strength at three months of treatment, but showed a decline in strength over the subsequent three months. The participants in Mendell 1989 who were treated with prednisone 0.75 mg/kg/day or 1.5 mg/kg/day were changed to 2.5 mg/kg on alternate days for six months in Fenichel 1991a; they showed a decline in muscle strength. Comparing the 1.25 mg/kg alternate day group of Fenichel 1991a with the contemporaneous 2.5 mg/kg alternate day group, and also with the placebo control group of the previous Mendell 1989 study, the trial authors concluded that daily dose prednisone was more effective than the alternate-day regimen.

Yilmaz 2004 treated 66 boys with prednisolone 0.75 mg/kg on alternate days (plus vitamin D 600 to 1200 units/day) and compared this group with a control group of 22 boys who had been followed up in the same centre in the past ("pre-steroid era"). The controls were reportedly chosen at random, but no details were given regarding this process. Duration of follow-up was 2.75 ± 0.1 years. Age at loss of walking ability was 10.0 ± 1.5 (range 7 to 14) years in the prednisolone group, compared to 8.6 ± 2.6 (range 6 to 11) years in the control group. Amongst the prednisolone-treated boys, 14 walked independently beyond the age of 12 years and three beyond 13 years, but all lost the ability to walk by the end of 14 years of age. At the end of the study, none of the prednisolone treatment group developed scoliosis during the follow-up period (by a mean age 10.8 ± 1.2 years), whereas seven boys in the control group had scoliosis by a mean age of 11.7 ± 2 years.

Daily prednisone therapy

At the end of Fenichel 1991a, 93 of the 103 participants entered an open study in which they were given prednisone 0.75 mg/kg/day for two years, the results of which were published in Fenichel 1991b. Muscle strength, described as average muscle score (previously described as muscle strength score) stabilised over a two-year period. Over the two-year period, the prednisone dose had to be decreased because of adverse effects, to as low as 0.15 mg/kg/day. Prednisone 0.65 mg/kg/day was considered to be the minimum effective dose, but only half of the participants could tolerate this dose by the end of the study.

Long-term daily prednisone therapy

Pandya 2001 reported the long-term outcome of 30 participants who had received prednisone for a mean period of 10 years. This cohort comprised a subgroup of participants treated with prednisone 0.75 mg/kg/day in Mendell 1989, who were followed up at the University of Rochester. At the initiation of prednisone, 18 of the 30 participants were ambulant: 13 independently and

five walking with long leg braces. At the time of the final visit, one participant was still walking independently at age 18 years, one participant was lost to follow-up, and three participants had discontinued prednisone because of weight gain. The average age of loss of independent ambulation was 14.5 years. This represents significant improvement in comparison to previous natural history studies, which reported loss of walking in untreated boys with DMD at mean ages of 8.8 years (Dubowitz 1978), 9.5 years (Gardner-Medwin 1980), and 10.5 years (Allsop 1981). The prednisone dose had to be decreased because of systemic side effects; in this cohort of 30 participants the mean prednisone dose tolerated was 0.35 mg/kg/day.

Studies comparing prednisone with corticosteroid-naïve patients (but drug regimen not specified)

Takeuchi 2013 utilised the national registry of Japanese DMD/Becker muscular dystrophy (BMD) patients set up in 2009 to report the age at loss of ambulation only between those treated with prednisone and those who were corticosteroid-naïve. The registry includes prednisone use status as current, past, or never, but does not record details of dose regimen, age at commencement, duration, or side effects. The study authors considered 245 patients in the prednisone-treated group (171 current, 74 past), and 315 who had never been treated. Ultimately, loss of ambulation data were available on 242 treated and 311 untreated boys, with loss of ambulation reported in 123 and 190, respectively. The median age at loss of ambulation in the untreated group was 10.1 years (interquartile range (IQR) 10 years to 10.5 years) compared to 11 years (IQR 10.5 years to 11.5 years) in the treated group.

Henricson 2013 was a multicentre, international, prospective cohort study assessing 340 patients with DMD, ranging in age from 2 to 28 years, at three-monthly (ambulant) or six-monthly (non-ambulant) intervals. Participants were divided into three groups: 82 corticosteroid-naïve patients (never treated or treated for less than one month total), 210 current corticosteroid users, and 48 past corticosteroid users (treated for more than one month previously, but not currently receiving corticosteroids). The study authors did not specify the preparation of corticosteroid, the regimen (daily versus intermittent), and whether these were the same for all patients studied. They additionally considered and tabulated outcomes by age group. Main outcomes focused on ambulation and functional milestones: each visit attempted to assess timed tests for standing from supine, climbing four standard stairs, walking or running 10 metres, upper limb function (Brooke scale), and lower limb function (Vignos). Over the age of six years, current corticosteroid users consistently demonstrated greater functional abilities than past users or naïve patients. Past users had less ability than current users, but performed better than the naïve group. None of the naïve boys walked beyond age 12, compared to the 8% of past users and 45% of current users still able to walk independently between 13 and 15 years of age. In 16- to 18-year-olds, only in the group currently taking corticosteroids were any members ambulant (12%). In the upper limbs, 37% of current corticosteroid users, aged 18 years or above, could still lift hand to mouth to feed independently, compared to none of the past user or corticosteroid-naïve groups. MRC manual muscle testing (MMT) scores did not significantly differ between the corticosteroid-treated group and the cohort as a whole. Pulmonary function as measured by FVC and FEV_1 (forced expiratory volume in one second) was comparatively better in the corticosteroid-treated group between the ages of 10 to 15 years. In terms of bone health, the trial authors reported a similar incidence of fractures between corticosteroid-users and the other groups among those more than 13 years old, although the need for surgical spinal stabilisation was reduced in the corticosteroid group between the ages of 13 and 15 years.

Daily dose deflazacort studies

Schara 2001, a retrospective study, reported 19 ambulant boys with DMD who were treated with deflazacort 0.9 mg/kg/day for more than two years (mean 65 months, range 49 to 79 months). Fourteen of the 19 boys aged 9.4 to 13.8 years were able to rise from a supine position. Five boys lost this function at a mean age of 13.5 years (range 10 to 16 years, which is a marked improvement as compared to natural history controls (mean 8.2 ± 1.9 years). All deflazacort-treated boys were able to walk independently during the study period to a mean age of 13 years (range 9.4 to 18.11 years). The key side effects reported were short stature and cataracts. Fourteen of the 19 deflazacort-treated boys developed cataracts; one patient's progressive cataracts led to implantation of lenses 56 months into the treatment.

Among the non-randomised studies, the most impressive functional results of corticosteroid therapy in DMD have been reported from Bloorview MacMillan Children's Centre in Toronto, Canada in a series of five publications: Alman 2004, Biggar 2001, Biggar 2004, Biggar 2006, and Silversides 2003. All five studies describe the use of daily dose deflazacort in clinical practice at the Bloorview MacMillan Children's Centre from January 1990 onwards, and they report an overlapping cohort of patients.

Biggar 2001 used a starting dose of deflazacort 0.9 mg/kg daily in 30 boys with DMD (age 7 to 15 years) over 3.8 years (SD 1.5) and compared this group with 24 boys who were followed up at the same clinic contemporaneously, who did not take up the option of deflazacort treatment because of parental choice (most commonly, fear of side effects). Seven of the 30 boys in the deflazacort group stopped walking at a mean of 12.3 (SD 2.7) years, and this contrasted with the non-treated participants, all 24 of whom stopped walking at a mean of 9.8 (SD 1.8) years. The FVC in the deflazacort-treated group was significantly greater at 15 years ($P < 0.001$), but the trial authors did not report the number of participants at 15 years. Ten of the 30 boys in the deflazacort treatment group developed asymptomatic cataracts. The two groups were significantly different in height; mean height in the deflazacort-treated group continued along the 3rd centile,

compared to mean height between the 25th and 50th centiles for the non-treated group.

The primary outcome of interest in Silversides 2003 was cardiac function. The trialists reported a cohort of 33 Duchenne patients who underwent echocardiographic evaluation. Twenty-one participants had been on deflazacort, for a mean duration of 5.1 years ± 2.4, and trialists compared this group with the other 12 who had not accepted the option of deflazacort treatment. The mean age at final follow-up was 14 (± 2) years for the deflazacort-treated group and 16 (± 2) years for the non-treated group. This age difference in the two groups was not statistically significant (P = 0.08), but the biological significance cannot be discounted. Cardiomyopathy, as indicated by left ventricular ejection fraction less than 45%, was demonstrated in only one of the 21 deflazacort-treated participants, compared to seven out of 12 non-treated participants (P = 0.001). The mean ejection fraction reduction was 33% (± 7) in the deflazacort group and 21% (± 8) in the non-treated group (P = 0.002).

Alman 2004 focused on the development of scoliosis in the cohort of 54 boys followed up at the Bloorview Macmillan Centre and initially reported in Biggar 2001. The mean age at follow-up was 16 years. Only five of the 30 deflazacort-treated boys developed scoliosis of more than 20°. In comparison, 16 of the 24 untreated boys developed scoliosis of more than 20°. Deflazacort treatment was associated not only with a reduced incidence of scoliosis, but also delayed the onset and/or development of scoliosis; of the boys who developed scoliosis of > 20°, the five deflazacort-treated boys required spinal surgery at a later age of 15.1 ± 2.0 years, compared with the 16 non-treated boys who underwent spinal surgery at 12.9 ± 2.4 years.

Biggar 2006 reported the updated and cumulative results of the overlapping cohorts from Alman 2004, Biggar 2001, Biggar 2004. and Silversides 2003. The included participants were 74 boys with DMD between 10 and 18 years old who could co-operate for reproducible muscle and pulmonary function testing and were followed up in Neuromuscular Clinics, Toronto, Canada between January 1990 and December 2004. (Investigators excluded four boys who stopped taking deflazacort within two to three years, before they were 10 years old; they are not included in these 74 patients). Boys were offered deflazacort treatment while they were still ambulant but had clinical evidence of worsening muscle function, as evidenced by frequent falls and difficulty in rising from the floor or climbing stairs. Of the 74 boys, 40 were treated with deflazacort; the remaining 34 who did not accept deflazacort (mainly due to fear of side effects, or family cultural or religious reasons) were used as the comparison group. Boys treated with deflazacort (and most boys not treated with deflazacort) received oral daily supplements of vitamin D (1000 units) and calcium (750 mg). Mean age at starting deflazacort was 7.7 ± 1.2 years. The deflazacort starting dose was 0.9 mg/kg daily, which gradually declined over the years as boys grew and gained weight, or was reduced because of side effects. By 10 years of age, the mean dose was 0.8 ± 0.18 mg/kg/day, by 15 years it was 0.55 ± 0.09 mg/kg/day, and by 18 years 0.5 ± 0.2 mg/kg/day. Mean age at the end of the study period was 15.2 ± 2.7 years in the deflazacort-treated group and 15.2 ± 2.5 years in the non-treated group. Mean time on deflazacort was 5.5 years. The key results are listed as follows.

Walking (10 metres): In the deflazacort-treated group, 25 of 31 (81%) could walk at 12 years, 13 of 17 (76%) at 15 years, and two of six boys walked independently at 18 years. By contrast, all 34 boys not treated stopped walking by 12 years of age (mean age 9.8 ± 1.8 years).

Scoliosis: Scoliosis is a frequent complication of DMD in the second decade of life, occurring in up to 90% of affected boys, and in the huge majority, is clinically evident in the 13 to 15 year age group. In the Biggar 2006 cohort, by 18 years of age (mean 13.8 ±1.6 years), 30 of 34 (90%) boys who were not treated developed a spinal curve of more than 20°. In contrast, only four of 40 (10%) deflazacort-treated boys developed scoliosis of more than 20° during the study period. The possible explanations for this could be deflazacort-related prolongation of the ambulatory phase, improvement in paraspinal and truncal muscle strength, or both.

Cardiac function: Moderate or severe left ventricular systolic dysfunction (ejection fraction below 45%) was noted in only four out of 40 boys in the deflazacort-treated group as compared with 20 of 34 boys in the not treated group.

Pulmonary function: FVC, reported as per cent predicted (for age and height) (FVC-PP), was remarkably preserved in the deflazacort treated group. Both groups of boys, treated and untreated, were reported to have similar FVC-PP before 10 years of age, but the report did not present the data. As anticipated, in line with the natural history of DMD, in the no treatment group, FVC-PP showed a gradual decline with age (65 ± 13% at 10 years, 47 ± 19% at 15 years, and 34 ± 10% at 18 years). In contrast, in the deflazacort-treated group, the FVC-PP was 95 ± 17% at 10 years, 88 ± 12% at 15 years, and 81 ± 13% at 18 years. The clinically-important implication was that by 18 years of age, 46% of the boys not treated required nocturnal ventilatory support, compared to none in the deflazacort-treated group.

Survival: To our knowledge, Biggar 2006 was the first study reporting the impact of corticosteroid therapy on survival in DMD. Twelve of the 34 (35%) boys not treated died at mean age 17.6 ± 1.7 years, of cardiorespiratory complications (details not reported). Only two of the 40 deflazacort-treated boys died; cause of death was left ventricular failure, and age at death was 13 years and 18 years.

Adverse events: The growth suppression effect of long-term glucocorticoid treatment was evident in short stature in the deflazacort-treated group; at age 15 years, the height of deflazacort-treated boys was 143 ± 9 cm, compared to 164 ± 8 cm for boys not treated. Twenty-two of the 40 deflazacort-treated boys developed bilateral cataracts, though they were asymptomatic for the duration of the

study.

Biggar 2006 gave dietary recommendations to all boys on each hospital visit, and referred boys to a nutritionist if weight exceeded expected weight by 5% to 10%, or if weight loss exceeded 10%. With this approach, excessive weight gain, which is a common side effect of corticosteroid therapy, was not noted to be a significant clinical problem amongst these 40 deflazacort-treated boys, over a mean treatment period of five years. Trialists reported only one boy from the Bloorview Macmillan Centre to have discontinued deflazacort because of excessive weight gain, and this boy was not included in the 74 participants reported in Biggar 2006. Three boys in the deflazacort-treated group developed fragility vertebral fractures compared with none in the non-treated group. Long-bone fractures were documented in 25% of boys in both groups, with no difference between groups.

Houde 2008 retrospectively analysed the medical charts of 105 boys with DMD over an eight-year period. The boys were divided into those receiving deflazacort for more than one year (treated) and those not receiving the drug or who had received it for less than six months (untreated). The trialists excluded five boys in the treated group; four because they had stopped taking the drug after two years, and one because he had received prednisone for six years before switching to deflazacort. Among the untreated group, they excluded 21 because of missing data or because boys were too young to participate in all regular assessments. Overall, 37 boys received deflazacort, and 42 were untreated. The starting dose was 0.9 mg/kg/day, adjusted according to progression or side effects, with a maximum of 1 mg/kg. The mean length of treatment was 66 months, with 70% taking deflazacort for more than five years, and 22% for more than eight years. The mean age on beginning treatment was 7.6 ± 1.7 years and the mean dose at the most recent clinic visit recorded was 0.69 ± 0.2 mg/kg. All boys, treated and untreated, were offered review every three months. The mean age of the treated group was 13.1 ± 3.2 years. Among the untreated patients, 24 were over 18 and no longer actively followed at the clinic. Of the 18 who were still under regular clinic review, the mean age was 9.5 ± 2.9 years. Key findings were as follows.

Ambulation: The trialists reported loss of ambulation as when a boy could no longer walk, even with help. For those who used long leg braces, it was recorded as the time when natural walking stopped or when the use of braces began. Twelve of 37 boys in the treated group had lost ambulation at a mean age of 11.5 ± 1.9 years, compared with 32/42, mean age of 9.6 ± 1.4 years ($P < 0.05$) in the untreated group. Of boys aged 12 years or more, 13/23 (53%) of the treated group could still walk compared to none of the untreated group.

Muscle strength: MRC score of 34 muscles was recorded every six months. Scores were cumulated and converted to a percentage of normal (where 100% = normal). Muscle strength at age 16 was 63% ± 4 in the treated group compared to 31% ± 3 in the untreated group, $P < 0.003$.

FVC: The treated group improved in FVC: 66% ± 14 treated versus 48% ± 22 untreated, $P < 0.007$.

Cardiac function: The deflazacort group improved in cardiac function, with significantly better values for fractional shortening and ejection fraction, and a lower incidence of dilated cardiomyopathy. Of note, angiotensin converting enzyme inhibitors were used more frequently in the treated group but their effect could not be isolated from those of deflazacort. The older age of the untreated group may also have biased the incidence of cardiomyopathy.

Scoliosis development: Fewer boys developed scoliosis in the treated group 10/37 (27%) than in the untreated group 28/42 (67%). Scoliosis when it did occur also tended to be less severe; none of the treated boys required corrective surgery in the treated group, compared with 12/28 (43%) of the untreated group.

Adverse events: All adverse events were more common in the treated group. Fractures occurred in both groups, with a similar incidence of long-bone fractures (24% treated group, 26% untreated group) but the incidence of vertebral fractures was greater in the treated group (20% versus 0%), although none contributed to any functional decline. Nineteen of the 37 participants in the treated group required bisphosphonates compared with none in the untreated group. Excess weight (BMI > 85% percentile) was present in both groups; 13/21 (62%) of the treated group versus 6/11 (55%) of the untreated group. Evidence of growth suppression and short stature was also seen in the treated group, with mean height gain being three times as much in the untreated group at age 12 years. Height values were not available for all children and some were younger than 12 years old, but the available data showed that only 3/20 (15%) of the treated group grew 4 cm per year or more, compared to 19/19 of the untreated group at age 12. Cataracts developed in 18/37 (49%) of the treated group; in 17 of 18 (94%) this was after more than five years of treatment. One patient required surgery.

Studies comparing deflazacort with prednisone daily dose regimens

Balaban 2005 reported a retrospective study of the long-term effect of daily dose corticosteroids in a cohort of 49 boys with DMD between the ages of 12 and 15 years. Eighteen boys were treated with prednisone, 12 with deflazacort, and 19 had no treatment. Parents had been informed about treatment alternatives and were offered the option of corticosteroid medication, and the choice of deflazacort or prednisone. The study site was in Denver, Colorado, USA; the authors report that the cost of deflazacort was much greater than prednisone (USD 3 per day versus USD 0.50 per day), and some families chose on the basis of cost.

The mean age of starting deflazacort was 7.45 ± 0.97 years, mean duration of treatment was 5.85 ± 1.5 years, and the starting dose was 0.9 mg/kg/day. The mean age of starting prednisone was 6.90 ± 1.0 years, mean duration of treatment 5.49 ± 1.98 years, and the starting dose 0.75 mg/kg/day. The benefits, including prolongation of the ability to walk 30 feet on level ground, were similar in groups treated with deflazacort or prednisone, as compared to the untreated boys. Excessive weight gain was more common in

prednisone-treated boys, leading to discontinuation of prednisone in three of the 18 boys in this group. Two of the 12 deflazacort-treated boys developed asymptomatic cataracts.

Intermittent corticosteroid regimens

Dubowitz regimen - prednisolone 10 days on, 10/20 days off

In order to lessen the adverse effects of long-term corticosteroid treatment, Dubowitz recommended an intermittent regimen of prednisolone 0.75 mg/kg/day for the first 10 days of every calendar month (treatment cycles of 10 days on prednisolone, 20 days off; Dubowitz 1991). An open study of 32 patients demonstrated that this intermittent regimen had a positive influence on strength at six months, followed by a slow decline at 12 and 18 months (Sansome 1993); weight gain and other side effects were much less than would be expected with continuous therapy. Subsequently, to increase efficacy, the investigators modified the regimen to a 10 days on prednisolone 0.75 mg/kg/day and 10 days off treatment cycle. The same research group highlighted the long-term tolerability of the intermittent (10 days on treatment, 10 days off) regimen of prednisolone (Dubowitz 2002; Kinali 2002). The four boys reported in these studies were started on prednisolone between four and five years of age, and followed up over a period of between 3.75 and over five years. These boys showed "remarkable improvement" (described by authors as gaining the ability to rise from the floor without Gowers' manoeuvre, hop on one or both legs, and run without waddle) and the functional benefit was partly sustained without the evidence of abnormal weight gain, demineralisation of bone, or other signs of chronic prednisolone toxicity. These studies, though including small numbers, also suggested that the beneficial effects of corticosteroids appear to be greater when treatment is initiated at a younger age, in the early ambulant phase (Dubowitz 2002; Kinali 2002). No long-term data exist reporting prolongation of ambulation with this intermittent regimen.

Kinali 2007 retrospectively analysed predictive factors for development of scoliosis in DMD in 123 DMD boys, aged 17 years or older. Thirty-seven of the 123 boys (30%) had received intermittent prednisolone (0.75 mg/kg/day, 10 consecutive days/month) for a median time of one year (two months to nine years), starting between 7.7 and 12.4 years (mean 9.5 years). The study authors used univariate analysis to relate age at onset of scoliosis and scoliosis severity at 17 years with glucocorticoid treatment and other factors. There was a positive relationship between age at scoliosis onset (later) and duration (longer) of prednisolone treatment ($r = 0.44$, $P = 0.01$, $n = 36$). Severity of scoliosis at 17 years and duration of prednisolone treatment showed no relationship ($P = 0.64$). The intermittent prednisolone regimen in Kinali 2007 appeared to be associated with a later onset of scoliosis; the trial author concluded that the observation of unchanged scoliosis severity at 17 years probably reflected the shorter overall glucocorticoid exposure in this cohort.

Parreira 2007 "sought to select a sequence of tests which can be applied in a practical and swift fashion in an outpatient setting to assess patients' response to steroid therapy" and reported its application to 32 boys with DMD who were treated with intermittent prednisolone (0.75 mg/kg/day in an intermittent course of 10 days on, 10 days off), or deflazacort (1 mg/kg/day). The trialists did not report the number of boys using prednisolone or deflazacort regimens. Age range at the start of treatment was 5 years 8 months to 8 years 8 months, and the boys were assessed on 10 visits, monthly for the first six months and then every two months until the 14-month end point. Of the 26 boys who complied with the medication and assessment regimen, eight lost ambulation during the study period. The benefit appeared modest. Over the 14-month period, muscle strength assessment showed worsening of MRC indices, but there was a statistically significant improvement in weight lifting test results ($P < 0.001$), and improvement in time taken to walk nine metres. The data presented did not allow comparison of the effect of intermittent prednisolone with that of daily dose deflazacort. The study authors did not describe adverse effects. Parreira 2007 emphasised that muscle strength measurements alone are not sufficient for evaluating the results of corticosteroid treatment, and that tests analysing function and execution should also be performed.

Connolly regimen - twice weekly prednisolone (5 mg/kg/dose)

In a further attempt to decrease long-term adverse effects, Connolly 2002 devised a twice-weekly regimen of prednisone given every Friday and Saturday (5 mg/kg/dose). Twenty treated boys (with an average age of eight years) were compared to historical controls. Strength, evaluated with hand-held manometer and grip meter, improved over six to 12 months. At least six of the 20 boys developed irritability, which led to discontinuation of treatment in two, and a 25% to 30% dose reduction in four patients. Long-term results for this treatment regimen have not been reported.

Nigro regimen - Deflazacort 0.6 mg/kg/day 20 days on, 10 days off

Professor Nigro's group in Naples, Italy, who studied 56 boys, utilised this intermittent regimen of deflazacort; Biggar 2004 reported the results, and compared them with the daily dose deflazacort regimen used in 32 of 60 boys in Toronto, Canada. (The Toronto patients were part of the overlapping patient cohorts described in Alman 2004, Biggar 2001, Bonifati 2006, and Silversides 2003).

In Professor Nigro's Naples group, 56 boys at mean age 6.0 ± 1.5 years, were started on the intermittent regimen of deflazacort 0.6 mg/kg given on the first 20 days of each month. Nineteen of the

56 stopped deflazacort within one month because of "economical and/or environmental reasons", and they served as a control group for comparison. The deflazacort-treated boys were also given daily supplements of vitamin D (880 iu) and calcium (1000 mg). Duration of deflazacort treatment was more than four years in all boys. In the control group of 19 boys from Naples, Italy, only four (21%) were able to walk 10 metres at nine years and none at 12 years. Of the 37 boys treated with intermittent deflazacort (0.6 mg/kg/day for the first 20 days of each month), 97% (36/37) could walk 10 metres at nine years, 35% (9/26) at 12 years and 25% (3/12) at 15 years. This represents significant improvement in comparison to the previous natural history studies, which reported loss of walking in untreated boys with DMD at mean ages of 8.8 years (Dubowitz 1978), 9.5 years (Gardner-Medwin 1980), and 10.5 years (Allsop 1981). However, in comparison, the daily dose deflazacort 0.9 mg/kg/day regimen used to treat the 32 boys in Toronto, Canada, appears to have a bigger impact on walking; all 32 were able to walk 10 metres at 9 years, 83% (19/23) at 12 years, and 77% (10/33) at 15 years. The key difference in side effects was with regards to cataracts. No cataracts were noted in the 37 patients treated with the intermittent 20 days on, 10 days off Nigro regimen, compared with the 30% who developed asymptomatic cataracts among 32 patients treated with daily dose deflazacort.

Long-term studies comparing daily prednisolone with intermittent prednisolone (10 days on, 10 days off)

Ricotti 2013 was an observational study utilising longitudinal clinical data entered into the UK North Star database from 17 participating paediatric neuromuscular centres. The investigators analysed data on 360 boys (age range 3 to 17 years) who had received prednisolone (191 on an intermittent regimen of 10 days on, 10 days off, and 169 on a daily dose regimen). The mean duration of treatment and follow-up was 3.9 years. The median time to loss of ambulation was 12 years in the intermittent treatment group and 14.5 years in the daily treatment group; the hazard ratio (HR) for intermittent treatment was 1.57 (95% CI 0.87 to 2.82). Longitudinal analysis of the North Star Ambulatory Assessment (a validated composite scale to measure function in ambulant DMD boys) showed a faster rate of decline after age seven in those on the intermittent versus the daily regimen, with the difference between the two regimens increasing by 1.58 units per year (95% CI 1.04 to 2.11, $P < 0.001$), although respiratory and cardiac outcomes did not differ between the two groups. Side effects were more common in the daily treatment group, including cushingoid features (33% versus 15%), hyperactivity (23% versus 15%), and hypertension (22% versus 5%). Both groups gained excessive weight. The daily group had a lower mean height, MD 1.09 (95% CI 0.78 to 1.40, $P < 0.001$). Overall increase in BMI was greatest in the daily treatment group: MD 0.43 (95% CI 0.11 to 0.74, $P < 0.01$). Ricotti 2013 reported vertebral fractures (vertebral wedging on lateral spine radiography) in 4% of boys on the intermittent regimen and 8% of boys on the daily regimen.

Studies selectively focusing on cardiac outcome

Markham 2005 reported cross-sectional echocardiographic shortening fraction data in a retrospective review of 111 subjects with DMD who had been followed up in two centres. Forty-eight subjects had been treated (29 with prednisolone, 19 with deflazacort) for six months or longer, and they were compared with the 63 untreated subjects. The dose regimen was not reported. Age range was three to 11 years (treated 11 ± 4, untreated 12 ± 5), and mean length of treatment was 3 ± 2.5 years. Of the 48 treated subjects, 10 had been treated with corticosteroids for 4.2 ± 1.6 years, but the treatment had been stopped because of adverse effects at the time of echocardiography.

The shortening fraction was lower in the untreated group than in the corticosteroid-treated group (30% ± 7% versus 36% ± 5%; $P < 0.001$). The difference in shortening fraction between the two groups was most obvious in subjects over 10 years of age: in comparison with the corticosteroid-treated subjects, the untreated subjects older than 10 years were 15 times more likely to have a shortening fraction less than 28% ($P < 0.01$). Though the two groups were similar with regards to baseline age, body mass and left ventricular indices, the retrospective design of this study carries the implicit risk of biased treatment allocation.

In this update we did not select any further studies selectively focusing on cardiac outcome, as a separate Cochrane review addressing this issue is in development (Quinlivan 2012).

Studies selectively focusing on cough efficiency and respiratory muscle strength

Daftary 2007 studied 10 corticosteroid-treated and 25 non-treated patients in a retrospective case-control study. The age range of the treated group was seven to 21 years (median 10 years). Three patients were treated exclusively with prednisone, five exclusively with deflazacort, and two were started on intermittent prednisone but later switched to daily deflazacort. Prednisone was started at a dosage of 0.75 mg/kg/day and deflazacort at 0.9 mg/kg/day. The mean duration of corticosteroid therapy was 8.2 years (range 1 to 14 years). Peak cough flow (PCF) and maximum expiratory pressure were significantly higher in the corticosteroid-treated group. Median PCF was 215.0 L/min in the treated group compared with 177.5 L/min in the non-treated group ($P \leq 0.05$). Median maximum expiratory pressure (MEP) was 62.5 cm H_2O in the treated group as compared with 44.5 cm H_2O in the non-treated group ($P \leq 0.05$). These results are suggestive that corticosteroid therapy is beneficial in preserving respiratory muscle strength and cough efficiency in DMD, and are in concordance with previous randomised (Griggs 1991; Mendell 1989) and non-randomised studies (Biggar 2006), which reported preservation of FVC. Of note, Daftary 2007 observed that patients with DMD were weak and therefore often unable to sustain exhalation for six seconds, as required by the American Thoracic Society to meet pulmonary function test acceptability criteria, and arbitrarily chose a three

second (or more) exhalation criterion for acceptability. This indicates the need for consensus on customisation of the test protocols, taking into consideration the marked respiratory muscle weakness in DMD.

In this update we did not select any further non-randomised studies selectively focusing on cough efficiency and respiratory muscle strength as these outcomes are not the primary focus of this review. A Cochrane review of Mechanical insufflation-exsufflation for people with neuromuscular disorders has been published (Morrow 2013).

Vertebral fractures with daily dose corticosteroid regimens

Bothwell 2003 highlighted the need for caution with the long-term use of corticosteroids. Twenty-five boys with DMD were treated with daily corticosteroids (one prednisolone, 13 deflazacort, and 11 prednisolone before switching to deflazacort) for a median duration of 4.5 years (inter-quartile range (IQR) 3 to 10 years). The dosage used was 1 mg/kg/day. The trial authors do not describe whether the dose was reduced over time, for example in response to excessive weight gain. All boys were prescribed calcium supplements and 22 of the 25 boys were also on vitamin D. Ten of the 25 boys (40%) sustained vertebral fractures; eight were symptomatic with backache and two had fractures detected on spinal radiographs taken because of low bone mineral density results. The first fracture occurred 40 months into treatment. Extrapolating from the 10 boys who sustained a vertebral fracture, Kaplan-Meier analysis predicted that 50% of treated boys would have a vertebral fracture by 53.5 months, and 75% by 100 months of treatment.

King 2007 reported vertebral and long-bone fractures among 75 boys in the course of long-term daily dose corticosteroid treatment, comparing them with 68 boys who had not been treated or had received brief submaximal doses. The mean age of treated boys was 16.9 ± 5.6 years (range 6.1 to 30.5 years) compared to 14.4 ± 8.1 years (range 1.1 to 39.6 years) in the non-treated group. Thirty-six boys were treated with prednisone, 25 with deflazacort, and 14 had been on both. The daily dose regimen starting dose was prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day. At the final clinic visit prior to data collation, the average corticosteroid dose of the treated group was 0.55 mg/kg (range 0.10 to 0.78 mg/kg). The mean duration of corticosteroid treatment was 8.04 years (± 5.2 years, range 0.5 to 18.5 years). The boys who began treatment were also prescribed calcium supplements, either as calcium carbonate 350 mg three times daily or a calcium tablet with vitamin D supplement (750 to 1200 mg daily), but the trialists did not report the degree of compliance with these supplements. Treated boys walked independently 3.3 years longer, had lower prevalence (31% versus 91%) and severity (Cobb angle 11˚ versus 33˚) of scoliosis as compared to the non-treated boys, but 32% of these 75 corticosteroid-treated boys developed a compression vertebral fracture. Eighty per cent of vertebral fractures were identified incidentally during routine scoliosis screening radiographs, and not because of patient complaint. Vertebral fractures were reported not to be a motivation for discontinuing corticosteroids. Vertebral compression fractures are not a feature in the natural history of DMD, and none were found in the 68 non-treated boys in this study (King 2007). A higher percentage of corticosteroid-treated boys experienced long-bone fractures, with a risk 2.6 times greater than boys on no treatment. Whether the long-bone fractures were more frequent in the boys who suffered vertebral fractures was not reported, and how these complications might best be prevented or treated was not discussed. The percentage of vertebral fractures with a long-term intermittent, versus a daily prednisolone regimen is discussed above.

Controversy in clinical role of corticosteroids in DMD

The 124th European Neuromuscular Centre (ENMC) International Workshop on treatment of DMD agreed "that the evidence for the use of daily steroids in DMD is now established and that trials of other treatments should be against this 'gold standard'" (Bushby 2004). The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society recommended that boys with DMD should be offered prednisone (at a dose of 0.75 mg/kg/day) as treatment, and that "the offer of treatment with corticosteroids should include a balanced discussion of potential risks" (Moxley 2005) . Dubowitz 2005 expressed concern regarding the adverse effects of long-term daily dose corticosteroid treatment and concluded, "What is now urgently needed is a prospective, collaborative, multicentre, comparative study of the time-honoured, and somewhat entrenched, daily regimen against some of the alternative schedules, in order to compare both efficacy and side-effects". He further recommended that "in the meantime, paediatricians as well as parents should be offered the choice of either the continuous or the intermittent schedule. Hopefully we shall not be having the same debate in another 10 years time".

For this review we were only able to identify one RCT comparing daily with intermittent prednisolone regimens over a 12-month period (Escolar 2011). This study, performed in boys with a mean age of 7.3 years, found no difference in efficacy between the regimens or overall side effect profile, with the notable exception of greater weight gain and lower linear height in the daily treatment group. A non-randomised longitudinal study over four years demonstrated consistent findings in terms of weight and height but also a divergence in efficacy for time to loss of ambulation and functional ability, favouring a daily regimen after the age of seven years. In this study, other side effects, including hypertension, were also more common on the daily regimen. Overall, the long-term (more than 12 months) risk/benefit ratio of daily versus intermittent prednisolone regimens remains unclear.

The FOR-DMD Study is currently open and aims to find the optimum corticosteroid regimen for DMD (Guglieri 2015). It is an international trial enrolling patients at 40 sites in five countries,

randomising them to one of three regimens: daily prednisolone, daily deflazacort or intermittent prednisolone (10 days on and 10 days off). It aims to follow participants for three to five years and may address remaining questions over the long-term outcomes of intermittent regimens.

Costs

The oral corticosteroids, including prednisone/prednisolone and deflazacort are not expensive. In the United Kingdom, the annual cost of prednisolone (soluble tablets) for a 30 kg boy is estimated at GBP 133 and the corresponding figure for deflazacort at the equivalent dosage of 0.9 mg/kg/day is GBP 480 (BNF 2016). The much bigger costs are those for drug administration and the surveillance required to monitor both benefits and adverse effects, and these have not been calculated. The issue of cost should not be underestimated, as in countries where the parent or patient has to buy medication, cost of the corticosteroid preparation may force the patient's choice in favour of the cheaper drug (Balaban 2005). The major aim of corticosteroids in the ambulant phase of DMD is to prolong the ability to walk. In the natural course of DMD, loss of walking ability at the mean age of 9.5 years (range 6 to 13) is followed by development of scoliosis, which is rapidly progressive during pubertal growth spurt years. This complication requires treatment with bracing, surgery, or both. Scoliosis and its treatment have implications for patients' quality of life and involve anaesthetic hazards and the surgical risks of extensive spine surgery. Data from non-randomised studies suggest that prolongation of ambulation, either with rehabilitation in calipers (Rodillo 1988), or pharmacologically with prednisolone (Tunca 2001; Yilmaz 2004), or deflazacort (Biggar 2006), reduces the risk of development and progression of scoliosis. The decrease in incidence and severity of scoliosis in corticosteroid-treated individuals has been postulated in part to the possible increase in paraspinal/axial muscle strength (Muntoni 2006). A decrease in incidence of scoliosis and avoidance of scoliosis surgery as a result of corticosteroid therapy would reduce the financial cost of managing these patients, but evidence for this from randomised studies is lacking. The same optimism and caution can be extended to respiratory and cardiac complications of DMD.

Overall completeness and applicability of evidence

DMD has a uniform course with regards to evolution of motor and function disabilities. Most of the participants in the included studies were between eight and 15 years old. There were not enough data available to stratify the participants according to age and to observe the response to corticosteroids in relation to age. Future updates could consider subgroup analysis by genotype or phenotype, although trials may be too small for this to be possible.

Data from the included studies and the non-randomised and cohort studies converge in suggesting a similar improvement in response to corticosteroids in DMD. It is very likely that the results are applicable to all boys with DMD, especially in their ambulant phase. We would not anticipate that in non-ambulant, wheelchair-dependent patients with DMD who have been corticosteroid-naïve in the past, corticosteroid treatment would restore the ability to walk. However, the benefit to upper limbs, cardiac and respiratory function remains a possibility, and this area needs further study.

The option of treatment with corticosteroids should be discussed in detail with the carers of ambulant boys with DMD. It would be prudent to undertake this treatment only in centres with expertise and facilities for comprehensive multidisciplinary pre-treatment assessment and regular long-term monitoring of benefits and adverse effects. Protocols of management, with close monitoring for adverse effects and adjustment of corticosteroid dose would be an essential prerequisite for patient safety.

Quality of the evidence

Corticosteroids versus placebo

Trials included in the meta-analyses for this comparison provided moderate quality evidence for effectiveness outcomes (muscle strength and functional tests) (Summary of findings for the main comparison). We downgraded the quality of evidence once because the risk of allocation bias was unclear in all studies that provided data for the analyses and for potential publication bias. Removal of a trial at high risk of bias did not substantially change the results of meta-analyses. Two studies were not fully published or did not report results in a form suitable for reporting (Brooke 1996; Todorovic 1998). Bäckman 1995 provided only adverse event data.

Angelini 1994 was a small two-year study (n = 28) with design limitations, and a very high dropout rate at two years. Although the trial assessed prolongation of ambulation, the statistical technique used to analyse the data was not appropriate. The change in MRC index favoured deflazacort over placebo at two years, but timed function test results at 24 months were very imprecise, allowing for the possibility of effects in either direction.

Weekend-only versus daily prednisone

Escolar 2011 (n = 64) was a year-long equivalence trial comparing weekend-only and daily dosing of prednisone. We judged the study to be at a low risk of bias other than for attrition and reporting bias. Results were very imprecise, producing a low quality of evidence for manual muscle testing (MMT), body mass index (BMI) and behavioural change. As CI fell within equivalence limits for muscle strength measured by quantitative muscle testing (QMT),

10-metre walk and four-stair climb, we considered the quality of evidence for these outcomes moderate (Summary of findings 2).

Deflazacort versus prednisone

For all assessed outcomes, the evidence comparing prednisone with deflazacort at one year was very low quality (Summary of findings 3). Two newly included studies comparing different corticosteroids did not fully report data, making only limited analysis possible (Bonifati 2000; Karimzadeh 2012). Karimzadeh 2012 was at a high risk of bias in most domains and Bonifati 2000 was at unclear risk of selection bias and high risk of selective reporting. We downgraded evidence from these studies twice for serious limitations in trial design and implementation. Brooke 1996, a large four-arm study (n = 196) comparing two doses of deflazacort, prednisone and placebo, also represented a risk of publication bias, being available only as an abstract, providing little useful data.

Potential biases in the review process

Searches were comprehensive, and studies we identified were consistent with other reviews of these interventions in DMD. We attempted to contact study authors for clarification or missing data; some responded but others did not. Methods have not substantially changed from previous versions of the review. We added some additional detail to comply with current Cochrane standards; however, the new trials presented few opportunities for meta-analysis.

Agreements and disagreements with other studies or reviews

The American Academy of Neurology (AAN) produced practice guidelines on corticosteroid treatment of Duchenne muscular dystrophy (DMD) following a systematic review of the literature from January 2004 to July 2014, and identification of 34 studies (Gloss 2016). The conclusions of this Cochrane review are compatible with the recommendations of the AAN committee, who found evidence that:

- prednisone and deflazacort should both be offered for improving muscle strength;
- prednisone and deflazacort are possibly equally efficacious in improving motor function;
- prednisone may be associated with greater weight gain than deflazacort;
- deflazacort may be associated with a higher risk of cataracts than prednisone;
- a weekend-only regimen of prednisone 10 mg/kg/weekend day may be equivalent to prednisone 0.75 mg/kg/day over a 12-month period;
- prednisone 0.75mg/kg/day is associated with significant risk of weight gain, hirsutism and cushingoid changes.

The AAN guidelines also examined other outcomes - cardiac and respiratory outcomes, and scoliosis that we did not address in this update.

AUTHORS' CONCLUSIONS

Implications for practice

Randomised controlled trials (RCTs) provide moderate quality evidence that treatment with corticosteroids in Duchenne muscular dystrophy (DMD) compared with placebo improves muscle strength and function, including respiratory muscle strength and function, for six months. There is evidence of continuing benefit on muscle strength and function at one year. On the basis of the evidence available, our confidence in the effect estimate for the efficacy of a 0.75 mg/kg/day dose of prednisolone or above is fairly secure. Little RCT evidence is available on longer-term effects of corticosteroids versus placebo; one small longer-term RCT found an improvement in muscle strength at two years with deflazacort, with imprecise results on function at two years. Not enough data were available to adequately compare the efficacy of prednisone and deflazacort, although there is very low quality data favouring deflazacort for less weight gain. In the short term (12 months), a weekend-only prednisolone regimen is as effective as daily prednisolone according to low to moderate quality evidence from a single trial. Low quality evidence did not show a difference between the regimens on change in body mass index (BMI). A greater increase in linear height occurred in the weekend-only regimen, but no appreciable difference in other side effects. The long-term benefits and harms of daily corticosteroids or daily versus intermittent regimens are not clear. Non-randomised studies suggest that clinically significant prolongation of time to loss of ambulation is possible with daily corticosteroids, though potential harms, including weight gain, behavioural changes, vertebral fractures, and cataracts, are significant. Non-randomised studies also suggest there may be a divergence in efficacy between daily and intermittent prednisolone regimens beyond the age of seven years, with greater side effects from daily regimens in the longer term.

Implications for research

Many issues, including the ideal age or functional stage for initiation of treatment, the optimal corticosteroid type, regimen and dose, strategies for prevention of osteoporosis, and the age for discontinuation of corticosteroid treatment still need to be clarified with RCTs. This will require national and international collaboration, standardised and comparable protocols of assessment, timely publication of studies and the facility of sharing anonymised individual patient data. While previous studies have focused mainly on muscle strength, walking, and motor aspects, studies are now

beginning to address respiratory, cardiac, and quality of life issues; this review or separate Cochrane reviews will examine these outcomes in future. The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society emphasised the need for studies to be long term to evaluate the effect of corticosteroids on ambulation, respiratory function, cardiac function, and quality of life. There is a need to identify and evaluate strategies to prevent the predictable adverse effects of long-term corticosteroid treatment, particularly excessive weight gain, osteoporosis, and growth retardation. The incorporation of patient and caregiver evaluations of the beneficial and adverse effects of treatment, as additional outcome measures, should be considered. The impact of corticosteroid therapy on quality of life of the patient and the family, in relation both to benefits and adverse effects, should also be evaluated.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Angelini 1994

Methods	Randomised double-blind trial. Randomisation followed 2:1 scheme
Participants	28 boys with DMD, all ambulant at entry into the trial DMD proven by dystrophin or DNA studies Mean age: • deflazacort 98.65 ± 13.70 months • placebo 96.55 ± 15.96 months
Interventions	Deflazacort 2 mg/kg on alternate days for 2 years (n = 17) or placebo (n = 11)
Outcomes	Age at loss of ambulation, age at loss of ability to rise from floor, MRC index from 4 muscles Monitoring of: weight and height every 2 months; blood pressure; WBC; RBC and haematocrit; plasma glucose; CPK and ions. ECG and x-rays of chest and hand for bone age at beginning and end of treatment. Assessment for cataracts every 2 years
Declarations of interest	Not stated
Funding sources	A grant from Telethon, Italy
Notes	Dates: not reported Location: Italy Ethical approval and consent procedures not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated to be randomised "randomization followed a 2:1 scheme. At the beginning of the trial the patients in each arm of the study, both in the drug and placebo group, were similar for motor function. At the beginning of trial, the two groups had the same age, MRC index, and functional grades"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placbo-controlled On balance, judged to be of low risk although "Blinding and maintenance of blinding during trial was possible since only

Angelini 1994 (*Continued*)

		the coordinator, but not the examiner, had the key of randomization. It is possible that, during prolonged treatment, blinding was destroyed by the appearance of side effects of the drug"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Blinding and maintenance of blinding during trial was possible since only the co-ordinator, but not the examiner, had the key of randomization. It is possible that, during prolonged treatment, blinding was destroyed by the appearance of side effects of the drug"
Incomplete outcome data (attrition bias) All outcomes	High risk	"During the 4 years of our study (1 year of natural history and 3 years of actual drug administration trial) lack of compliance was seen in 5 placebo and 4 drug-treated patients" and 11 deflazacort and 6 placebo participants dropped out for other reasons. Authors state "lack of significance in some tests may be due to dropout of DMD patients"
Selective reporting (reporting bias)	Unclear risk	Data reporting comprehensive in tables at 6, 12 and 24 months, but not specified in detail in methods
Other bias	Low risk	None identified

Beenakker 2005

Methods	Randomised, double-blind, placebo-controlled, cross-over trial
Participants	17 ambulant boys with DMD, mean age 6.29 (SD 0.92) years Inclusion criteria: boys 5 to 8 years old with clinically classic DMD, grossly elevated serum CK, almost no dystrophin on muscle biopsy (less than 5% of fibres), able to walk without assistance Exclusion criteria: use of steroids within the 2 months before start of trial
Interventions	Prednisolone 0.75 mg/kg/day (n = 7) or placebo (n = 10) for the first 10 days of every month, given for 6 months, then crossed over to the alternative treatment after a 2-month washout period
Outcomes	Total muscle force measured by hand-held dynamometry, timed 9-metre run, 4-stair climbing and rising from floor times, quality of life assessed by DUX-25, weight, blood pressure, upper and lower extremity functional grade (Brooke 1996). Adverse events were evaluated at each visit by physical examination, and patient and parent interview using a standard list of steroid-related adverse events

	Measurements were performed each month on days 1, 10 and 30 by a single investigator. Quality of life was assessed at the start and end of the 6-month treatment periods
Declarations of interest	Not stated
Funding sources	Prinses Beatrix Fonds
Notes	Ethical approval and informed parental consent obtained Dates: not stated Location: the Netherlands (assumed)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Low risk	No information in paper. Randomisation by pharmacist. Assessed as low risk as trial authors provided information indicating adequate allocation concealment to the review authors for a previous version of this review
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled, double-blind, but does not state whether placebo and active drug were the same in appearance or taste Unblinding likely because of higher incidence of adverse effects
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, but adverse effects may have unblinded outcome assessors in this study
Incomplete outcome data (attrition bias) All outcomes	Low risk	17 participants (10 placebo), 7 prednisone. 1 in placebo group unavailable for follow-up (fracture after 10 days' prednisone treatment) and excluded from analyses
Selective reporting (reporting bias)	Low risk	Largely well reported although some data missing for some outcomes e.g. quality of life - paper indicates no difference between groups Adverse events well reported
Other bias	Low risk	Cross-over, with 6-month treatment periods. 20-day untreated period then 2-month washout between interventions. Authors

		tested for a period effect

Bonifati 2000

Methods	Double-blind, randomised, multicentre, equivalence study
Participants	19 boys with DMD (1 not included in evaluations as he received both drugs, each for 6 months) Inclusion criteria: diagnosis confirmed by dystrophin immunohistochemistry, age over 5 years, preserved ability to ambulate independently, and no previous steroid therapy. No patient had any recognised contraindication to steroid therapy • Deflazacort: mean age 8.6 years (range 5.3 to 14.6 years) • Prednisone: mean age 7.5 years (range 5.1 to 10 years) (Natural history controls not considered in this review)
Interventions	Deflazacort or equivalent dose of prednisone Deflazacort (0.9 mg/kg/day) (n = 8) Prednisone (0.75 mg/kg/day) (n = 11) Duration of treatment: 1 year
Outcomes	Muscle strength evaluated by MRC scale in 4 muscles, 2 in the right upper limb (deltoid and triceps) and 2 in the right lower limb (iliopsoas and quadriceps femoris); the summed MRC score was used in comparing the 2 groups in statistical analyses Functional tests: gait (walk for 10 metres), rising from a chair and from the floor, and climbing 4 steps. Sum of the grades in the functional scores calculated. Lower score = better performance At baseline and 3-monthly thereafter: biochemical and neurological screening (serum CK, glucose, electrolytes, haematocrit, complete blood count); height, weight and BP monitoring for corticosteroid side effects. Occurrence of cushingoid features, acne, hirsutism evaluated clinically Parents were asked to report behavioural changes, insomnia, anorexia, increased appetite, and GI problems X-ray of left hand for bone age and eye examination for cataract conducted at baseline and after 1 year of corticosteroid treatment Time points reported 3, 6, 9 and 12 months (graphically)
Declarations of interest	Not stated
Funding sources	Telethon (grant number 916C)
Notes	Dates: not stated Children were recruited from 2 neuromuscular centres (Pavia and Padua, Italy) Informed consent obtained

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Bonifati 2000 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"The two groups were randomized and stratified on the basis of age and disease severity" - precise method unclear There was some baseline imbalance "The absolute values of scores appeared better in the deflazacort group, but the difference did not reach statistical significance. This type of response could be related to slightly less severe baseline values"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the treating physician nor the patient's family knew whether a child was on prednisone or deflazacort"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Report suggests the outcome assessor was the treating physician, who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	One dropout in prednisone group. Paper does not discuss how this was managed; however we consider this unlikely to represent an important risk of bias
Selective reporting (reporting bias)	High risk	Efficacy data reported without measures of variability graphically. Trial authors did not respond to request for raw data Adverse events fully reported
Other bias	Low risk	None identified

Brooke 1996

Methods	Randomised, double-blind, placebo-controlled trial with 4 arms
Participants	196 boys with DMD randomised
Interventions	Initially: • prednisone 0.75 mg/kg/day • deflazacort 0.9 mg/kg/day • deflazacort 1.2 mg/kg/day • placebo After 3 months the placebo group was re-randomised to one of the other interventions
Outcomes	Primary outcome measures: • Average muscle score • Weight

Brooke 1996 (*Continued*)

	Time points: 3 months, end of 12 months' treatment (not stated whether other time points were measured) "Features of steroid toxicity were rated as none, mild, moderate and severe"
Declarations of interest	Not stated
Funding sources	Muscular Dystrophy Association Canada and Nordic Merrell Dow Research
Notes	No other study characteristics reported - abstract only Dates: not stated Location: Canada (assumed)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised, methods not described in abstract
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information other than stated to be double-blind. Placebo-controlled (placebo not described)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	High risk	Available as abstract only
Other bias	Unclear risk	No other bias identified, but the abstract presented little information by which to form a judgement. Participants in the placebo group were randomly assigned to other deflazacort or prednisone groups after 3 months

Bäckman 1995

Methods	Randomised double-blind, cross-over trial
Participants	37 boys with DMD (22 ambulant and 15 wheelchair-dependent at entry to the trial), 4 boys with Becker muscular dystrophy (all ambulant) DMD established by positive Gower sign, pseudohypertrophy of calf muscles, CK 10

	times upper limit of reference value (dystrophin was measured in 26 boys, all had none) ; BMD diagnostic criteria not stated (all 4 had reduced dystrophin) Mean age DMD (years): ambulant, 7.8 +/- 2.1 (range 4.0 to 10.9), wheelchair-dependent 12.5 years +/- 3.3 (range 8.0 to 19.4) Mean age BMD (years): 9.6 +/- 3.4 (range 6.1 to 13.8 years)
Interventions	Prednisolone 0.35 mg/kg/day given for 6 months, then crossed over to placebo, or vice versa
Outcomes	MRC score on 26 muscle groups, myometry on 24 muscle groups, modified Brooke and Scott scores, hand-grip, timed 4-stair test and 10-metre walk test. Additionally, the maximum height the boy could achieve with a single step and lowest height from which it was possible to rise from a chair unaided, weight gain, and laboratory tests. Patients were evaluated before treatment and every 3rd month afterwards Parents were asked to report signs and symptoms "possibly related to treatment" at end of study
Declarations of interest	Not stated
Funding sources	Grants from Sven Johansson Foundation
Notes	Dates: not stated Location: university hospital and rehabilitation centre in Sweden Local ethics committee approval obtained

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both prednisolone and placebo were administered as white powder in gelatin capsules of the same weight"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as "double-blind" - investigator was also outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 withdrawal (weight gain and slight cardiac insufficiency) of a wheelchair-dependent boy. 2 deaths: 1 pneumonia and 1 cardiac arrhythmia during appendectomy; report does not say from which group

Bäckman 1995 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No protocol. Outcomes not fully specified but are reported as listed
Other bias	Low risk	None identified. Student's t-test used to reveal any learning or carry-over effects following cross-over - none identified

Escolar 2011

Methods	Randomised, double-blind, placebo-controlled, multicentre, international, prospective, equivalence trial
Participants	64 participants Ambulant, steroid-naïve boys with a confirmed diagnosis of DMD, age 4 to 10 years ("confirmed diagnosis" not defined) Mean age 7.3 years, median age 7.2 years Inclusion criteria: "evidence of muscle weakness by clinical or functional assessment and the ability to provide a reproducible unilateral quantitative muscle testing (QMT) biceps score within 15% of the first assessment" Exclusion criteria: • history of significant concomitant illness or significant impairment of renal or hepatic function, or other contraindication to steroid therapy • symptomatic DMD carrier • positive purified protein derivative test (for tuberculosis) • lack of prior exposure to chickenpox or immunisation • use of carnitine, glutamine, coenzyme Q10, other amino acids or any herbal medications within the last 3 months • history of symptomatic cardiomyopathy • prior attainment of quota for the age group in which the patient belongs Child Behaviour Checklist scores for aggressive behaviour and externalising • mean externalising score weekend • mean aggressive score weekend
Interventions	Weekend-only oral prednisone: 5 mg/kg on Saturday and 5 mg/kg on Sunday, plus a daily placebo Daily dose group: daily prednisone 0.75 mg/kg/day, plus placebo on Saturday and Sunday 32 participants in each group Concomitant medications allowed during the study included vitamin D, calcium, ranitidine, and Tums. Participants were advised to follow a high protein, low carbohydrate, low fat diet Criteria for dose reduction: 1. An increase in BMI (kg/m^2) greater than 10% over 3 months 2. A fasting blood sugar greater than 100 mg/dL after dietary modification 3. An increase in diastolic blood pressure greater than 10 mm Hg over upper limit of normal for age 4. An increase in systolic blood pressure greater than15 mm Hg since last visit, after 1 month of low sodium diet 5. Otherwise non-manageable side effects

Escolar 2011 (*Continued*)

	Compliance checks done by pill counts and review of medication diaries
Outcomes	8 visits total 2 screening visits (baseline) Month 1, 3, 6, 9, 12 (the DEXA and ophthalmology assessments baseline and month 12 visits only) Post-study visit - within 1 month of month 12 Efficacy: • Muscle strength: QMT arm score, lb; QMT leg score, lb; QMT elbow flexors, lb; QMT elbow extensors, lb; QMT knee flexors, lb; QMT knee extensors, lb; QMT grip score, lb; manual muscle testing score • Timed tests (log seconds): 10-metre walk; 4-stair climb; supine to standing • Pulmonary function: forced vital capacity % predicted; forced expiratory volume in 1 second % predicted; maximal voluntary ventilation and maximal inspiratory pressure • Mobility function scales: Brooke upper extremity; Vignos lower extremity Adverse effects: Anthropometrics: BMI in kg/m^2; height in cm; weight in kg Vitals: • systolic BP, mmHg • diastolic BP, mmHg • blood glucose mg/dL DEXA: lumbar spine Z scores Child Behavior Checklist: total problems; internalising; externalising; anxious/depressed; somatic complaints; withdrawn/depressed; attention problems; aggressive behaviour Analysis: The average of QMT scores from 2 screening visits and 2 x 12 month visits i. e. change from baseline to 12 months The equivalence limit was defined using the baseline data and choosing an equivalence limit of approximately 1 SD or less of the baseline distribution For each endpoint, the observed difference from baseline (+SD) and the 95% confidence limits of the differences in changes between treatments were calculated
Declarations of interest	Full disclosures listed in report. Several authors have received honoraria or are on advisory committees for pharmaceutical companies but none seems to have direct role in this study or drug
Funding sources	Muscular Dystrophy Association, General Clinical Research Center (GCRC), and the National Institutes of Health
Notes	"Recruitment took place over 3 years beginning November 2003; last participant completing November 2007 Location: multicentre, US Approved by the Institutional Review Board at each institution. Written informed consent obtained from parents or caregivers

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	"Eligible participants were randomized by the CINRG Coordinating Center within site and equal-sized age stratum (4-6 years, 7-10 years) using a random permuted block randomization scheme (block sizes 2 and 4)" "CBCL T scores of aggressive behavior and externalizing were the only significant differences at baseline and were not believed to be clinically meaningful; thus, the randomization procedure was successful"
Allocation concealment (selection bias)	Low risk	Communication from trial author (D Escolar): "At enrollment the randomization database is accessed to obtain and consume the next preallocated enrollment slot that will designate the patient's random group assignment. The enrollee's PIN number is added to the consumed record in the randomization database as documentation of that assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial author provided information: "Blinded were participants, physicians, clinical evaluators, coordinators and central medical monitor/ research team. Unblinded: research pharmacist" Double-blind. Trial authors confirmed "capsules identical in appearance and taste"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial author provided information: "Blinded were participants, physicians, clinical evaluators, coordinators and central medical monitor/ research team. Unblinded: research pharmacist" Double-blind. Trial authors confirmed "capsules identical in appearance and taste" Each treatment group had similar outcomes e.g. improvements in strength, increase in BMI so it would be difficult to predict treatment group from individual results
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 participants withdrew before the end of the study (4 in the weekend-only group and 2 in the daily group). Study flow chart indicates that all 32 participants starting trial

Escolar 2011 (*Continued*)

		in each group were analysed Unclear whether analysis took dropouts into account
Selective reporting (reporting bias)	High risk	Outcomes measured at 3-month intervals but report only includes data for 12-month time point in tables
Other bias	Low risk	None identified

Griggs 1991

Methods	Randomised, double-blind trial with 2 treatment groups and 1 placebo group
Participants	99 boys with DMD, age range 5 to 15 years. Mean age (SD) years; placebo group 9.55 (± 2.44); 0.3 mg/kg 9.63 (± 2.53); 0.75 mg/kg 9.36 years (± 2.88) 70 of the 99 subjects were ambulant, either independently or in calipers, at entry to the study; 48 of the 67 in the prednisone groups and 22 of the 32 in the placebo group were ambulant
Interventions	Prednisone 0.75 mg/kg/day for 6 months (n = 34) or prednisone 0.3 mg/kg/day (n = 33) for 6 months or placebo for 6 months (n = 32)
Outcomes	Muscle strength reported as muscle strength score, based on grading of 34 muscle groups on 10-point modified MRC score, lifting weights, timed 9-metre walk, climbing 4 stairs and rising from lying to standing, leg functional grades, and pulmonary function tests (forced vital capacity, maximum voluntary ventilation, and maximum expiratory pressure) (Brooke 1981; Mendell 1989) Assessments took place on 2 consecutive days on initial admission, after which prednisone was started. Reassessment as outpatients at 10 days, 1, 2, 3, and 6 months Participants were examined and parents interviewed for side effects at both visits before initiation of treatment and at 1, 2, 3, and 6 months of treatment
Declarations of interest	Not stated
Funding sources	Supported by the Muscular Dystrophy Association and National Institutes of Health
Notes	Multicentre national trial (five centres, one in Canada, four in United States) Dates: not stated Ethical approval and informed consent obtained

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised. No further information

Griggs 1991 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Gelatin capsules…containing powdered prednisone…or placebo were prepared and dispensed from the pharmacy" Placebo was the same weight as the drug
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"There were independent roles for clinical evaluators involved in assessment of strength and function, and principal investigators, who assessed side effects" "the improvement in strength at 10 days occurred prior to the onset of demonstrable side effects, excluding observable differences between treatment and placebo groups as a potentially unblinding factor"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appear to be no dropouts. Some participants did not contribute data for some outcomes because of disability We made the assumption that any missing data are missing at random
Selective reporting (reporting bias)	Low risk	Average muscle strength chosen "a priori" as primary outcome. Reporting comprehensive for 6-month data. Interim measurements other than for the primary outcome not reported
Other bias	Low risk	None identified Authors state that "variables were evaluated individually with no correction for multiple comparisons. Such correction would not materially affect the conclusions, since the uncorrected P values were very small

Hu 2015

Methods	Prospective, randomised, placebo-controlled
Participants	73 boys with DMD who were independently ambulant; age 4 to 12 years 66 randomised (7 excluded: 3 screen failures, 3 refused to participate in the trial, 1 was noncompliant) • prednisone: mean age 7.73, SD ± 2.09, n = 36 • placebo mean age 7.56, SD ± 2.15, n = 30 Diagnosis based initially on clinical history and neuromuscular findings, later confirmed by dystrophin gene testing or muscle biopsy Exclusions:

	• severe or moderate learning difficulties or behavioural problems • previous corticosteroid treatment • non-ambulant • severe to moderate learning difficulties • female sex or the family's unwillingness to participate
Interventions	Daily prednisone: 0.75 mg/kg/day in white gelatin capsules (n = 36), for 1 year Placebo: white gelatin capsules of same weight containing wheat flour (n = 30), for 1 year Allowed co-interventions: vitamin D, calcium, ranitidine, and an over the counter antacid; high protein, low carbohydrate, low fat diet. Respiratory, cardiac and rehabilitation interventions given to both groups
Outcomes	Measured at initiation of prednisone treatment, 6 and 12 months Outcomes: • muscle strength (lower limb muscles (right hip flexion and right knee extension) assessed on expanded MRC scale (10-point scale, Brooke 1983) • time (in seconds; absolute values at given time points) required to: ○ walk 10 metres ○ climb 4 standard steps ○ stand from supine (Gowers' time) • patient and carer quality of life measured using the Chinese version of the Pediatric Quality of life Inventory (PedsQL) 3.0 Neuromuscular Module. Items were rated on a 5-point scale and transformed linearly to a 100-point scale (higher = better). Score = sum of items/number of items answered • adverse events (time points unclear - at the beginning and the during study): weight, height, BMI and diastolic BP • other adverse events are only reported for the prednisone group
Declarations of interest	No conflict of interest declaration provided
Funding sources	Research Project of Chongqing Municipal Health Bureau and Medical Innovation Project of Fujian Province
Notes	Recruitment between December 2010 and December 2012; 1 year follow-up Location: Children's Hospital, Chongqing Medical University, China (SW China)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Participants were randomized into prednisone and placebo groups according to a random number table." Baseline imbalances assessed - none identified
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Hu 2015 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo and prednisone were both white gelatin capsules; some possibility of unblinding due to adverse events but, on balance, judged to be of low risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Each outpatient visit included independent clinical and side effect evaluations obtained by a clinical evaluator and the principal investigator, respectively Outcome assessors likely to be blinded to the intervention; some possibility of unblinding due to adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 dropouts (not included in analyses): • at 6-month follow-up: 2 lost to follow-up and 1 dropped out due to economic hardship • at 12-month follow-up, 2 lost to follow-up and 3 dropped out due to loss of ambulation The lost-to-follow-up rates were 5.56%, 13.89%, and 3.33%, 10.00% in the prednisone and placebo groups at the 6- and 12-month time-points, respectively Report states "There were no statistical differences between the participants who were lost to follow-up and included in the main aspects of age, gender and condition"
Selective reporting (reporting bias)	Low risk	Efficacy outcomes and adverse event measurements (height, weight, BMI, and diastolic BP) described in methods and fully reported at 6 and 12 months. Other adverse events partially reported - high risk for adverse events
Other bias	Low risk	None identified

Karimzadeh 2012

Methods	Single-blind, randomised clinical trial
Participants	34 participants (17 in each group) Participants met these 5 diagnostic criteria for DMD: • muscular weakness onset under the age of 5 • male • proximal muscle weakness • greater than 40-fold increase in CK at the beginning of symptoms

	• confirmation by muscle biopsy to prove dystrophin deficiency or genetic evaluation to confirm dystrophin gene deletion • Deflazacort group: mean age 7.1 ± 1.98 • Prednisone group: mean age 7.37 ± 1.27
Interventions	Deflazacort group: 0.9 mg/kg in a single dose daily. Reduced to 0.5 mg/kg if complications occurred; exclusion if complications not controllable at that dose Prednisone group: 0.75 mg/kg in a single dose daily as 50 mg tablets. Reduced to 0.3 mg/kg in the event of complications with discontinuation if still complications Treatment continued for 18 months (some participants had dosage reduction at 1 year Co-interventions: 500 mg calcium and 400 IU vitamin D
Outcomes	Movement function measured every 3 months, using 1-3 grading (accomplished without assistance, accomplished with assistance, not able to accomplish the task) of: • climbing four 17 cm stairs • sit to stand • 10-metre walk • change in height every 3 months • weight measured every 3 months • measurement of blood pressure every 3 months and comparing it with the standard blood pressure chart for children • check for glucosuria every 3 months • eye examination for cataract • orthopaedic examination for scoliosis • annual spirometry and vital lung capacity as an index for respiratory function (abnormal defined as vital capacity less than 80% of normal based on age and gender) • annual cardiac evaluation: measurement of ejection fraction (abnormal defined as less than 55% normal based on age and gender)
Declarations of interest	"Not declared"
Funding sources	Grant from the pediatric neurologic research centre of Shahid Beheshti University of Medical Sciences
Notes	Dates: enrolment 23 September 2008 to 21 March 2009 Location: Iran

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"The patients were treated alternatively by prednisone or deflazacort" Appears to be quasi-randomised
Allocation concealment (selection bias)	High risk	Unlikely with this method of randomisation

Karimzadeh 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind. Paper does not specify who was blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind. Paper does not specify who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 8 cases who did not continue therapy, 3 were on deflazacort and 5 on prednisone. At 1 year a further 4 dropouts occurred in the prednisone group because of uncontrollable weight gain. Dropouts at 1 year were boys with worse outcomes
Selective reporting (reporting bias)	High risk	Data were not reported for every time point
Other bias	Low risk	None identified

Mendell 1989

Methods	Randomised, double-blind, placebo-controlled trial with 3 groups
Participants	103 boys with DMD aged 5 to 15 years, mean (SD) age: • prednisone 0.75 mg/day: 9.16 (2.95) • prednisone 1.5 mg/day: 9.16 (2.95) • placebo: 8.99 (2.64) 85 of the participants were ambulant, either independently or in calipers, at entry to the study; 55 of the 69 in the prednisone groups and 30 of the 33 in the placebo group were ambulant
Interventions	Prednisone 0.75 mg/kg/day (n = 33) or prednisone 1.5 mg/kg/day (n = 34) or placebo (n = 36) for 6 months. One boy in the 1.5 mg/kg group was not treated because of baseline hypertension
Outcomes	Muscle strength reported as muscle strength score, based on grading of 34 muscle groups on 10-point modified MRC score, lifting weights, timed 9-metre walk, climbing 4 stairs and rising from lying to standing, leg functional grades, and forced vital capacity (Brooke 1981; Mendell 1989)
Declarations of interest	Not stated
Funding sources	Grants from the Muscular Dystrophy Association and the National Institutes of Health
Notes	Multicentre national trial Dates: not stated Location: USA (4 centres)

Mendell 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "randomized" "No significant differences were seen between the three patient groups in any baseline values"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Gelatin capsules (No. 3, Eli Lilly) containing powdered prednisone or placebo were prepared and dispensed from a single pharmacy...Placebo was administered in a gelatin capsule that weighed 240 mg and contained powdered lactose, and prednisone in a capsule that held the appropriate dose and enough lactose so that the capsule weighed 240 mg" Some possibility of unblinding as cushingoid appearance present in 4 participants in each corticosteroid group at 1 month
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Implied: "The clinical evaluations were carried out by clinical evaluators who did not inquire about side effects" "The examination for side effects was performed by the principal investigators in an area separate from that of the clinical evaluation" Some possibility of unblinding as cushingoid appearance apparent in 4 participants in each corticosteroid group at 1 month
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants dropped out: 2 in the low dose prednisone group required surgery, and a participant on placebo was removed by parents after analysis of the drug to find out its composition. Another placebo group participant stopped taking medication because of "adverse events" but completed all required visits
Selective reporting (reporting bias)	Low risk	Reporting appears complete
Other bias	Low risk	None identified

Rahman 2001

Methods	Randomised, parallel-group, controlled trial
Participants	19 participants with DMD (16 of the 19 participants were ambulant at entry to the study; 8 of the 10 boys in the prednisolone group and 8 of the 9 boys in the control group were ambulant) Inclusion criteria: onset of weakness under 5 years, CK at least 10 times upper limit of normal Exclusion criteria: findings suggestive of other diagnoses
Interventions	• Prednisolone 0.75 mg/kg/day for 6 months (n = 10) or • vitamin (not further specified) (n = 9) Both groups received physiotherapy
Outcomes	Muscle strength score, 30-ft walking, lying to standing time, 4-stair climbing times, functional scores (Brooke 1981). Trial authors state "any adverse events were noted during evaluation" Outcomes evaluated at 0, 1, 2, and 6 months following start of therapy. After 6 months, a full evaluation was repeated on 2 occasions separated by 1 to 7 days
Declarations of interest	Not stated
Funding sources	Not stated
Notes	Dates: not stated Location: Dhaka, Bangladesh

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised but method not described
Allocation concealment (selection bias)	Low risk	Assessed as low risk as trial authors provided information indicating adequate allocation concealment to the review authors for a previous version of this review
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group received vitamin - unlikely to be matched
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Report does not mention dropouts; the trial author reported one dropout in response to the Cochrane authors' request for an earlier

Rahman 2001 (*Continued*)

		version of this review
Selective reporting (reporting bias)	High risk	Outcomes not clearly defined in methods. Results reported at end of treatment but not at interim time points. Adverse events are not mentioned in results although methods state that data were collected
Other bias	Low risk	None identified

Todorovic 1998

Methods	Randomised controlled trial
Participants	34 boys (5 to 17 years) with DMD
Interventions	Prednisone 2 mg/kg alternate days (high dose) versus placebo. Abstract does not state number of participants in each group
Outcomes	Mean follow-up 20 months Change in muscle function assessed by myometry, MRC score, motor ability score, and walking times for ambulant boys, prolongation of ambulation, side effects
Declarations of interest	Not stated
Funding sources	Not stated
Notes	Dates: not stated Location: not stated Reported in an abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, with no further details
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo said to be used and 'blinded' with no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information

Todorovic 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	High risk	Results not comprehensively reported in abstract. No known full report
Other bias	Unclear risk	None identified, but insufficient information to make a judgement

BMI: body mass index
BP: blood pressure
CK: creatine kinase
CPK: creatine phosphokinaseDEXA: dual energy x-ray absorptiometry
DMD: Duchenne muscular dystrophy
DNA: deoxyribonucleic acid
ECG: electrocardiogram
MRC: Medical Research Council
QMT: quantitative muscle testing
RBC: red blood cell
SD: standard deviation
WBC: white blood cell

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahlander 2003	Retrospective study; published as abstract only
Alman 2004	Non-randomised study
Angelini 1995	Non-randomised study; published as abstract only
Angelini 2007	Review article
Angelini 2012	A review of corticosteroid treatment; not a clinical study
Aviles 1982	Non-randomised study; published as abstract only
Balaban 2005	Non-randomised study
Biggar 2001	Non-randomised study
Biggar 2004	Non-randomised study

(*Continued*)

Biggar 2006	Non-randomised study
Bonifati 2006	Non-randomised study
Bothwell 2003	Retrospective case note review and telephone interview study
Brooke 1987	Non-randomised open study
Campbell 2003	Systematic online review of deflazacort in Duchenne muscular dystrophy
Connolly 2002	Non-randomised study; historical controls
Daftary 2007	Non-randomised study
de Groot 2002	Non-randomised cohort study
DeSilva 1987	Non-randomised study
Drachman 1974	Non-randomised open study
Dubowitz 2002	Non-randomised open study
Dubrovsky 1999	Non-randomised study; published as abstract only
Fenichel 1991a	Three randomised groups (prednisone 0.75 mg/kg/day versus prednisone 1.5 mg/kg/day versus placebo) from previous Mendell 1989 study were all put on alternate-day prednisone, without breaking the randomisation code. There was no washout period between the two studies. All patients went on to alternate-day prednisone treatment and there was no contemporary placebo control group
Fenichel 1991b	Open study on previous cohort of patients from Mendell 1989 and Fenichel 1991a
Flanigan 2012	Not randomised or quasi-randomised
Griggs 1993	Randomised study with prednisone group compared with azathioprine. No placebo group
Griggs 2013	Study discussing different practices in corticosteroid regimen used. No outcome measures assessed
Henricson 2013	Not randomised or quasi-randomised. Prospective cohort study
Houde 2008	Not randomised or quasi-randomised. Retrospective cohort study
Kinali 2002	Non-randomised; case-series of 4 patients
Kinali 2007	Non-randomised study
King 2007	Non-randomised study

(*Continued*)

Markham 2005	Non-randomised study
Mayhew 2013	Not randomised or quasi-randomised
Mazzone 2013	Not randomised or quasi-randomised
McAdam 2012	A review of 7 studies
Merlini 2003	Non-randomised; open, parallel-group study
Mesa 1991	Non-randomised, double-blind controlled study "Two groups of 14 patients each were formed after an initial evaluation designed to balance the scores and composition of the groups"
Pandya 2001	Non-randomised, long-term cohort follow-up of patients from clinical investigation of DMD therapeutic trials (Griggs 1991; Mendell 1989) at University of Rochester. Published as abstract only
Parreira 2007	Non-randomised
Pradhan 2006	Randomised, open study of deflazacort versus prednisolone. In addition to a very high dropout rate in the prednisolone group (24/44 participants dropped out because of adverse effects), treatment was stopped in a further five patients because of no improvement in power. No intention-to-treat analysis performed
Reitter 1995	Not stated to be randomised
Resende 2001	Non-randomised, cohort study; published as abstract only
Ricotti 2013	Not randomised. Prospective, longitudinal observational study
Sansome 1993	Non-randomised open study
Schara 2001	Non-randomised study
Schram 2013	Retrospective cohort review
Siegel 1974	Non-randomised study. Clinically matched double-blind evaluation
Silva 2012	Longitudinal study primarily designed to assess the outcome measure tool. Compared quality of life scores between different age groups but no comparison between different corticosteroid regimens or with any control
Silversides 2003	Non-randomised study; retrospective cohort study
Simon 2011	Not randomised; no comparison of corticosteroid with control or other group
Takeuchi 2013	Not randomised; retrospective cohort study
Tunca 2001	Non-randomised cohort study; published as abstract only

(*Continued*)

Vasanth 1996	Interim results of a randomised study of prednisone, ayurvedic medicine, and placebo, published as an abstract. Further unpublished data were provided by colleagues at Dr Vasanth's Instituition as she had died. Study design was modified during the trial with amalgamation of the placebo control group with the ayurvedic treatment group. At completion of the study, prednisone group was compared with ayurvedic drug treatment group (See Table 2 for more details)
Wong 2002	Review of previous studies
Yilmaz 2004	Non-randomised study

Characteristics of studies awaiting assessment *[ordered by study ID]*

ACTRN12605000075684

Methods	Randomised, blinded, parallel-group, phase III controlled trial
Participants	Diagnosis of Duchenne muscular dystrophy, ambulant, steroid naïve, aged 4 to 10 years No exclusion criteria
Interventions	Daily low-dose (0.75mg/kg/day) prednisone to high-dose prednisone over 2 days (10 mg/kg/week)
Outcomes	Primary: • muscle strength measured at the start of the trial, and 1,3,6,9 and 12 months after starting prednisone Secondary: • "minimum" adverse events
Notes	First enrollment: 1 July 2005 Target sample size: 140 Primary sponsor: The Children's Hospital at Westmead, Australia; Cooperative International Neuromuscular Research Group, USA listed as a collaborative group

Bello 2015

Methods	Longitudinal, multicentre, observational
Participants	340 participants
Interventions	Prednisone, prednisolone, or deflazacort (14 different regimens)
Outcomes	"Assessments obtained every 3 months for 1 year, at 18 months, and annually thereafter included: clinical history; anthropometrics; goniometry; manual muscle testing; quantitative muscle strength; timed function tests; pulmonary function; and patient-reported outcomes/ health-related quality-of-life instruments"
Notes	Average follow-up 3.8 ± 1.8 years For consideration for the Discussion

Pane 2015

Methods	Observational. Longitudinal, multicentre, cohort study
Participants	96 ambulant participants with genetically proven DMD
Interventions	Various: no steroids, or intermittent or daily regimens of prednisone or deflazacort
Outcomes	6-metre walk test North Star Ambulatory Assessment
Notes	For consideration for the Discussion

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2009/091/000738

Trial name or title	A clinical trial to compare the two ways of giving steroids (daily versus intermittent) in ambulatory patients with Duchenne muscular dystrophy
Methods	Randomised, parallel-group, open-label, active controlled trial
Participants	Patients with DMD, 5 to 10 years old meeting the European Neuromuscular Centre DMD diagnostic criteria (Emery 1997) Inclusion criteria: • onset of proximal muscle weakness before 5 years of age • 10-fold elevation in serum CK • dystrophic muscle biopsy • absent or minimal dystrophin on muscle biopsy or DMD mutation in the dystrophic gene, or both Exclusion criteria: • at least 7 days corticosteroid use within 2 months of the start of the trial • non-ambulatory • unable to rise from the floor without assistance • contraindications to corticosteroid use
Interventions	• Intervention: prednisolone 0.75 mg/kg/day once daily 10 days/month for 6 months • Control intervention: prednisolone 0.75 mg/kg/day once daily for 6 months
Outcomes	Primary outcome: • muscle strength measured by MMT score and isokinetic muscle testing at 6 months Secondary outcomes: • timed functional capacities at 3 and 6 months • muscular dystrophy-specific functional rating score at 3 and 6 months • pulmonary function as measured by spirometry at 6 months • adverse effects like weight gain, hypertension, excessive hair growth, cushingoid facies, infection, cataract at 3 and 6 months
Starting date	First enrollment 20 January 2009

CTRI/2009/091/000738 (*Continued*)

Contact information	Sheffali Gulati, Department of Pediatrics, AIIMS 110029 New Delhi, Delhi, India
Notes	Location: India Supported by All India Institute of Medical Sciences (AIIMS). Drug supplied by pharmaceutical company Status unclear

Guglieri 2015

Trial name or title	Finding the optimum regimen for Duchenne muscular dystrophy (FOR-DMD)
Methods	Randomised, safety/efficacy, parallel assignment, double-blind
Participants	Boys with DMD ages 4 to 7 years
Interventions	Daily prednisone (0.75 mg/kg/day); intermittent prednisone (0.75 mg/kg/day, 10 days on, 10 days off), daily deflazacort (0.9 mg/kg/day)
Outcomes	Primary: 3-dimensional (multivariate) outcome consisting of the following 3 components (each averaged over month 3, 6, 12, 18, 24, 30, and 36 visits): • time to stand from lying (log-transformed) • forced vital capacity • participant/parent global satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication Secondary • The North Star Ambulatory Assessment (NSAA): 17-item timed function tests to evaluate motor ability in ambulant children with DMD. Total score = sum of all graded items. "Of primary interest will be the average value of these outcomes over all post-baseline visits over the three year follow-up period" • 6-minute walk test: once during the screening period (1 to 3 months prior to baseline), at baseline (month 0), and at months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 • Range of motion (goniometry): once during the screening period (1 to 3 months prior to baseline), at baseline, and at months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60). Range of motion at the ankle joint in dorsiflexion measured in degrees from plantigrade • Regimen tolerance at months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60, defined as completing 3 to 5 years of follow-up on study medication with no deviation from the initially prescribed dosage level (increases in dosage band to accommodate growth and weight gain allowed) • Adverse event profile at months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60. The occurrence and severity of the following predictable adverse events (i.e. known side effects of corticosteroids) will be recorded. Behavior problems, bone fractures, cataracts, cushingoid features, GI symptoms, hypertension, immune/adrenal suppression, slow growth (height restriction), skin changes, weight gain, diabetes • Child self report and carer quality of life, at months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60. Measured by child self report and by proxy (parent(s)/guardian(s)) report for all children. Generic Peds Quality of life (23 questions) neuromuscular disease-specific module (25 questions). The average values of these outcomes over all post-baseline assessments during the 3-year follow-up period will be of primary interest • Cardiac function every 2 years to the age of 10 years, and annually thereafter or at the onset of cardiac signs and symptoms and the year 3 visit. Monitored by trans-thoracic echocardiogram and 12-lead ECG.

Guglieri 2015 (*Continued*)

	The findings will be categorised as: normal; abnormal but not clinically significant; abnormal; and clinically significant. The earliest definite, echo-detectable impairment of left ventricular function is defined as ejection fraction < 55%, fractional shortening < 28%, or both. Monitored 12-lead ECG. If ECG shows any impaired left ventricular function or evidence of regional motion abnormalities (posterior wall), the interval between evaluations will be reduced and treatment initiated
Starting date	January 2013
Contact information	Kimberley Hart: kim_hart@urmc.rochester.edu, University of Rochester, MN, USA
Notes	Estimated study completion date: August 2019 International, multicentre: 40 centres (USA, Canada, UK, Germany, and Italy) NCT01603407

DMD: Duchenne muscular dystrophy; ECG: electrocardiogram; GI: gastrointestinal

DATA AND ANALYSES

Comparison 1. Corticosteroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in MRC index (%) after 6 months of treatment - deflazacort 2 mg/kg alternate days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 MRC - Average muscle score after 6 months of treatment - prednisone	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 0.3 mg/kg/day	1	61	Mean Difference (IV, Random, 95% CI)	0.34 [0.17, 0.51]
2.2 0.75 mg/kg/day	3	147	Mean Difference (IV, Random, 95% CI)	0.52 [0.33, 0.71]
2.3 1.5 mg/kg/day	1	65	Mean Difference (IV, Random, 95% CI)	0.45 [0.23, 0.67]
3 Change in MRC index (%) after 24 months of treatment - deflazacort 2 mg/kg alternate days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4 Lower limb muscle strength grade after 6 months of treatment - prednisone	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Hip flexion (right)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Knee extension (right)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Lower limb muscle strength grade after 12 months of treatment - prednisone	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Hip flexion (right)	1	58	Mean Difference (IV, Random, 95% CI)	1.27 [0.74, 1.80]
5.2 Knee extension (right)	1	58	Mean Difference (IV, Random, 95% CI)	1.23 [0.71, 1.75]
6 Time taken to rise from floor after 6 months of treatment - prednisone	5		Mean Difference (Random, 95% CI)	Subtotals only
6.1 0.75 mg/kg for 1st 10 days every month	1		Mean Difference (Random, 95% CI)	-1.08 [-2.51, 0.35]
6.2 0.3 mg/kg/ daily	1		Mean Difference (Random, 95% CI)	-1.59 [-3.75, 0.57]
6.3 0.75 mg/kg daily	4		Mean Difference (Random, 95% CI)	-2.28 [-3.12, -1.44]
6.4 1.5 mg/kg daily	1		Mean Difference (Random, 95% CI)	-2.74 [-3.98, -1.50]
7 Change in time taken to rise from floor after 6 months of treatment - deflazacort 2 mg/kg alternate days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8 Time taken to rise from floor after 12 months of treatment (daily prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

9 Change in time taken to rise from floor after 24 months of treatment - deflazacort 2 mg/kg alternate days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
10 9-metre walking/running time after 6 months of treatment - prednisone	4		Mean Difference (Random, 95% CI)	Subtotals only
10.1 0.75 mg/kg for 1st 10 days every month	1		Mean Difference (Random, 95% CI)	-0.68 [-1.15, -0.21]
10.2 0.3 mg/kg daily	1		Mean Difference (Random, 95% CI)	-1.18 [-2.65, 0.29]
10.3 0.75 mg/kg daily	3		Mean Difference (Random, 95% CI)	-2.73 [-3.97, -1.50]
10.4 1.5 mg/kg daily	1		Mean Difference (Random, 95% CI)	-2.64 [-4.45, -0.83]
11 Timed walk (assumed in seconds) - after 6 months of treatment - deflazacort 2 mg/kg alternate days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
12 10-metre walking time 6 months post-treatment (daily prednisone 0.75 mg/kg)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
13 10-metre walk time 1 year post-treatment (daily prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
14 Timed walk (assumed in seconds) - after 24 months of treatment - deflazacort 2 mg/kg alternate days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
15 Lifting weight (kg) after 6 months of treatment - prednisone	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 0.3 mg/kg/day	1	39	Mean Difference (IV, Random, 95% CI)	0.38 [0.13, 0.63]
15.2 0.75 mg/kg/day	2	94	Mean Difference (IV, Random, 95% CI)	0.75 [0.50, 0.99]
15.3 1.5 mg/kg/day	1	57	Mean Difference (IV, Random, 95% CI)	0.96 [0.52, 1.40]
16 Four-stair climbing time after 6 months of treatment - prednisone	5		Mean Difference (Random, 95% CI)	Subtotals only
16.1 0.75 mg/kg for 1st 10 days every month	1		Mean Difference (Random, 95% CI)	-1.93 [-3.56, -0.30]
16.2 0.3 mg/kg daily	1		Mean Difference (Random, 95% CI)	-2.68 [-4.06, -1.30]
16.3 0.75 mg/kg daily	4		Mean Difference (Random, 95% CI)	-3.09 [-4.33, -1.85]
16.4 1.5 mg/kg daily	1		Mean Difference (Random, 95% CI)	-3.05 [-4.41, -1.69]
17 Timed function: stair climb after 6 months of treatment - deflazacort 2 mg/kg alternate days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
18 Four-stair climbing time after 12 months of treatment (daily prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
19 Change in timed stair climb after 24 months of treatment - deflazacort 2 mg/kg alternate days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

20 Dynamometry - total muscle force after 6 months of treatment - prednisone	1		Mean Difference (Random, 95% CI)	Subtotals only
21 Leg function grade after 6 months of treatment - prednisone	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 0.3 mg/kg/day	1	58	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.79, 0.01]
21.2 0.75 mg/kg/day	2	129	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.73, -0.09]
21.3 1.5 mg/kg/day	1	68	Mean Difference (IV, Random, 95% CI)	-0.49 [-0.93, -0.05]
22 Forced vital capacity after 6 months of treatment - prednisone	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 0.3 mg/kg/day	1	59	Mean Difference (IV, Random, 95% CI)	0.16 [0.05, 0.27]
22.2 0.75 mg/kg/day	2	127	Mean Difference (IV, Random, 95% CI)	0.17 [0.10, 0.24]
22.3 1.5 mg/kg/day	1	62	Mean Difference (IV, Random, 95% CI)	0.14 [0.05, 0.23]
23 Quality of life after six months of treatment (daily prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
23.1 Child self report	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23.2 Parent proxy-report	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
24 Quality of life after 12 months of treatment (daily prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
24.1 Child self report	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
24.2 Parent proxy-report	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
25 Mean % weight gain - prednisone - daily dose regimen	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1 0.3 mg/kg/day	1	56	Mean Difference (IV, Random, 95% CI)	4.21 [0.76, 7.66]
25.2 0.75 mg/kg/day	2	126	Mean Difference (IV, Random, 95% CI)	9.27 [6.87, 11.68]
25.3 1.5 mg/kg/day	1	67	Mean Difference (IV, Random, 95% CI)	8.78 [5.46, 12.10]
26 Weight gain - prednisone - intermittent, given 1st 10 days every month	1		Mean Difference (Random, 95% CI)	Subtotals only
27 Mean % weight gain - deflazacort 2 mg/kg alternate days	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
28 Body weight at 6 months (prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
29 Body weight at 12 months (prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
30 BMI at 6 months (daily prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
31 BMI at 12 months (daily prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
32 Excessive hair growth - prednisone	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.1 0.3 mg/kg/day	1	65	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.18, 3.00]
32.2 0.75 mg/kg/day	2	135	Risk Ratio (M-H, Random, 95% CI)	2.60 [1.47, 4.60]
32.3 1.5 mg/kg/day	1	69	Risk Ratio (M-H, Random, 95% CI)	2.32 [1.16, 4.64]
33 Behavioural changes - prednisone	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.1 0.3 mg/kg/day	1	65	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.67, 1.56]

33.2 0.75 mg/kg/day	2	135	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.94, 2.06]
33.3 1.5 mg/kg/day	1	69	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.92, 2.24]
34 Cushingoid appearance - prednisone	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
34.1 0.3 mg/kg/day	1	65	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.60, 2.17]
34.2 0.75 mg/kg/day	2	135	Risk Ratio (M-H, Random, 95% CI)	2.37 [1.53, 3.67]
34.3 1.5 mg/kg/day	1	69	Risk Ratio (M-H, Random, 95% CI)	4.36 [2.04, 9.33]
35 Acne - prednisone	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
35.1 0.3 mg/kg/day	1	65	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.18, 3.00]
35.2 0.75 mg/kg/day	2	135	Risk Ratio (M-H, Random, 95% CI)	1.78 [0.96, 3.32]
35.3 1.5 mg/kg/day	1	69	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.84, 3.73]
36 Increased appetite - prednisone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
36.1 0.3 mg/kg daily	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
36.2 0.75 mg/kg daily	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
37 Height at 6 months (daily prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
38 Height at 12 months (daily prednisone 0.75 mg/kg/day)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 2. Weekend-only versus daily prednisone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Muscle strength (change from baseline to 12 months)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 MMT score	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 QMT arm score, lb	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 QMT leg score, lb	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 QMT elbow flexors, lb	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 QMT elbow extensors, lb	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 QMT knee flexors, lb	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.7 QMT knee extensors, lb	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.8 QMT grip score, lb	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Functional outcome measures (change from baseline to 12 months)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Time taken to rise from the floor (Gowers' time) (log seconds)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 10-metre walking time (log seconds)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Four-stair climb (log seconds)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Change in mobility function (lower extremity score - Vignos)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Change in mobility function (upper extremity score - Brooke)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

5 FVC % predicted	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
6 FEV1 % predicted	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Maximal inspiratory pressure	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Maximal voluntary ventilation	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Weight (BMI kg/m2)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Weight (kg)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Child Behavior Checklist: total problems (higher = more severe)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Child Behavior Checklist: internalising	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
13 Child Behavior Checklist: externalising	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
14 Child Behavior Checklist: anxious/depressed	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
15 Child Behavior Checklist: somatic complaints	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
16 Child Behavior Checklist: withdrawn/depressed	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
17 Child Behavior Checklist: attention problems	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
18 Child Behavior Checklist: aggressive behaviour	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
19 Osteoporosis: lumbar spine Z scores (DEXA)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
20 Height (m)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
21 Mean growth in cm	1	Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 3. Deflazacort versus prednisone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight gain (%)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 At 1 year	2	43	Mean Difference (IV, Random, 95% CI)	-9.52 [-14.91, -4.12]
2 Adverse events at six months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Cushingoid appearance	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Appetite increase	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Behavioural changes	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Gastric symptoms	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Hirsutism	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Cushingoid appearance	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Appetite increase	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Behavioural changes	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Gastric symptoms	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Hirsutism	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Corticosteroids versus placebo, Outcome 1 Change in MRC index (%) after 6 months of treatment - deflazacort 2 mg/kg alternate days.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 1 Change in MRC index (%) after 6 months of treatment - deflazacort 2 mg/kg alternate days

Study or subgroup	Deflazacort N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Angelini 1994	16	-0.78 (6.5)	10	-2.75 (3.22)			1.97 [-1.79, 5.73]

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Corticosteroids versus placebo, Outcome 2 MRC - Average muscle score after 6 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 2 MRC - Average muscle score after 6 months of treatment - prednisone

Study or subgroup	Steroid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 0.3 mg/kg/day							
Griggs 1991	31	5.82 (0.06)	30	5.48 (0.47)		100.0 %	0.34 [0.17, 0.51]
Subtotal (95% CI)	**31**		**30**			**100.0 %**	**0.34 [0.17, 0.51]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.93 (P = 0.000084)							
2 0.75 mg/kg/day							
Griggs 1991	34	6 (0.46)	30	5.48 (0.47)		43.5 %	0.52 [0.29, 0.75]
Mendell 1989	30	6.23 (0.36)	35	5.8 (0.52)		46.8 %	0.43 [0.21, 0.65]
Rahman 2001	10	3.88 (0.58)	8	2.92 (0.67)		9.8 %	0.96 [0.37, 1.55]
Subtotal (95% CI)	**74**		**73**			**100.0 %**	**0.52 [0.33, 0.71]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 2.79, df = 2 (P = 0.25); I^2 =28%							
Test for overall effect: Z = 5.32 (P < 0.00001)							
3 1.5 mg/kg/day							
Mendell 1989	30	6.25 (0.4)	35	5.8 (0.52)		100.0 %	0.45 [0.23, 0.67]
Subtotal (95% CI)	**30**		**35**			**100.0 %**	**0.45 [0.23, 0.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.94 (P = 0.000082)							

Analysis 1.3. Comparison 1 Corticosteroids versus placebo, Outcome 3 Change in MRC index (%) after 24 months of treatment - deflazacort 2 mg/kg alternate days.

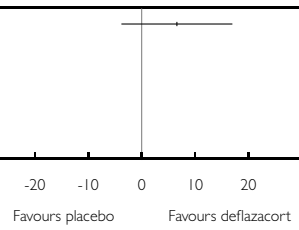
Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 3 Change in MRC index (%) after 24 months of treatment - deflazacort 2 mg/kg alternate days

Study or subgroup	Deflazacort N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Angelini 1994	9	-2.78 (7.23)	4	-9.38 (9.44)			6.60 [-3.79, 16.99]

Test for subgroup differences: Not applicable



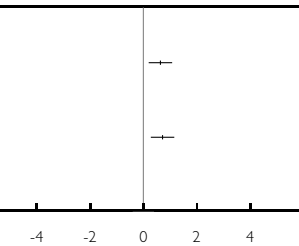
Analysis 1.4. Comparison 1 Corticosteroids versus placebo, Outcome 4 Lower limb muscle strength grade after 6 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 4 Lower limb muscle strength grade after 6 months of treatment - prednisone

Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Hip flexion (right)						
Hu 2015	34	6.88 (0.95)	29	6.24 (0.83)		0.64 [0.20, 1.08]
2 Knee extension (right)						
Hu 2015	34	7.26 (0.86)	29	6.55 (0.91)		0.71 [0.27, 1.15]



Analysis 1.5. Comparison 1 Corticosteroids versus placebo, Outcome 5 Lower limb muscle strength grade after 12 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 5 Lower limb muscle strength grade after 12 months of treatment - prednisone

Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Hip flexion (right)							
Hu 2015	31	6.84 (0.99)	27	5.57 (1.07)		100.0 %	1.27 [0.74, 1.80]
Subtotal (95% CI)	**31**		**27**			**100.0 %**	**1.27 [0.74, 1.80]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.67 (P < 0.00001)							
2 Knee extension (right)							
Hu 2015	31	7.16 (0.96)	27	5.93 (1.05)		100.0 %	1.23 [0.71, 1.75]
Subtotal (95% CI)	**31**		**27**			**100.0 %**	**1.23 [0.71, 1.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.63 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.92), I^2 =0.0%							

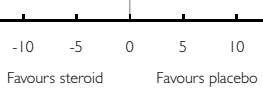
Analysis 1.6. Comparison 1 Corticosteroids versus placebo, Outcome 6 Time taken to rise from floor after 6 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 6 Time taken to rise from floor after 6 months of treatment - prednisone

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 0.75 mg/kg for 1st 10 days every month				
Beenakker 2005	-1.08 (0.73)		100.0 %	-1.08 [-2.51, 0.35]
Subtotal (95% CI)			**100.0 %**	**-1.08 [-2.51, 0.35]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.48 (P = 0.14)				
2 0.3 mg/kg/ daily				
Griggs 1991	-1.59 (1.104)		100.0 %	-1.59 [-3.75, 0.57]
Subtotal (95% CI)			**100.0 %**	**-1.59 [-3.75, 0.57]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.44 (P = 0.15)				
3 0.75 mg/kg daily				
Griggs 1991	-3.67 (1.0366)		15.9 %	-3.67 [-5.70, -1.64]
Hu 2015	-1.62 (0.8119)		24.8 %	-1.62 [-3.21, -0.03]
Mendell 1989	-2.02 (0.5113)		53.3 %	-2.02 [-3.02, -1.02]
Rahman 2001	-3.63 (1.7164)		6.1 %	-3.63 [-6.99, -0.27]
Subtotal (95% CI)			**100.0 %**	**-2.28 [-3.12, -1.44]**
Heterogeneity: Tau^2 = 0.08; Chi^2 = 3.33, df = 3 (P = 0.34); I^2 =10%				
Test for overall effect: Z = 5.32 (P < 0.00001)				
4 1.5 mg/kg daily				
Mendell 1989	-2.74 (0.6351)		100.0 %	-2.74 [-3.98, -1.50]
Subtotal (95% CI)			**100.0 %**	**-2.74 [-3.98, -1.50]**
Heterogeneity: not applicable				
Test for overall effect: Z = 4.31 (P = 0.000016)				
Test for subgroup differences: Chi^2 = 3.35, df = 3 (P = 0.34), I^2 =11%				



Analysis 1.7. Comparison 1 Corticosteroids versus placebo, Outcome 7 Change in time taken to rise from floor after 6 months of treatment - deflazacort 2 mg/kg alternate days.

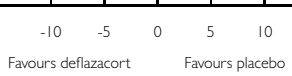
Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 7 Change in time taken to rise from floor after 6 months of treatment - deflazacort 2 mg/kg alternate days

Study or subgroup	Deflazacort N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Angelini 1994	12	1.08 (6.11)	7	3.14 (4.18)			-2.06 [-6.70, 2.58]

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Corticosteroids versus placebo, Outcome 8 Time taken to rise from floor after 12 months of treatment (daily prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 8 Time taken to rise from floor after 12 months of treatment (daily prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2015	27	7.42 (3.19)	23	9.63 (2.85)			-2.21 [-3.88, -0.54]

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Corticosteroids versus placebo, Outcome 9 Change in time taken to rise from floor after 24 months of treatment - deflazacort 2 mg/kg alternate days.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 9 Change in time taken to rise from floor after 24 months of treatment - deflazacort 2 mg/kg alternate days

Study or subgroup	Deflazacort N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Angelini 1994	7	2.14 (3.24)	3	7 (5)			-4.86 [-11.01, 1.29]

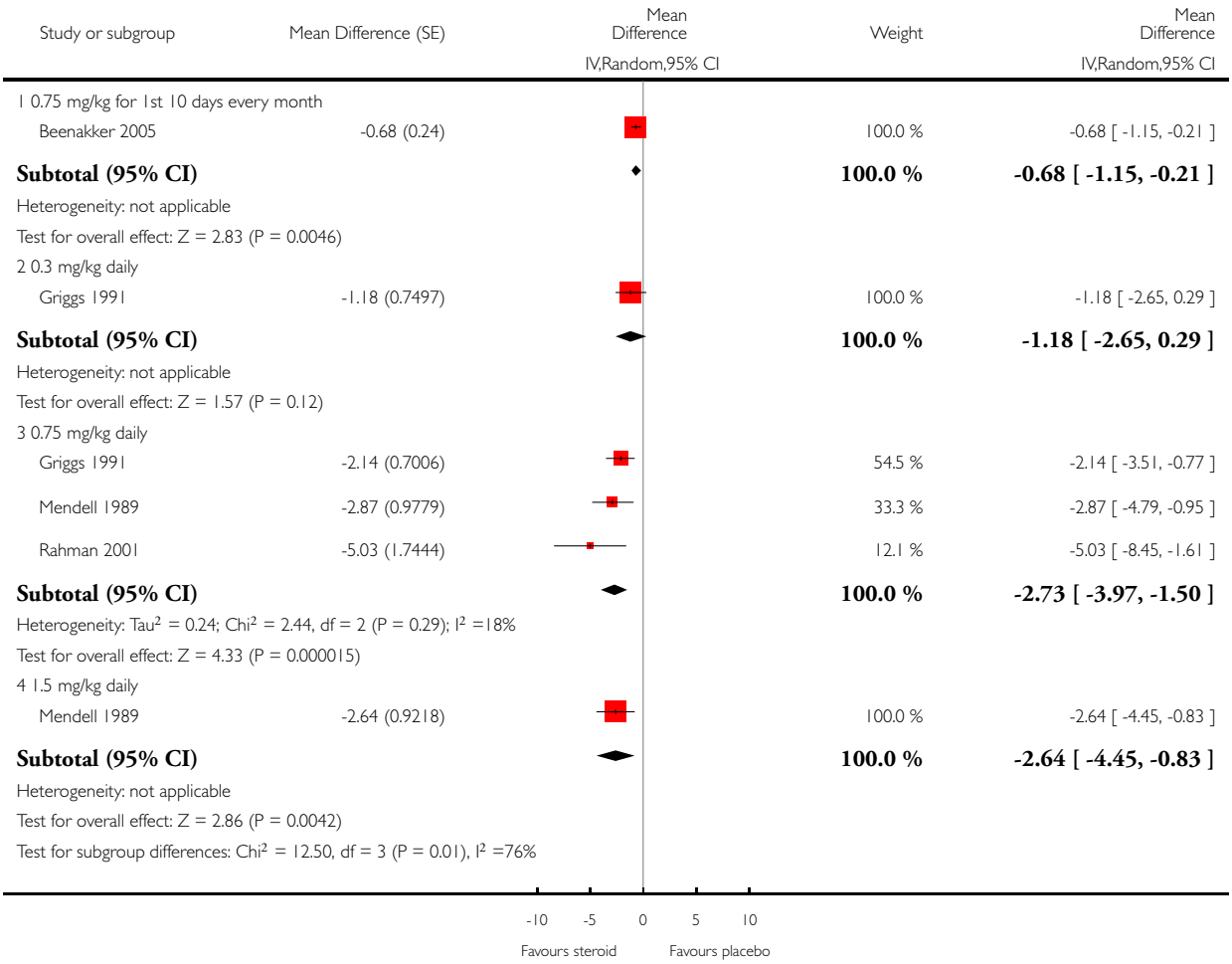
Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Corticosteroids versus placebo, Outcome 10 9-metre walking/running time after 6 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 10 9-metre walking/running time after 6 months of treatment - prednisone



Analysis 1.11. Comparison 1 Corticosteroids versus placebo, Outcome 11 Timed walk (assumed in seconds) - after 6 months of treatment - deflazacort 2 mg/kg alternate days.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 11 Timed walk (assumed in seconds) - after 6 months of treatment - deflazacort 2 mg/kg alternate days

Study or subgroup	Deflazacort N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Angelini 1994	14	-1.57 (2.21)	9	1.44 (2.01)			-3.01 [-4.76, -1.26]
Test for subgroup differences: Not applicable							

Analysis 1.12. Comparison 1 Corticosteroids versus placebo, Outcome 12 10-metre walking time 6 months post-treatment (daily prednisone 0.75 mg/kg).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 12 10-metre walking time 6 months post-treatment (daily prednisone 0.75 mg/kg)

Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2015	34	9.78 (1.83)	29	10.72 (1.38)			-0.94 [-1.73, -0.15]
Test for subgroup differences: Not applicable							

Analysis 1.13. Comparison 1 Corticosteroids versus placebo, Outcome 13 10-metre walk time 1 year post-treatment (daily prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 13 10-metre walk time 1 year post-treatment (daily prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2015	31	9.55 (2.16)	27	11.26 (1.86)			-1.71 [-2.74, -0.68]

Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 Corticosteroids versus placebo, Outcome 14 Timed walk (assumed in seconds) - after 24 months of treatment - deflazacort 2 mg/kg alternate days.

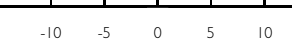
Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 14 Timed walk (assumed in seconds) - after 24 months of treatment - deflazacort 2 mg/kg alternate days

Study or subgroup	Deflazacort N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Angelini 1994	9	0 (2.4)	3	0.67 (0.58)			-0.67 [-2.37, 1.03]

Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1 Corticosteroids versus placebo, Outcome 15 Lifting weight (kg) after 6 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 15 Lifting weight (kg) after 6 months of treatment - prednisone

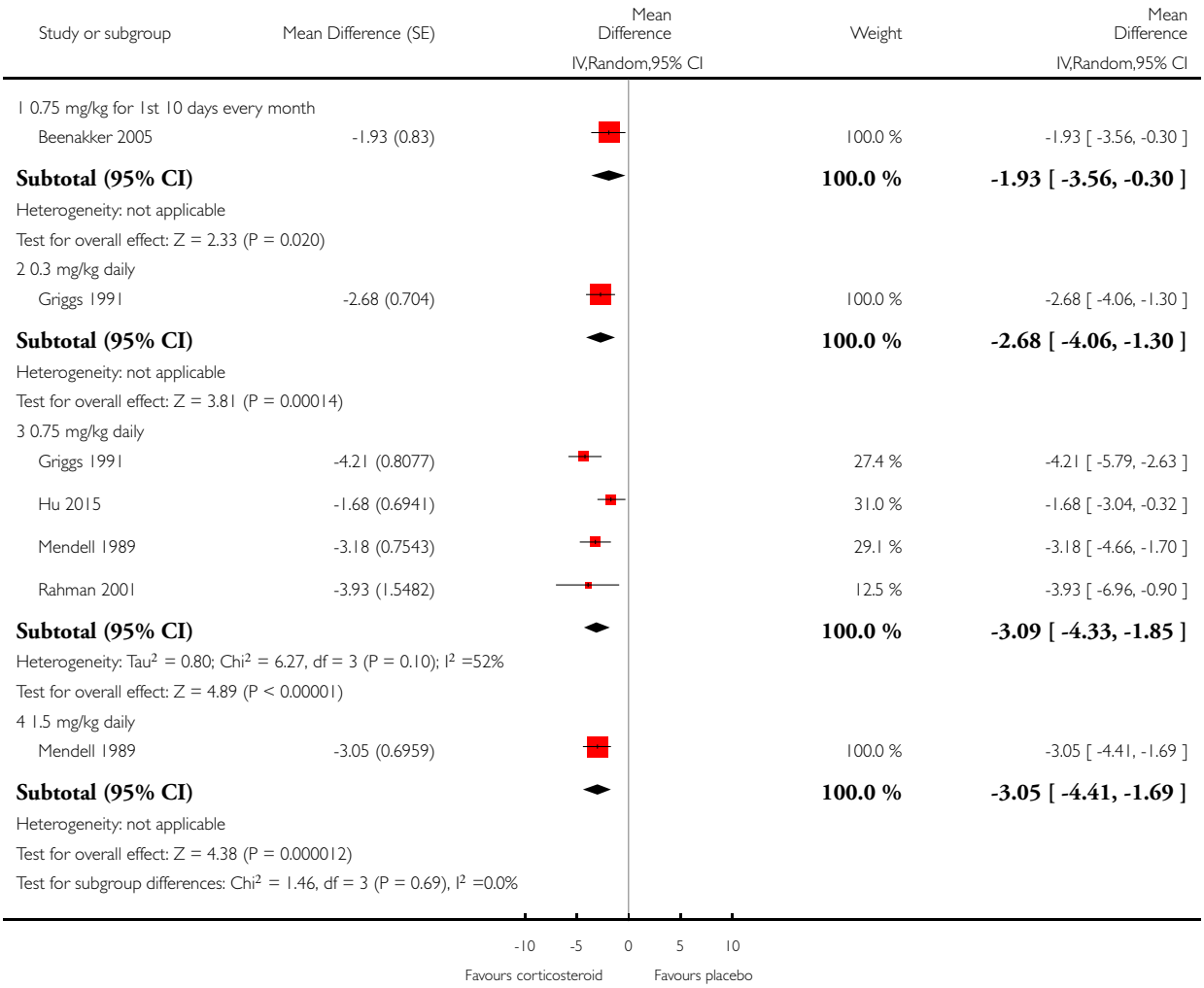
Study or subgroup	Steroid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 0.3 mg/kg/day							
Griggs 1991	21	1.64 (0.11)	18	1.26 (0.54)		100.0 %	0.38 [0.13, 0.63]
Subtotal (95% CI)	**21**		**18**			**100.0 %**	**0.38 [0.13, 0.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.93 (P = 0.0033)							
2 0.75 mg/kg/day							
Griggs 1991	22	2.04 (0.53)	18	1.26 (0.54)		53.3 %	0.78 [0.45, 1.11]
Mendell 1989	26	1.88 (0.06)	28	1.17 (0.96)		46.7 %	0.71 [0.35, 1.07]
Subtotal (95% CI)	**48**		**46**			**100.0 %**	**0.75 [0.50, 0.99]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%							
Test for overall effect: Z = 6.01 (P < 0.00001)							
3 1.5 mg/kg/day							
Mendell 1989	29	2.13 (0.71)	28	1.17 (0.96)		100.0 %	0.96 [0.52, 1.40]
Subtotal (95% CI)	**29**		**28**			**100.0 %**	**0.96 [0.52, 1.40]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.28 (P = 0.000019)							

Analysis 1.16. Comparison 1 Corticosteroids versus placebo, Outcome 16 Four-stair climbing time after 6 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 16 Four-stair climbing time after 6 months of treatment - prednisone



Analysis 1.17. Comparison 1 Corticosteroids versus placebo, Outcome 17 Timed function: stair climb after 6 months of treatment - deflazacort 2 mg/kg alternate days.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 17 Timed function: stair climb after 6 months of treatment - deflazacort 2 mg/kg alternate days

Study or subgroup	Deflazacort N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Angelini 1994	15	-0.33 (5.69)	8	2.63 (4.14)			-2.96 [-7.02, 1.10]

Test for subgroup differences: Not applicable

Analysis 1.18. Comparison 1 Corticosteroids versus placebo, Outcome 18 Four-stair climbing time after 12 months of treatment (daily prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 18 Four-stair climbing time after 12 months of treatment (daily prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2015	27	7.15 (3.12)	25	8.78 (2.1)			-1.63 [-3.07, -0.19]

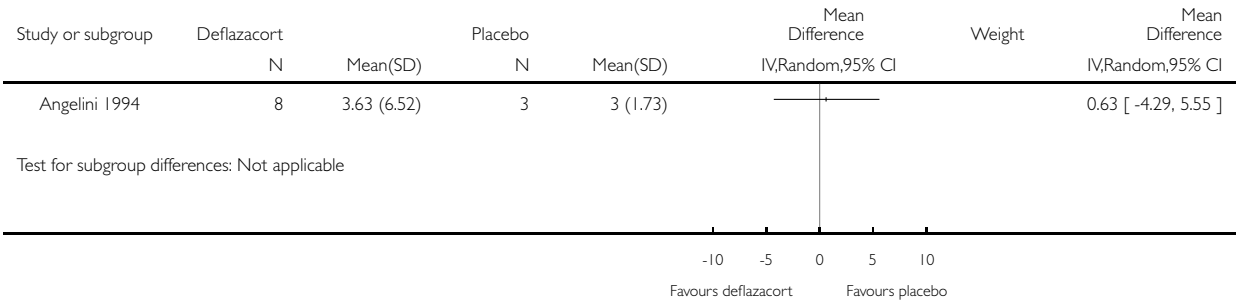
Test for subgroup differences: Not applicable

Analysis 1.19. Comparison 1 Corticosteroids versus placebo, Outcome 19 Change in timed stair climb after 24 months of treatment - deflazacort 2 mg/kg alternate days.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 19 Change in timed stair climb after 24 months of treatment - deflazacort 2 mg/kg alternate days

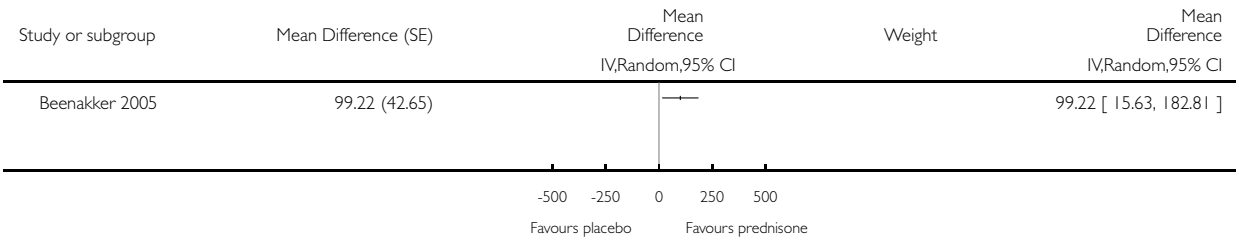


Analysis 1.20. Comparison 1 Corticosteroids versus placebo, Outcome 20 Dynamometry - total muscle force after 6 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 20 Dynamometry - total muscle force after 6 months of treatment - prednisone

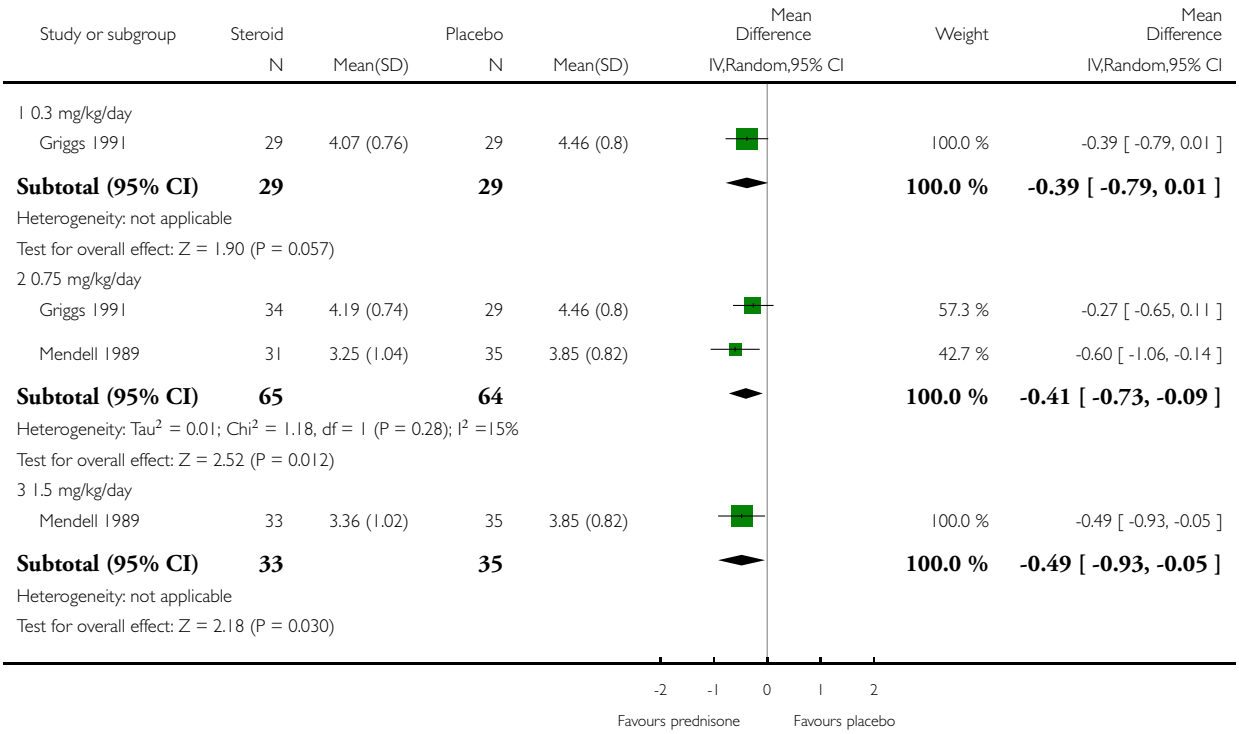


Analysis 1.21. Comparison 1 Corticosteroids versus placebo, Outcome 21 Leg function grade after 6 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 21 Leg function grade after 6 months of treatment - prednisone



Analysis 1.22. Comparison 1 Corticosteroids versus placebo, Outcome 22 Forced vital capacity after 6 months of treatment - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 22 Forced vital capacity after 6 months of treatment - prednisone

Study or subgroup	Steroid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 0.3 mg/kg/day							
Griggs 1991	29	1.64 (0.27)	30	1.48 (0.16)		100.0 %	0.16 [0.05, 0.27]
Subtotal (95% CI)	**29**		**30**			**100.0 %**	**0.16 [0.05, 0.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.76 (P = 0.0058)							
2 0.75 mg/kg/day							
Griggs 1991	34	1.67 (0.29)	30	1.48 (0.16)		38.2 %	0.19 [0.08, 0.30]
Mendell 1989	29	1.68 (0.16)	34	1.52 (0.2)		61.8 %	0.16 [0.07, 0.25]
Subtotal (95% CI)	**63**		**64**			**100.0 %**	**0.17 [0.10, 0.24]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.17, df = 1 (P = 0.68); I^2 =0.0%							
Test for overall effect: Z = 4.81 (P < 0.00001)							
3 1.5 mg/kg/day							
Mendell 1989	28	1.66 (0.16)	34	1.52 (0.2)		100.0 %	0.14 [0.05, 0.23]
Subtotal (95% CI)	**28**		**34**			**100.0 %**	**0.14 [0.05, 0.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.06 (P = 0.0022)							

Analysis 1.23. Comparison 1 Corticosteroids versus placebo, Outcome 23 Quality of life after six months of treatment (daily prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 23 Quality of life after six months of treatment (daily prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Child self report						
Hu 2015	23	64.92 (14.58)	15	54.05 (16.43)		10.87 [0.64, 21.10]
2 Parent proxy-report						
Hu 2015	34	63.46 (15.1)	29	53.49 (17.03)		9.97 [1.96, 17.98]

Analysis 1.24. Comparison 1 Corticosteroids versus placebo, Outcome 24 Quality of life after 12 months of treatment (daily prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 24 Quality of life after 12 months of treatment (daily prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Child self report						
Hu 2015	24	67.38 (16.2)	17	51.33 (14.87)		16.05 [6.46, 25.64]
2 Parent proxy-report						
Hu 2015	31	65.33 (16.53)	27	50.91 (16.67)		14.42 [5.85, 22.99]

Analysis 1.25. Comparison 1 Corticosteroids versus placebo, Outcome 25 Mean % weight gain - prednisone - daily dose regimen.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 25 Mean % weight gain - prednisone - daily dose regimen

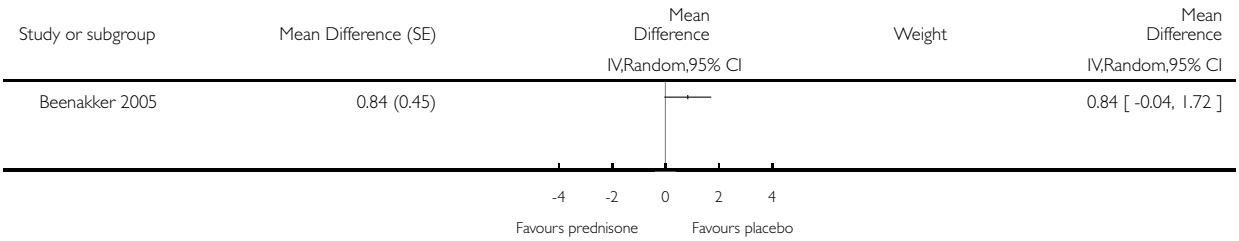
Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 0.3 mg/kg/day							
Griggs 1991	27	11.11 (7.01)	29	6.9 (6.07)		100.0 %	4.21 [0.76, 7.66]
Subtotal (95% CI)	**27**		**29**			**100.0 %**	**4.21 [0.76, 7.66]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.39 (P = 0.017)							
2 0.75 mg/kg/day							
Griggs 1991	32	15.78 (7.47)	29	6.9 (6.07)		50.1 %	8.88 [5.48, 12.28]
Mendell 1989	30	16.67 (7.55)	35	7 (6.27)		49.9 %	9.67 [6.26, 13.08]
Subtotal (95% CI)	**62**		**64**			**100.0 %**	**9.27 [6.87, 11.68]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =0.0%							
Test for overall effect: Z = 7.55 (P < 0.00001)							
3 1.5 mg/kg/day							
Mendell 1989	32	15.78 (7.47)	35	7 (6.27)		100.0 %	8.78 [5.46, 12.10]
Subtotal (95% CI)	**32**		**35**			**100.0 %**	**8.78 [5.46, 12.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.19 (P < 0.00001)							

Analysis 1.26. Comparison 1 Corticosteroids versus placebo, Outcome 26 Weight gain - prednisone - intermittent, given 1st 10 days every month.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 26 Weight gain - prednisone - intermittent, given 1st 10 days every month

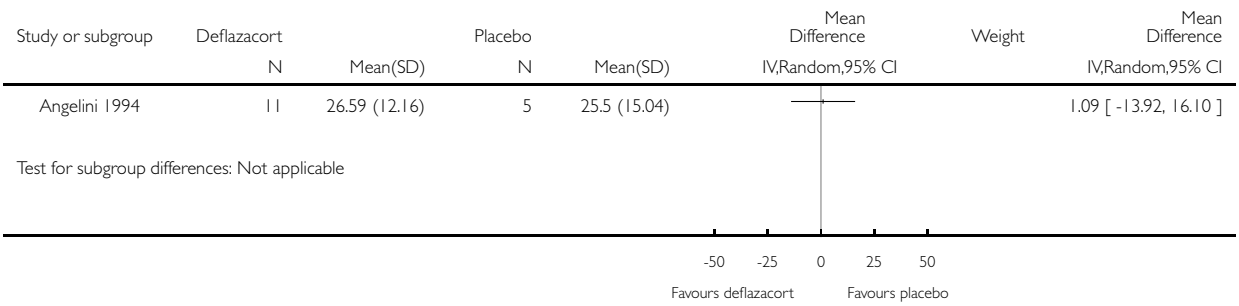


Analysis 1.27. Comparison 1 Corticosteroids versus placebo, Outcome 27 Mean % weight gain - deflazacort 2 mg/kg alternate days.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 27 Mean % weight gain - deflazacort 2 mg/kg alternate days



Analysis 1.28. Comparison 1 Corticosteroids versus placebo, Outcome 28 Body weight at 6 months (prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 28 Body weight at 6 months (prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2015	34	23.09 (4.15)	29	21.93 (3.91)			1.16 [-0.83, 3.15]

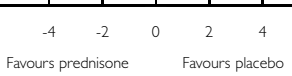
Analysis 1.29. Comparison 1 Corticosteroids versus placebo, Outcome 29 Body weight at 12 months (prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 29 Body weight at 12 months (prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)[kg]	Placebo N	Mean(SD)[kg]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2015	31	24.61 (3.78)	27	22.87 (4.19)			1.74 [-0.33, 3.81]



Analysis 1.30. Comparison 1 Corticosteroids versus placebo, Outcome 30 BMI at 6 months (daily prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 30 BMI at 6 months (daily prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)[kg/m2]	Placebo N	Mean(SD)[kg/m2]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2015	34	16.11 (2.05)	29	15.76 (1.92)			0.35 [-0.63, 1.33]

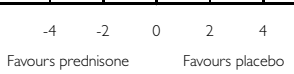
Analysis 1.31. Comparison 1 Corticosteroids versus placebo, Outcome 31 BMI at 12 months (daily prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 31 BMI at 12 months (daily prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)[kg/m2]	Placebo N	Mean(SD)[kg/m2]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2015	31	17.02 (2.13)	27	16.17 (2.09)			0.85 [-0.24, 1.94]
Test for subgroup differences: Not applicable							

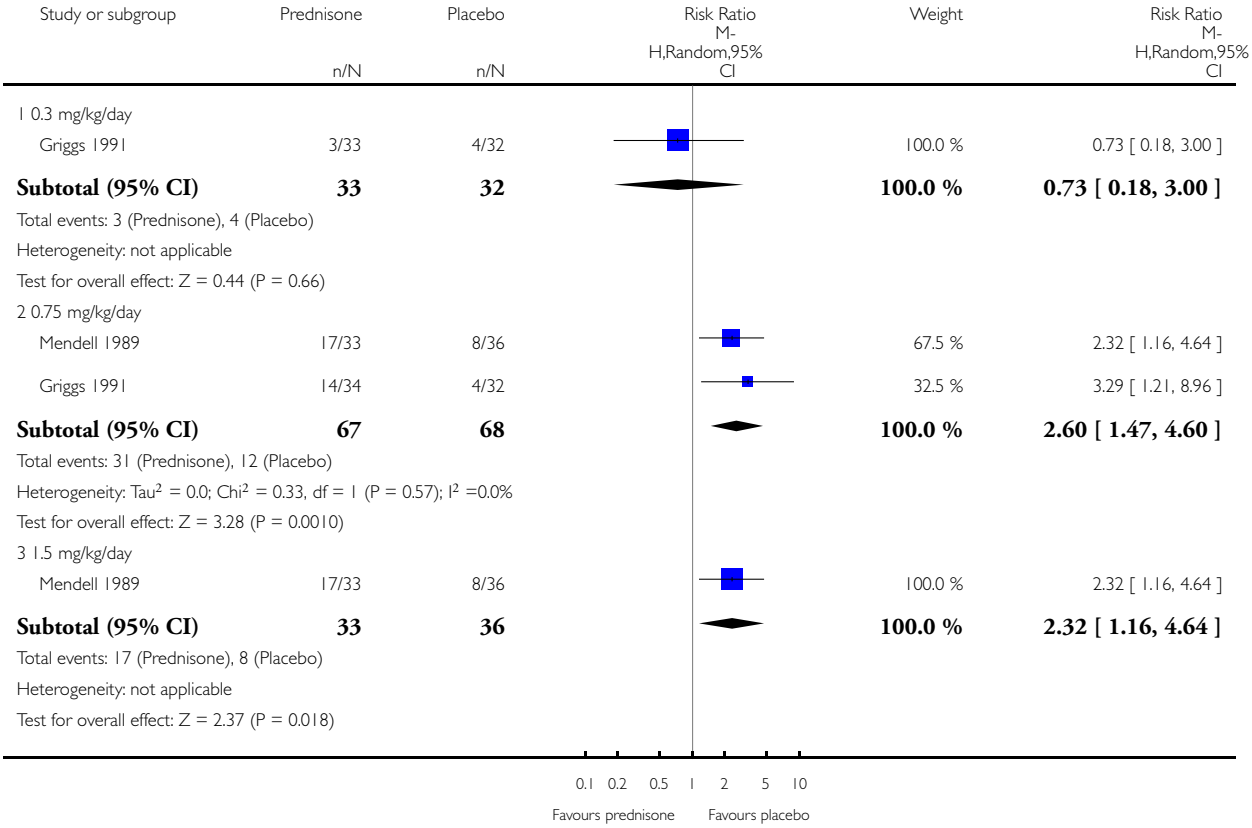


Analysis 1.32. Comparison 1 Corticosteroids versus placebo, Outcome 32 Excessive hair growth - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 32 Excessive hair growth - prednisone

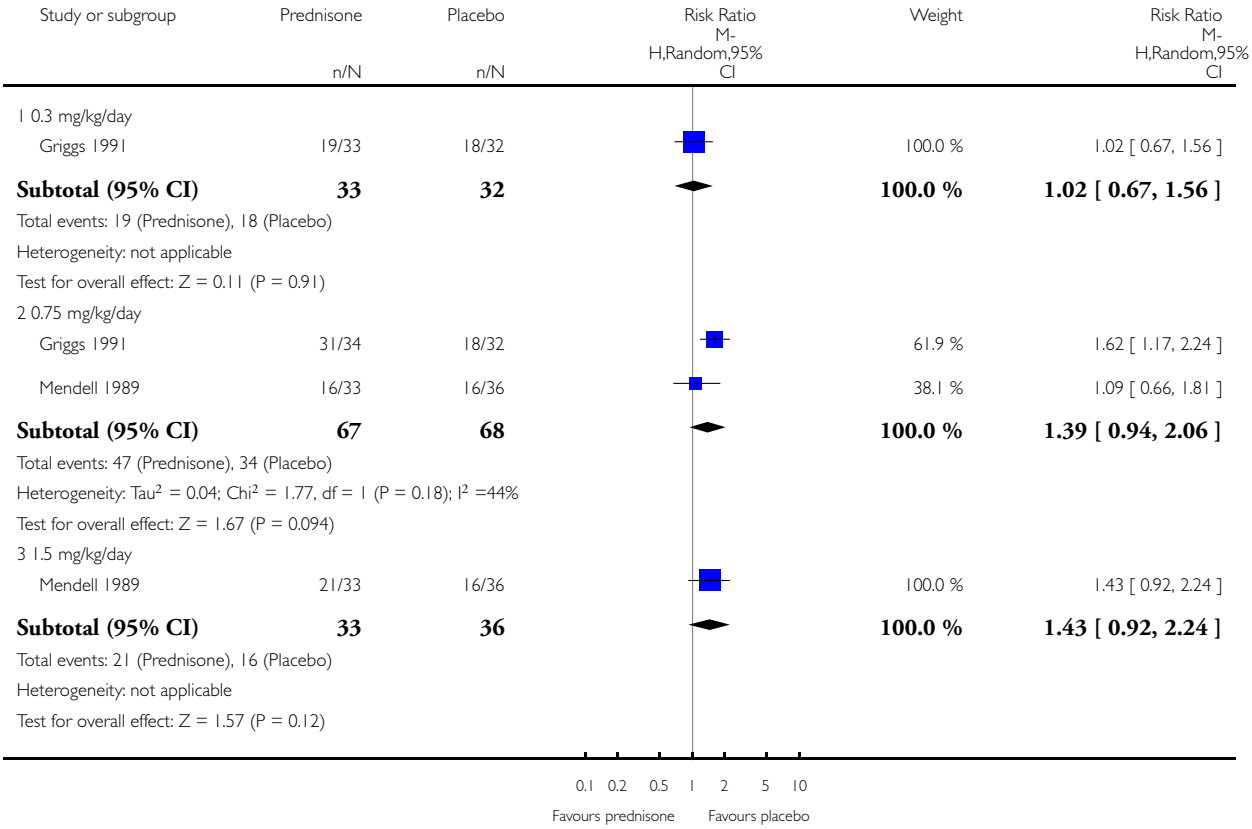


Analysis 1.33. Comparison 1 Corticosteroids versus placebo, Outcome 33 Behavioural changes - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 33 Behavioural changes - prednisone

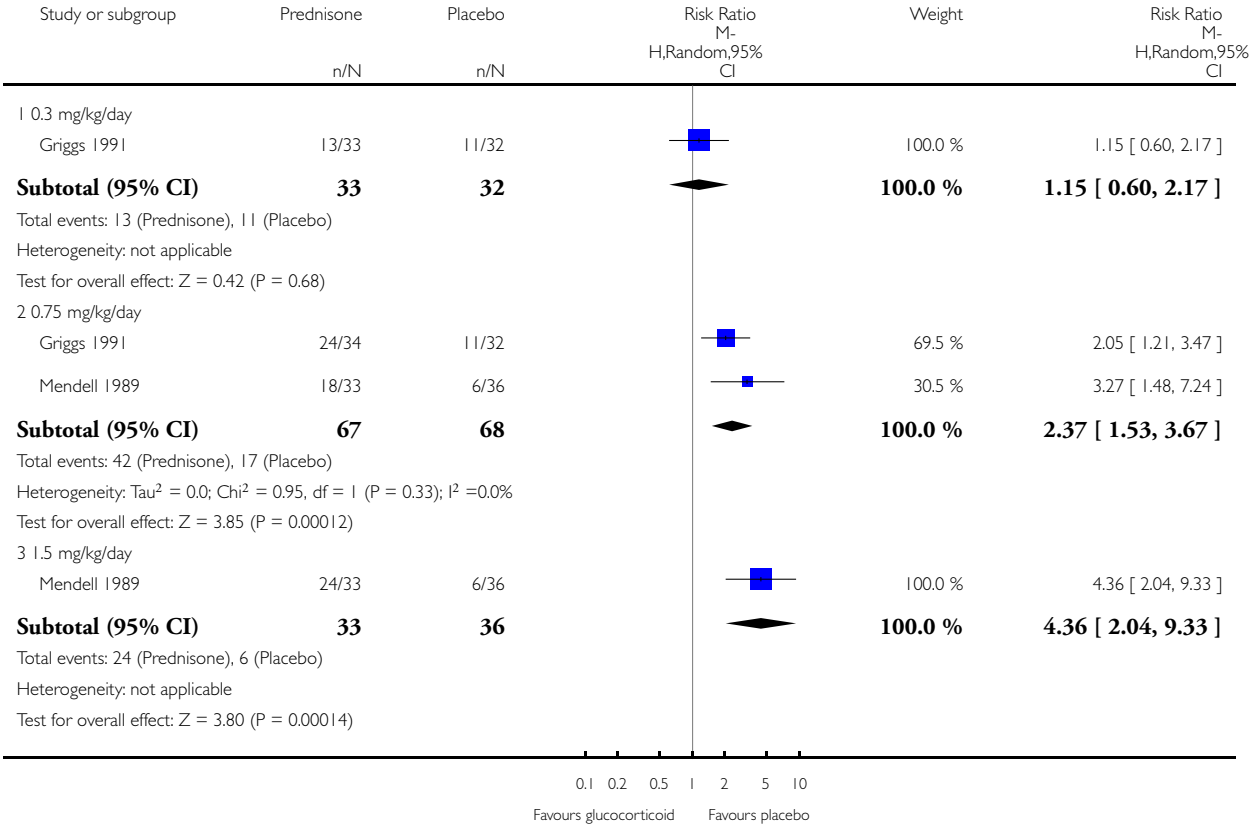


Analysis 1.34. Comparison 1 Corticosteroids versus placebo, Outcome 34 Cushingoid appearance - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 34 Cushingoid appearance - prednisone

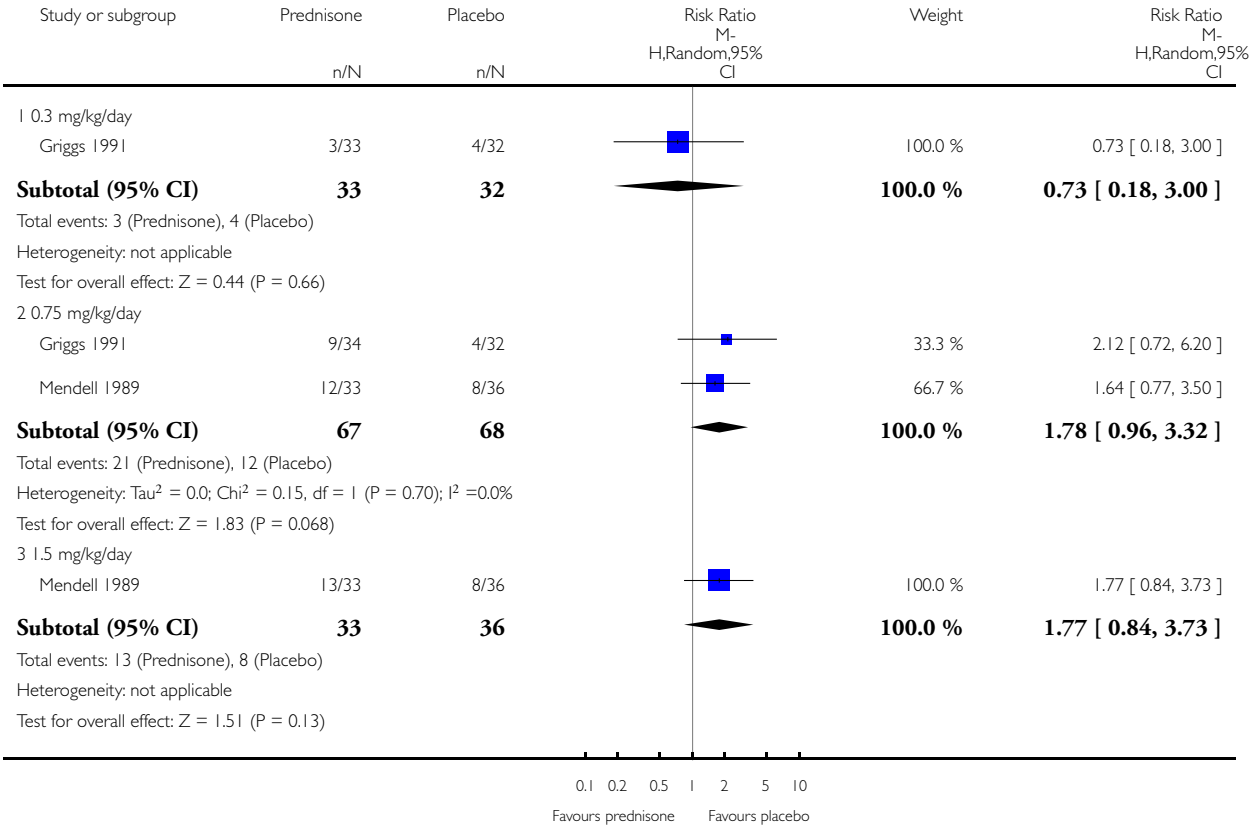


Analysis 1.35. Comparison 1 Corticosteroids versus placebo, Outcome 35 Acne - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 35 Acne - prednisone

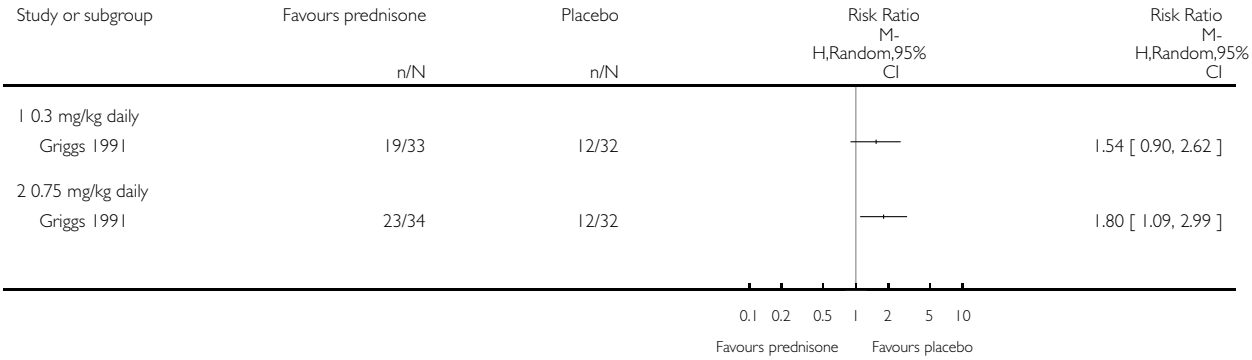


Analysis 1.36. Comparison 1 Corticosteroids versus placebo, Outcome 36 Increased appetite - prednisone.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 36 Increased appetite - prednisone

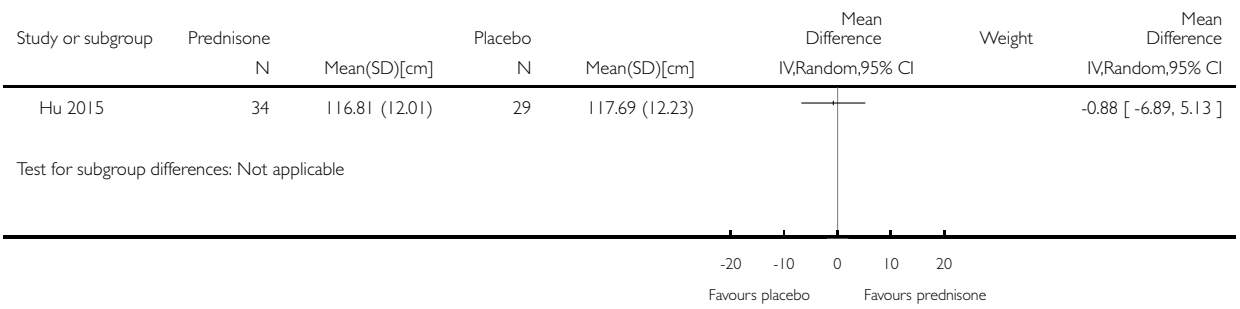


Analysis 1.37. Comparison 1 Corticosteroids versus placebo, Outcome 37 Height at 6 months (daily prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 37 Height at 6 months (daily prednisone 0.75 mg/kg/day)



Analysis 1.38. Comparison 1 Corticosteroids versus placebo, Outcome 38 Height at 12 months (daily prednisone 0.75 mg/kg/day).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 1 Corticosteroids versus placebo

Outcome: 38 Height at 12 months (daily prednisone 0.75 mg/kg/day)

Study or subgroup	Prednisone N	Mean(SD)[m]	Placebo N	Mean(SD)[m]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2015	31	118.02 (11.37)	27	120.64 (11.98)			-2.62 [-8.66, 3.42]

Test for subgroup differences: Not applicable

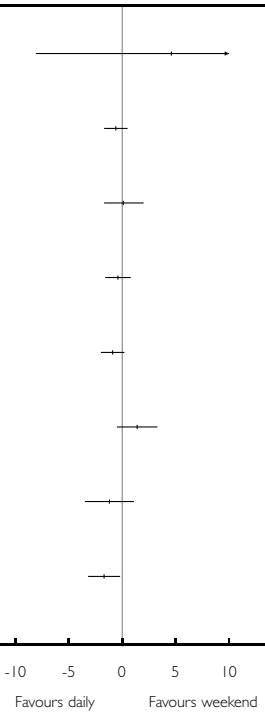
Analysis 2.1. Comparison 2 Weekend-only versus daily prednisone, Outcome 1 Muscle strength (change from baseline to 12 months).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 1 Muscle strength (change from baseline to 12 months)

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 MMT score						
Escolar 2011	27	4 (24.3)	27	-0.6 (23.2)		4.60 [-8.07, 17.27]
2 QMT arm score, lb						
Escolar 2011	27	0.7 (1.7)	30	1.3 (2.4)		-0.60 [-1.67, 0.47]
3 QMT leg score, lb						
Escolar 2011	27	2.2 (3.7)	30	2.1 (3.4)		0.10 [-1.75, 1.95]
4 QMT elbow flexors, lb						
Escolar 2011	27	0.9 (1.9)	30	1.3 (2.7)		-0.40 [-1.60, 0.80]
5 QMT elbow extensors, lb						
Escolar 2011	27	0.5 (1.7)	30	1.4 (2.5)		-0.90 [-2.00, 0.20]
6 QMT knee flexors, lb						
Escolar 2011	27	2.5 (3.5)	30	1.1 (3.8)		1.40 [-0.50, 3.30]
7 QMT knee extensors, lb						
Escolar 2011	27	1.8 (4.6)	30	3 (4.3)		-1.20 [-3.52, 1.12]
8 QMT grip score, lb						
Escolar 2011	27	2.5 (2.4)	30	4.2 (3.4)		-1.70 [-3.22, -0.18]



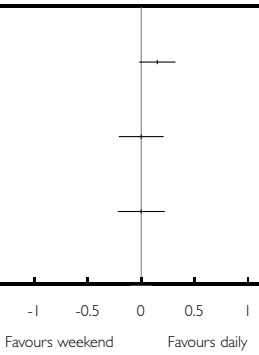
Analysis 2.2. Comparison 2 Weekend-only versus daily prednisone, Outcome 2 Functional outcome measures (change from baseline to 12 months).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 2 Functional outcome measures (change from baseline to 12 months)

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Time taken to rise from the floor (Gowers' time) (log seconds)						
Escolar 2011	21	-0.05 (0.3)	25	-0.2 (0.3)		0.15 [-0.02, 0.32]
2 10-metre walking time (log seconds)						
Escolar 2011	27	0.1 (0.4)	29	0.1 (0.4)		0.0 [-0.21, 0.21]
3 Four-stair climb (log seconds)						
Escolar 2011	26	-0.06 (0.3)	29	-0.06 (0.5)		0.0 [-0.22, 0.22]



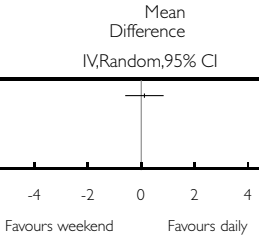
Analysis 2.3. Comparison 2 Weekend-only versus daily prednisone, Outcome 3 Change in mobility function (lower extremity score - Vignos).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 3 Change in mobility function (lower extremity score - Vignos)

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Escolar 2011	28	0.6 (1.4)	30	0.5 (1.4)		0.10 [-0.62, 0.82]



Analysis 2.4. Comparison 2 Weekend-only versus daily prednisone, Outcome 4 Change in mobility function (upper extremity score - Brooke).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 4 Change in mobility function (upper extremity score - Brooke)

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Escolar 2011	28	-0.1 (0.4)	30	0.2 (0.5)		-0.30 [-0.53, -0.07]

Analysis 2.5. Comparison 2 Weekend-only versus daily prednisone, Outcome 5 FVC % predicted.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 5 FVC % predicted

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Escolar 2011	15	5 (15.7)	16	0.6 (24)		4.40 [-9.79, 18.59]

Analysis 2.6. Comparison 2 Weekend-only versus daily prednisone, Outcome 6 FEV1 % predicted.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 6 FEV1 % predicted

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Escolar 2011	15	2 (22.5)	16	-4 (20.4)		6.00 [-9.15, 21.15]

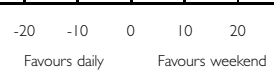
Analysis 2.7. Comparison 2 Weekend-only versus daily prednisone, Outcome 7 Maximal inspiratory pressure.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 7 Maximal inspiratory pressure

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Escolar 2011	23	9 (12)	19	9 (13)		0.0 [-7.63, 7.63]



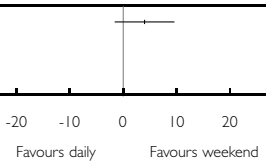
Analysis 2.8. Comparison 2 Weekend-only versus daily prednisone, Outcome 8 Maximal voluntary ventilation.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 8 Maximal voluntary ventilation

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	12	2 (6)	15	-2 (9)		4.00 [-1.68, 9.68]



Analysis 2.9. Comparison 2 Weekend-only versus daily prednisone, Outcome 9 Weight (BMI kg/m2).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 9 Weight (BMI kg/m2)

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	28	17.8 (3.3)	30	19.6 (4.2)		-1.80 [-3.74, 0.14]

Analysis 2.10. Comparison 2 Weekend-only versus daily prednisone, Outcome 10 Weight (kg).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 10 Weight (kg)

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Escolar 2011	28	28.2 (8.5)	30	30.7 (11)		-2.50 [-7.54, 2.54]

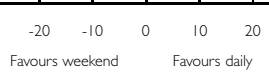
Analysis 2.11. Comparison 2 Weekend-only versus daily prednisone, Outcome 11 Child Behavior Checklist: total problems (higher = more severe).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 11 Child Behavior Checklist: total problems (higher = more severe)

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Escolar 2011	26	49 (10)	28	48 (10)		1.00 [-4.34, 6.34]



Analysis 2.12. Comparison 2 Weekend-only versus daily prednisone, Outcome 12 Child Behavior Checklist: internalising.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 12 Child Behavior Checklist: internalising

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	26	52 (9)	28	48 (9)		4.00 [-0.80, 8.80]

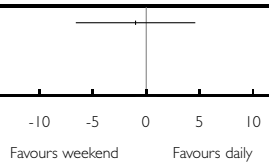
Analysis 2.13. Comparison 2 Weekend-only versus daily prednisone, Outcome 13 Child Behavior Checklist: externalising.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 13 Child Behavior Checklist: externalising

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	26	50 (11)	28	51 (10)		-1.00 [-6.62, 4.62]



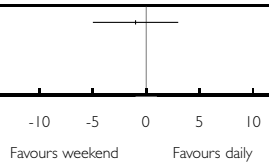
Analysis 2.14. Comparison 2 Weekend-only versus daily prednisone, Outcome 14 Child Behavior Checklist: anxious/depressed.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 14 Child Behavior Checklist: anxious/depressed

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	26	47 (8)	29	48 (7)		-1.00 [-4.99, 2.99]



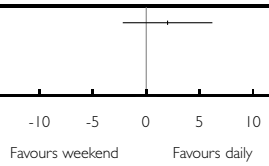
Analysis 2.15. Comparison 2 Weekend-only versus daily prednisone, Outcome 15 Child Behavior Checklist: somatic complaints.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 15 Child Behavior Checklist: somatic complaints

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	26	50 (7)	29	48 (9)		2.00 [-2.24, 6.24]



Analysis 2.16. Comparison 2 Weekend-only versus daily prednisone, Outcome 16 Child Behavior Checklist: withdrawn/depressed.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 16 Child Behavior Checklist: withdrawn/depressed

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	26	50 (9)	29	46 (7)		4.00 [-0.30, 8.30]

Analysis 2.17. Comparison 2 Weekend-only versus daily prednisone, Outcome 17 Child Behavior Checklist: attention problems.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 17 Child Behavior Checklist: attention problems

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	26	48 (10)	30	46 (6)		2.00 [-2.40, 6.40]

Analysis 2.18. Comparison 2 Weekend-only versus daily prednisone, Outcome 18 Child Behavior Checklist: aggressive behaviour.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 18 Child Behavior Checklist: aggressive behaviour

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	26	48 (9)	29	47 (8)		1.00 [-3.52, 5.52]

Analysis 2.19. Comparison 2 Weekend-only versus daily prednisone, Outcome 19 Osteoporosis: lumbar spine Z scores (DEXA).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 19 Osteoporosis: lumbar spine Z scores (DEXA)

Study or subgroup	Weekend		Daily		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Escolar 2011	25	-0.88 (0.85)	28	-1.33 (0.91)		0.45 [-0.02, 0.92]

Analysis 2.20. Comparison 2 Weekend-only versus daily prednisone, Outcome 20 Height (m).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 20 Height (m)

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Escolar 2011	28	124 (11)	30	123 (11)		1.00 [-4.67, 6.67]

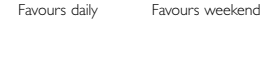
Analysis 2.21. Comparison 2 Weekend-only versus daily prednisone, Outcome 21 Mean growth in cm.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 2 Weekend-only versus daily prednisone

Outcome: 21 Mean growth in cm

Study or subgroup	Weekend N	Mean(SD)	Daily N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Escolar 2011	28	6.6 (2.93)	30	4.1 (2.93)		2.50 [0.99, 4.01]



Analysis 3.1. Comparison 3 Deflazacort versus prednisone, Outcome 1 Weight gain (%).

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 3 Deflazacort versus prednisone

Outcome: 1 Weight gain (%)

Study or subgroup	Deflazacort N	Mean(SD)	Prednisone N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 At 1 year							
Bonifati 2000	9	9 (11.88)	8	21.3 (11.88)		22.7 %	-12.30 [-23.61, -0.99]
Karimzadeh 2012	14	12.95 (9.23)	12	21.65 (6.68)		77.3 %	-8.70 [-14.84, -2.56]
Subtotal (95% CI)	**23**		**20**			**100.0 %**	**-9.52 [-14.91, -4.12]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.30$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 3.46 (P = 0.00054)

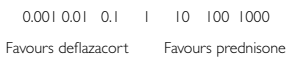
Analysis 3.2. Comparison 3 Deflazacort versus prednisone, Outcome 2 Adverse events at six months.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 3 Deflazacort versus prednisone

Outcome: 2 Adverse events at six months

Study or subgroup	Deflazacort n/N	Prednisone n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Cushingoid appearance				
Bonifati 2000	2/9	3/8		0.59 [0.13, 2.70]
2 Appetite increase				
Bonifati 2000	2/9	6/8		0.30 [0.08, 1.07]
3 Behavioural changes				
Bonifati 2000	4/9	4/8		0.89 [0.32, 2.43]
4 Gastric symptoms				
Bonifati 2000	1/9	2/8		0.44 [0.05, 4.02]
5 Hirsutism				
Bonifati 2000	5/9	4/8		1.11 [0.45, 2.75]

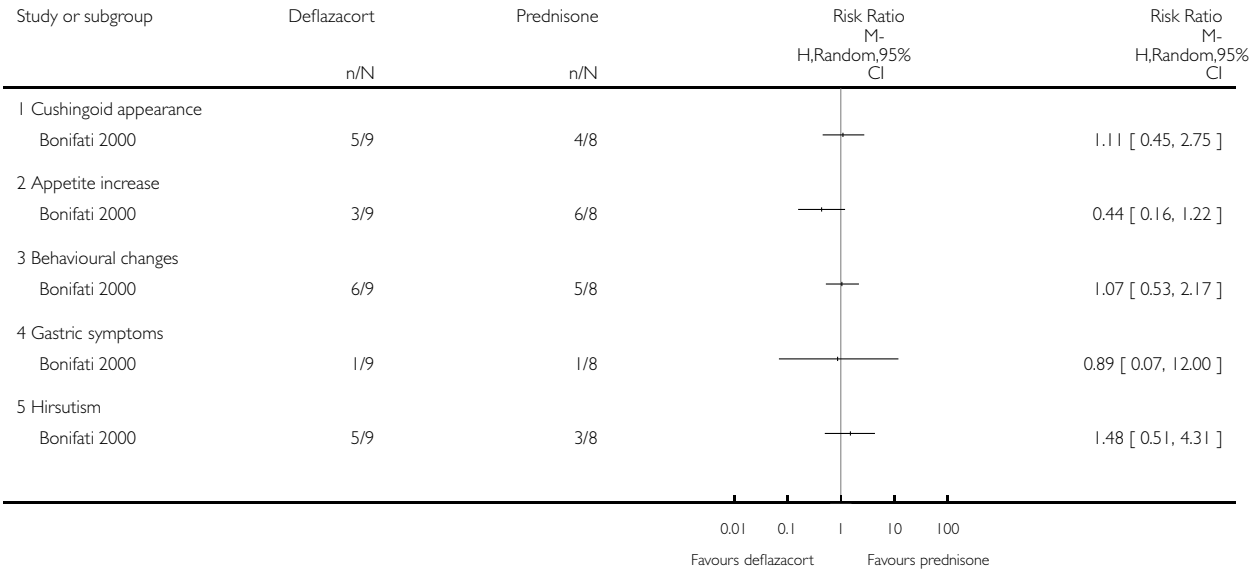


Analysis 3.3. Comparison 3 Deflazacort versus prednisone, Outcome 3 Adverse events at 1 year.

Review: Corticosteroids for the treatment of Duchenne muscular dystrophy

Comparison: 3 Deflazacort versus prednisone

Outcome: 3 Adverse events at 1 year



ADDITIONAL TABLES

Table 1. Excluded non-randomised studies

Study ID	Design	No. of patients	Age (years)	Regimen	Treatment period	Outcome	Adverse events
Drachman 1974	Open	14	4 to 10.5	Prednisone 2 mg/kg/day for 3 months, then two-thirds dose on alternate days	3 weeks to 28 months	Improvement	Adverse events in 4 patients
Siegel 1974	Double-blind	14	6 to 9	Prednisone 5 mg/kg on alternate days	24 months	No benefit	

Table 1. Excluded non-randomised studies (*Continued*)

Brooke 1987	Open	33	5 to 15	Prednisone 1. 5 mg/kg/day	6 months	Improvement	6 dropouts
DeSilva 1987	Open	16	3 to 10	Prednisone 2 mg/kg/day for 3 months, then two-thirds dose on alternate days	1 to 11 months	Walking prolonged by 2 yrs	Excessive weight gain in 12 patients; cataracts in 2
Fenichel 1991b	Open	92	5 to 15	Prednisone 0. 75 mg/kg/day	2 yrs	Stabilisation for 2 yrs Prednisone 0.56 mg/kg/day least effect dose	Cataracts in 10 patients; glycosuria in 10 patients; significant weight gain
Mesa 1991	Double-blind	28	5 to 11	DFZ 1 mg/kg/day	9 months	Improved up to 6 months, then stable	35% cushingoid; no significant weight gain
Sansome 1993	Open	32	6 to 14	Prednisolone 0.75 mg/kg/day for 10 days/months (given 10 days on, 20 days off)	From 6 to 18 months	Strength improved at 6 months; slow decline at 18 months	Fewer adverse events, but 26% of boys had more than 20% weight gain
Biggar 2001	Open	30	7 to 15	DFZ 0.9 mg/kg/day	3.8 (+/- SD 1. 5) yrs	Ambulation prolonged FVC preserved: mean % predicted FVC 72% in DFZ group; 35% in non-treated group	Cataracts in 30%
Dubowitz 2002	Open	2	3 yrs 10 months	Prednisolone 0.75 mg/kg/day (given 10 days on, 10 days off)	5 yrs	Stabilisation of motor function for up to 5 yrs	Irritability in 1 patient

Table 1. Excluded non-randomised studies (*Continued*)

Connolly 2002	Open, historical controls	20 treated	5 to 10	Prednisolone 5 mg/kg twice weekly (every Friday and Saturday).	22 (+/- 1.5) months	Improved strength over 6 to 12 months in majority	Irritability in 6. 2 stopped, 4 reduced prednisone dose
Merlini 2003	Open, parallel-group, double consent	5 treated, 3 control	2 to 4	Prednisone 0.75 mg/kg for 2 weeks, then 1.25 mg/kg on alternate days	47 to 63 months	Ability to rise from floor prolonged; stairs and 10-metre walking time similar	Growth rate decline; irritability requiring niaprazine in 1 patient
Kinali 2002	Open	4 (including 2 patients from Dubowitz 2002)	3 yrs 10 months to 4.5 yrs	Prednisolone 0.75 mg/kg/day (given 10 days on, 10 days off)	2.5 yrs to over 5 yrs	Stabilisation of motor function for up to 5 yrs; loss of ambulation in 1 boy at age 9 yrs, after 5 yrs of treatment	Bone mineral density on DEXA scans at 1 to 6 yrs of treatment was normal
Silversides 2003	Retrospective cohort study; patients refusing treatment formed control group	33 (21 treated)	8.4 (+/-2)	DFZ Start: 0.9 mg/kg/day (gradual decrease in dose with age) At 18 yrs: 0.59 +/-0. 15 mg/kg/day	5.1 (+/- 2.4) yrs	Walking prolonged, 48% ambulant at 14 +/- 2 yrs of age Mean % predicted FVC: 83% in treated, 41% control group Cardiomyopathy: 5% of DFZ vs 58% of controls	Marked retardation of height gain; weight gain similar to controls; cataracts in 50% (asymptomatic)
Aviles 1982 (Published as abstract only)	Open	-	-	Prednisone 3 mg/kg on alternate days.	-	-	-
Dubrovsky 1999 (published as abstract only)	Open	30 (compared to 59 age-matched controls)	7 to 21 yrs	DFZ 0.5 to 1 mg/kg/day.	2 yrs to 9 yrs	FVC significantly preserved in DFZ-treated group	Not described

Table 1. Excluded non-randomised studies (*Continued*)

Tunca 2001 (published as abstract only)	Open	66 (compared with 22 historical controls)	2.5 to 11 yrs	Prednisolone 0.75 mg/kg on alternate days; Vit D	0.5 to 5 (mean 2.75) yrs	Mean age at loss of ambulation - prednisolone 10 yrs, controls 7.69 yrs); no scoliosis at a mean age of 11 .7 yrs	Not described
Pandya 2001 (published as abstract only)	Open	13 independently ambulant patients from clinical Investigation group of Duchenne Dystrophy (CIDD) studies		Prednisone 0.75 mg/kg/day, gradually decreased over time	10 yrs	Mean age of loss of ambulation prolonged to 14.5 yrs	Not described
Resende 2001 (published as abstract only)	Open	36	Not described	DFZ 1 mg/kg/day	15 treated for 12 to 43 months	11 of the 15 boys ambulant beyond 10 yrs	GI disturbances and depression needing discontinu- ation of treatment in 1 patient; cataracts in 2 patients
de Groot 2002 (published as abstract only)	Open	18	4.5 to 9 yrs	Prednisolone 0.75 mg/kg/day (given 10 days on,10 days off)	Not described	"Functional ability improved"	"Osteoporosis 2 -3 SD at the start, but did not change under treatment"
Ahlander 2003 (published as abstract only)	Retrospective review	43 (15 not treated)		Prednisone 0. 35 mg/kg/day	Up to 7.5 yrs	Authors perceived a prolongation of walking by 0.9 yrs, but the patient groups compared are from different eras and there may be con-	Behavioural problems; weight gain; dyspepsia; growth retardation

Table 1. Excluded non-randomised studies (*Continued*)

						founding factors	
Biggar 2006	Open cohort study; patients declining treatment formed comparison (control) group	40 treated, 34 not treated	10 to 18 yrs	DFZ 0.9 mg/kg/day	Mean of 5.5 yrs	DFZ-treated boys were able to rise from supine to standing walk 10 metres without aids, 3 to 5 yrs longer than boys not treated At 18 yrs, only 4/40 treated boys had scoliosis greater than 20 degrees, compared to 30/34 untreated boys At 18 yrs, 4/40 boys treated with DFZ had cardiac left ventricular ejection fraction of < 45%, compared with 20/34 untreated boys Two of the 40 DFZ-treated boys died by 18 yrs of age, compared with 12/34 boys in the untreated group	DFZ-treated boys were significantly shorter, but did not have excessive weight gain 22/40 treated boys had asymptomatic cataracts
Biggar 2004	Description and comparison of 2 cohorts in open study of 2 DFZ protocols, in 2 dif-	56 boys started on DFZ 30 boys on DFZ	4 to 8 yrs 6 to 8 yrs	DFZ 0.6 mg/kg/day for 1st 20 days every month, Vit D 880 iu & Ca 1000 mg daily	4 yrs + 4 yrs +	At 15 yrs of age 25% able to walk 10 metres	No cataracts Cataracts in 30%. Shorter in height than

Table 1. Excluded non-randomised studies (*Continued*)

	ferent centres: 1. Naples protocol (retrospective); 2. Toronto protocol (Biggar 2001 cohort)			DFZ 0.9 mg/kg/day, Vit D 1000 iu & Ca 750 mg daily		At 15 yrs of age 77% able to walk 10 metres	the Naples study cohort
Yilmaz 2004	Prospective cohort study with historical controls	66 treated 22 controls	6.8 ± 2.1	Prednisolone 0.75 mg/kg given on alternate days, Vit D 600 to 1200 iu daily	2.75 ± 1.1 yrs	No scoliosis > 24° in prednisolone-treated group at end of study (mean age 10.8±1.2 yrs) 7/22 in the historical controls had scoliosis > 45° aged 11.7± 0.8 yrs	Duration of follow-up limited with young mean age at end of study Scoliosis appears postponed as compared to historical controls, but potential for worsening in pubertal growth spurt in early teens remains
Alman 2004	Prospective cohort study (same cohort as Biggar 2001)	54 (30 treated)	7 to 10	DFZ Start: 0.9 mg/kg/day (gradual decrease in dose with age)	7.3 (5 to 8) yrs	Scoliosis > 20° developed in 5/30 DFZ group versus 16/24 in non-treated	Symptomatic stress fractures in 3/30 in DFZ group Cataracts in 33% of DFZ group
Balaban 2005	Retrospective review	n = 49 18 prednisone-treated 12 DFZ-treated 19 no drug treatment	12 to 15	Prednisone starting dose: 0.75 mg/kg/day DFZ starting dose: 0.9 mg/kg/day	Corticosteroid therapy for > 2 yrs before loss of ambulation Mean duration of treatment was 5.49 yrs and 5.85 yrs in prednisone and	Similar benefit for walking in both prednisone and DFZ- treated groups, with approximate prolongation of walking of 2 yrs as com-	Dose decrease required in prednisone group because of excessive weight gain DFZ dose decreased in 3 boys be-

Table 1. Excluded non-randomised studies (*Continued*)

					DFZ-treated groups, respectively	pared to non-treated control group Markedly decreased need for scoliosis surgery in DFZ and prednisone groups	cause of hypertension, behavioural changes and vertebral fracture
Schara 2001	Retrospective review	19 DFZ-treated boys	9 to 18	DFZ starting dose 0.9 mg/kg/day	More than 2 yrs	All DFZ-treated boys were able to walk independently during the study period to a mean age of 13 yrs (range 9.4 to 18.11 yrs)	Fourteen of the 19 DFZ-treated boys developed cataracts; one patient's progressive cataracts lead to implantation of lenses after 56 months into the treatment
King 2007	Retrospective review	n = 143 75 prednisone or DFZ-treated boys 68 non-treated (or briefly treated, and therefore considered appropriate as controls)	mean 16.9 (6 to 30 yrs)	Daily dose prednisone or DFZ Average "steroid" dose at last clinic review 0.55 mg/kg/day (range 0.1 - 0.78) Corticosteroid-treated boys were given Ca carbonate 350 mg 3 times daily, or a calcium tablet with vit D (750 to 1200 mg) daily	Mean 8 yrs (+/-5.2 yrs, range 0.5 to 18 yrs)	Treated boys walked 3.3 yrs longer than the untreated group Lower prevalence (31% versus 91%) and severity (Cobb angle 11° versus 33°) in the corticosteroid-treated as opposed to the non-treated boys	Vertebral compression fractures reported in 32% of the treated group (none in the steroid-naïve group) Long-bone fractures were 2.6 times greater in corticosteroid-treated patients Eight of the 75 treated boys discontinued corticos-

Table 1. Excluded non-randomised studies (*Continued*)

							teroid treatment because of adverse effects. Another 2 boys stopped treatment as it was thought that the maximum benefit had been achieved
Daftary 2007	Retrospective, case-control study	n = 35 10 prednisone or DFZ-treated 25 non-treated	7 to 21 yrs in the treated group	Prednisone 0.75 mg/kg/day and DFZ at 0.9 mg/kg/day, were the starting doses	8.2 yrs (range 1 yr to 14 yrs)	IRLS model suggested that the corticosteroid-treated group had higher peak cough flow values (27 L/min higher than the non-treated group (95% CI 2 to 52 L/min; P = 0.0328) Longitudinal effect on peak cough flow could not be assessed because of the study design	Not reported
Kinali 2007	Retrospective study analysing predictive factors for scoliosis in DMD	n = 123 37 prednisolone-treated	All boys 17 yrs or older at time of study	Prednisolone 0.75 mg/kg/day, 10 consecutive days/month (Prednisolone started at mean age of 9.5 yrs (range 7.7 to 12.4)	Median 1 yr (range 2 months to 9 yrs)	There was a positive relationship between age at scoliosis onset (later) and duration (longer) of prednisolone treatment (r = 0.44, P = 0.01, n = 36) There was no	Not reported

Table 1. Excluded non-randomised studies (*Continued*)

						re- lationship be- tween severity of scoliosis at 17 yrs and du- ration of pred- nisolone treat- ment (P = 0. 64)	
Parreira 2007	Prospective single (treated) cohort study	n = 32	Age at start of treatment: 5 yrs 8 months to 8 yrs 8 months	Prednisolone 0. 75 mg/kg/day in an intermit- tent course of 10 days on, 10 days off or DFZ 1 mg/kg/day	14 months	Focus of the study was to select an as- sessment pro- tocol which could be ap- plied in outpa- tient settings 8 boys stopped walk- ing during the study period Muscle strength MRC score decreased over time, but there was some functional im- provement in lift- ing weights, 9- metre walking time	2 withdrew from treatment and 2 took it irreg- ularly
Markham 2005	Retrospective review	n = 111 Prednisone- treated n = 29 DFZ-treated n = 19	3 to 11 yrs Treated 11 ± 4 yr Non-treated 12 ± 5 yr	Not described	Mean length of treat- ment was 3 ± 2.5 yr	Article focuses on cardiac outcome and presents cross- sectional echocardio- graphic data The shorten- ing frac- tion was lower in the non-	Not described

Table 1. Excluded non-randomised studies (*Continued*)

						treated group than in the corticosteroid-treated group (30% ± 7% vs 36% ± 5%; P < 0.001) In comparison with the corticosteroid-treated boys, the non-treated boys older than 10 yrs were 15 times more likely to have a shortening fraction less than 28% (P < 0.01)	
Houde 2008	Retrospective cohort study (patients declining to take corticosteroid or used for less than 6 months formed the control group)	37 treated 42 untreated	Mean 13.1 +/- 3.2 yrs treated group Mean 9.5 +/ -2.9 yrs untreated group	DFZ started at 0.9 mg/kg Adjusted according to evolution or side effects (max 1 mg/kg) Mean dose at most recent visit 0.69 +/- 0.22 mg/kg	Mean treatment 66 months	Walking prolonged: mean age loss of ambulation 11. 5 years treated versus 9.6 yrs control Muscle strength improved: 63% of normal in DFZ group versus 32% of normal in control group FVC improved: 66% DFZ versus 48% control Cardiomy-	All fractures: 43% DFZ versus 26% control At least 1 limb fracture: 24% DFZ versus 26% control Vertebral fractures: 20% DFZ versus 0% control Decline in bone density: Z-score -1.8 after 1 yr DFZ and -4.5 after 7 yrs Weight excess: 62% DFZ versus 55% con-

Table 1. Excluded non-randomised studies (*Continued*)

						opathy reduced: present in 32% DFZ versus 58% control Scoliosis reduced: present in 27% DFZ versus 67% control (43% of whom required surgery)	trol Mean height gain: 3 times as much in controls versus DFZ group Cataracts: developed in 49% of DFZ group (1 required surgery)
Henricson 2013	Prospective cohort study over 12 months of 3 groups: GC-naïve (treated < 1 month total or never), current GC users, past GC users (treated in past for > 1 month but not currently receiving GC)	340 total 82 GC-naïve 210 current GC 48 past GC	Age range 2 to 28 yrs	Not specified	Assessments performed over a 12-month period	Better upper and lower extremity function in current GC group versus GC-naïve P < 0.001 Better functional milestones in GC users versus GC-naïve P = 0.0022 No significant differences in MMT scores although rate of decline slower than compared with historical GC-naïve controls Requirement for surgical spinal stabilisation reduced in GC group versus GC-naïve between	Fractures: no significant differences between groups

Table 1. Excluded non-randomised studies (*Continued*)

						ages 13 to 15 yrs P = 0.013 Better FVC in GC-treated versus GC- naïve in ages 10 to 15 yrs	
Takeuchi 2013	Retrospective cohort study of prednisolone-treated (current and past) versus steroid-naïve	553 total 242 prednisolone-treated, 311 steroid-naïve	Age range > 5 to < 40	Prednisolone (no data on dose, regimen or duration)	Review of registry data compiled from July 2009 to June 2012	Increased age at loss of ambulation: steroid-naïve median 10.1 yrs prednisolone-treated 11.0 yrs	Not examined
Ricotti 2013	Prospective longitudinal observational study	360	Age range 3 to 15 yrs	Daily versus intermittent GC regimens	Mean duration of treatment 4 yrs	Increased age at loss of ambulation for daily regimen: median 12 yrs intermittent versus 14.5 yrs daily Slower decline in NSAA score after age 7 for daily versus intermittent regimen No difference in respiratory or cardiac outcomes between groups	Cushingoid features: 33% daily versus 15% intermittent Hyperactivity: 23% daily versus 15% intermittent GI symptoms: 14% daily versus 6% intermittent Hypertension: 22% daily versus 5% intermittent Excessive weight gain in both groups but greatest increase in overall BMI and shorter heights seen in daily regimen

Table 1. Excluded non-randomised studies (*Continued*)

							Low bone mineral density z scores < 2.5 in 8% daily versus 5% intermittent Vertebral fractures: 8% daily versus 4% intermittent

BMI: body mass index; Ca: calcium; CI: confidence interval; DEXA: dual energy x-ray absorptiometry; DFZ: deflazacort; FVC: forced vital capacity; GC: glucocorticosteroid; GI: gastrointestinal; IRLS: iteratively reweighted least squares; MMT: manual muscle testing; MRC: Medical Research Council; NSAA: North Star Ambulatory Assessment; SD: standard deviation; vit D: vitamin D; yr: year;

Table 2. Excluded randomised studies

Study ID	Design	No. of patients	Age (years)	Regimen	Treatment period	Outcome	Adverse events
Fenichel 1991a	Double-blind	103	5 to 15 yrs	Prednisone 1.25 mg/kg/alternate day Prednisone 2.5 mg/kg alternate day	6 months	Improved at 3 months	Similar adverse events on daily and alternate day regimens
Griggs 1993	Randomised	107	5 to 15 yrs	Prednisone 0.75 mg/kg/day Azathioprine 2.5 mg/kg/day	18 months 12 months	Strength and function improved	No additional benefit of azathioprine
Pradhan 2006	Open controlled study with participants randomised in 2:1 proportion, to prednisolone (+ multivitamins) treatment group or control (multivitamins	67 (44 in prednisolone treatment group) (23 in control group)	Mean ages 8.8 and 8.1 yrs in prednisolone and control groups, respectively Participants were enrolled into the study when they had started falling several times	Prednisolone 0.75 mg/kg daily	2 yrs or longer until completely wheelchair-dependent	Of the 44 participants in the prednisolone treatment group, 24 dropped out because of adverse effects and treatment was stopped in a further 5 partic-	24 of the 44 patients in the prednisolone group dropped out because of adverse effects; 14 dropped out because of excessive weight gain, 12 within the

Table 2. Excluded randomised studies (*Continued*)

	only) Note: Data from only a subgroup (15/44) of participants in the prednisolone-treated group who did not drop out because of adverse effects and improved, were used for comparison with the control group		during the day and had appreciable difficulty in rising from the floor (Gowers' sign time of more than 10 seconds)			ipants because of no improvement in power. Of the remaining 19, only 15 participants in the treatment group could be followed up regularly for 2 yrs and then up to wheelchair-dependent stage; data from only these 15 participants was used for comparison with the control group In this subgroup of 15 participants from the prednisolone group, the mean age of becoming wheelchair-dependent was 169 ± 9 months compared to 132 ± 8 months in the control group	3 months of starting treatment; 4 dropped out because of tuberculosis and 2 because of recurrent infections
Reitter 1995 (Data reported in Dubowitz 2000)	Double-blind	100	5 until ambulant	Prednisone 0.75 mg/kg/day DFZ 0.9 mg/kg/day	2 yrs	Muscle function stabilised	Excessive weight gain in prednisolone group; cataracts in 27% of DFZ group

Table 2. Excluded randomised studies (*Continued*)

Vasanth 1996 (published as abstract only)	RCT of prednisone, ayurvedic drug and placebo	28	Not reported	Prednisone 1 mg/kg/day	7 months	Stability in prednisone group; deterioration in the other two groups	"mild weight gain" in prednisolone group
Vasanth 1996 (unpublished data provided by Dr AB Taly National Institute of Mental Health & Neuro-Sciences, Bangalore)	Randomised, non-blinded trial comparing prednisone with a combination of ayurvedic drugs (participants who had been given placebo in the initial part of the study, were put on ayurvedic drug treatment)	128 (32 on prednisone treatment, and 96 on ayurvedic drug treatment)	Not reported	Prednisone 1 mg/kg/day	2 yrs (2-yr follow-up data available for only 18/32 participants in the prednisone group and 29/96 in the ayurvedic treatment group)	Strength and function not statistically different in the 2 groups at 2 yrs Of the boys who lost walking ability, mean age of loss of ambulation in 13 boys in the prednisone group was 11.88 (SD 2.7) yrs and 10.97 (SD 2.2) yrs in the 42 boys in the ayurvedic treatment group	"Most children had weight gain and developed striae"

DFZ: deflazacort: RCT: randomised controlled trial; SD: standard deviation; yr: year

APPENDICES

Appendix 1. Cochrane Neuromuscular Disease Group Specialized Register (CRS) search strategy

#1 duchenne [REFERENCE] [STANDARD]
#2 MeSH DESCRIPTOR Adrenal Cortex Hormones Explode All [REFERENCE] [STANDARD]
#3 prednisone or prednisolone or deflazacort [REFERENCE] [STANDARD]
#4 steroid or steroids or corticosteroid or corticosteroids or glucocorticoid [REFERENCE] [STANDARD]
#5 steroid or steroids or corticosteroid or corticosteroids or glucocorticoid [REFERENCE] [STANDARD]
#6 #2 or #3 or #4 or #5 [REFERENCE] [STANDARD]
#7 #1 and #6 [REFERENCE] [STANDARD]
#8 (#1 and #6) AND (INREGISTER) [REFERENCE] [STANDARD]

Appendix 2. CENTRAL search strategy

#1 (duchenne NEAR dystrophy)
#2 steroid OR corticosteroid OR prednisone OR prednisolone OR deflazacort OR "adrenal cortex hormone" OR "adrenal cortex hormones"
#3 (#1 AND #2)

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to February Week 1 2016>
Search Strategy:
---
1 randomized controlled trial.pt. (405759)
2 controlled clinical trial.pt. (90039)
3 randomized.ab. (302966)
4 placebo.ab. (154812)
5 drug therapy.fs. (1817824)
6 randomly.ab. (214567)
7 trial.ab. (312188)
8 groups.ab. (1358843)
9 or/1-8 (3445960)
10 exp animals/ not humans.sh. (4184674)
11 9 not 10 (2934178)
12 Duchenne muscular dystrophy/ or (Duchenne$ adj3 Dystrophy).tw. (8530)
13 (steroid$ or corticosteroid$).mp. (332729)
14 Adrenal Cortex Hormones/ (56962)
15 PREDNISONE/ or Prednisone.tw. (45973)
16 PREDNISOLONE/ or Prednisolone.tw. (38806)
17 DEFLAZACORT/ or deflazacort.mp. (457)
18 or/13-17 (419754)
19 11 and 12 and 18 (234)
20 remove duplicates from 19 (231)

Appendix 4. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2016 Week 07>
Search Strategy:
---
1 crossover-procedure.sh. (46034)
2 double-blind procedure.sh. (126073)
3 single-blind procedure.sh. (21489)
4 randomized controlled trial.sh. (392427)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (1220611)
6 trial.ti. (192615)
7 or/1-6 (1367162)
8 (animal/ or nonhuman/ or animal experiment/) and human/ (1439993)
9 animal/ or nonanimal/ or animal experiment/ (3483059)
10 9 not 8 (2890621)
11 7 not 10 (1258007)
12 limit 11 to embase (1039155)
13 Duchenne Muscular Dystrophy/ (11290)
14 13 or (duchenne* adj3 dystrophy).mp. (13716)
15 (steroid$ or corticosteroid$).mp. (545220)
16 Corticosteroid Therapy/ (34287)
17 PREDNISONE/ or Prednisone.mp. (142485)
18 PREDNISOLONE/ or Prednisolone.mp. (109310)
19 deflazacort.mp. or DEFLAZACORT/ (1949)
20 or/15-19 (710093)
21 12 and 14 and 20 (126)
22 remove duplicates from 21 (124)

Appendix 5. CINAHL Plus (EBSCOhost) search strategy

Tuesday, February 2016 8:48:54 AM

S27 S18 and S26
S26 S19 and S25
S25 S20 or S21 or S22 or S23 or S24
S24 deflazacort
S23 (”prednisolone“) or (MH ”Prednisolone“)
S22 (”prednisone“) or (MH ”Prednisone“)
S21 (MH ”Adrenal Cortex Hormones“)
S20 (steroid* or corticosteroid*)
S19 (Duchenne and dystrophy) or (MH ”Duchenne Muscular Dystrophy“)
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S17 ABAB design*
S16 TI random* or AB random*
S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy))
S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*))
S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*))
S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*))
S11 PT (”clinical trial“ or ”systematic review“)
S10 (MH ”Factorial Design“)

S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies")
S8 (MH "Meta Analysis")
S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison")
S6 (MH "Quasi-Experimental Studies")
S5 (MH "Placebos")
S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies")
S3 (MH "Clinical Trials+")
S2 (MH "Crossover Design")
S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample")

Appendix 6. LILACS (IAHx) search strategy

(Duchenne) and (prednisone or prednisolone or deflazacort or steroid or steroids or corticosteroid or corticosteroids or glucocorticoid or "adrenal cortex hormone" or "adrenal cortex hormones") and ((PT:"Randomized Controlled Trial" or "Randomized Controlled trial" or "Ensayo Clínico Controlado Aleatorio" or "Ensaio Clínico Controlado Aleatório" or PT:"Controlled Clinical Trial" or "Ensayo Clínico Controlado" or "Ensaio Clínico Controlado" or "Random allocation" or "Distribución Aleatoria" or "Distribuição Aleatória" or randon$ or Randomized or randomly or "double blind" or "duplo-cego" or "duplo-cego" or "single blind" or "simples-cego" or "simples cego" or placebo$ or trial or groups) AND NOT (B01.050$ AND NOT (humans or humanos or humanos)))

Appendix 7. Trials registers search strategy

Duchenne AND steroids

F E E D B A C K

Feedback from Luca Bello, Postdoctoral Fellow, University of Padua, Italy, 16 May 2016

Summary

Results from a 2015 paper by Bello et al. are not included in this review. In this study, the authors report that in a large observational study of 340 boys with Duchenne muscular dystrophy (DMD) (CINRG Duchenne Natural History Study), participants treated ≥ 1 year with glucocorticoids (GCs) while ambulatory (n = 252/340) showed a 3-year median delay in loss of ambulation (LoA) ($p < 0.001$). Participants aged 2 to 28 years at baseline were recruited in 20 CINRG centers in the USA, Canada, Argentina, Sweden, Italy, Israel, India, and Australia. Average dose was lower for daily prednisone or prednisolone (0.56 mg/kg/day, 75% of recommended) than daily deflazacort (0.75 mg/kg/day, 83% of recommended, $p<0.001$), and non-daily treatment was more common for prednisone or prednisolone (37%) than deflazacort (3%). In a Cox regression analysis adjusted for dose and regimen, deflazacort was associated with a lower yearly risk of LoA than prednisone or prednisolone (HR 0.294 ± 0.053 vs. 0.490 ± 0.08, $p=0.003$). In participants treated with a daily regimen, a later median LoA was observed with deflazacort compared to prednisone or prednisolone (13.9 years vs. 11.2 years). Deflazacort showed higher frequencies of reported growth delay ($p<0.001$), Cushingoid appearance ($p=0.002$), and cataracts ($p<0.001$), but not of weight gain. Although this was a non-randomized, observational study, at risk of bias from potential differences in standards of care because of geographical location and age, we feel that the important results described therein should have been included in this review, along with those of other large observational studies.

Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?

I was the first author of the paper mentioned in my comment, which was written during a research fellowship at Children's National Medical Center in Washington DC. I also write on behalf of the other authors of said paper.

Reply

The 2015 paper by Bello et al was published after the initial literature and trial search was conducted for this review in February 2015. Cochrane practice requires that searches for all relevant databases be run (or re-run) within 12 months before publication of the review or review update. The completion date of this review was very close to this timeframe (within one month). As such a late update search was performed, we included all new RCTs identified within the year that met the inclusion criteria. The observational study by Bello was noted and given its large size was of interest. However, as a non-randomized study it did not meet our inclusion criteria and the conclusions of the study mirrored those of earlier long-term observational studies that were already discussed. As the study provided supporting evidence to already presented data it was not included at such a late editorial stage. However, it is of interest to future updates and we have listed the study and another non-randomised study identified in the final search as 'Studies awaiting classification' for consideration when the review is next updated.

Contributors

Emma Matthews and co-authors, Rosaline Quinlivan (Cochrane Neuromuscular Co-ordinating Editor), Brian Dickie (Cochrane Neuromuscular Feedback Editor)

WHAT'S NEW

Last assessed as up-to-date: 16 February 2016.

Date	Event	Description
26 May 2016	Amended	Two observational studies added to those awaiting assessment. For consideration in future update
26 May 2016	Feedback has been incorporated	Feedback incorporated 26 May 2016

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 2, 2004

Date	Event	Description
16 February 2016	New citation required and conclusions have changed	Review authors expanded the scope of the review at this update to include comparisons of corticosteroids and dosing regimens. We included three trials comparing different corticosteroids or dosing regimens and one new published trial comparing corticosteroid and placebo. We included two previously excluded abstracts that met selection criteria, as this is current practice

(*Continued*)

16 February 2016	New search has been performed	Search updated to February 2016. Tony Swan and Mike Pike withdrew from authorship; Ruth Brassington joined the authors. Review authors updated the methodology and assessed all studies using the current Cochrane 'Risk of bias' tool. We added 'Summary of findings' tables
26 May 2008	Amended	Converted to new review format.
14 November 2007	New citation required and conclusions have changed	We updated the searches of the Neuromuscular Disease Trials Register (August 2006), MEDLINE (July 2007), EMBASE (August 2006), CINAHL (August 2006) and LILACS (August 2006). We identified one randomised controlled trial which fulfilled the inclusion criteria. Another new randomised controlled trial was identified, but did not meet the inclusion criteria, and is described in this update. Twelve new non-randomised studies were identified, and are tabulated and discussed in this update

CONTRIBUTIONS OF AUTHORS

AM wrote the first draft of the original review, selected studies, assessed methodological quality and extracted the data, which the Review Group Co-ordinator checked. TK selected studies and assessed their quality. AS gave statistical advice and helped with inference of data. All four authors (AM, TK, MP, AS) approved the final text.

For this update EM, AM and TK selected new studies. EM and RB assessed risk of bias, extracted data and drafted additional sections of the review. RB entered outcome data into RevMan, which EM checked. FJ provided statistical advice. TK and AM provided advice and commented on the draft.

DECLARATIONS OF INTEREST

Dr Emma Matthews has no conflicts of interest.

Dr Ruth Brassington is Managing Editor of Cochrane Neuromuscular, of which The National Institute for Health Research (NIHR) is the largest single funder. The NIHR provided an incentive award to Cochrane Neuromuscular for the updating of this review (see Acknowledgements). A grant from the Motor Neurone Disease Association to Cochrane Neuromuscular contributed to her salary in 2011-2015. She has no financial conflicts of interest. She withdrew from the later stages of the editorial process of this review.

Dr Thierry Kuntzer has no conflicts of interest.

Fatima Jichi has no known conflicts of interest.

Dr Adnan Y Manzur, at the time of preparation and submission of the protocol for this review was the principal investigator of a proposed UK multicentre trial of prednisolone in Duchenne muscular dystrophy. However, this trial was not funded. Currently, Dr Manzur is the lead clinician of the UK North Star Clinical Network for Neuromuscular Disorders. The clinicians on this clinical network have a consensus on approach to use of corticosteroids (prednisolone) and plans for future collaboration to audit and modify clinical practice in line with available evidence.

SOURCES OF SUPPORT

Internal sources

- Ruth Brassington, UK.

Employed as Managing Editor of Cochrane Neuromuscular by University College London Hospitals (UCLH) NHS Foundation Trust. Her work on this review was supported by NIHR under its Cochrane Incentive Award scheme (award number 13/175/49) and through Cochrane Review Group Infrastructure funding to Cochrane Neuromuscular

- Fatima Jichi, UK.

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External sources

- Emma Matthews, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Tony Swan and Mike Pike withdrew from authorship at this 2016 update; Ruth Brassington joined as an author.

At this update, we extended the scope of the review to include comparisons of corticosteroids and of dosing regimens. We added quality of life and pulmonary function as outcome measures at a previous update and updated the methods in this version of the review accordingly. We revised the objectives to reflect this change and to better reflect specified outcomes.

We added additional adverse events to those specifically listed in the Types of outcomes.

We updated the methods section according to Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidance. We used the current Cochrane 'Risk of bias' tool and included 'Summary of findings' tables. We extended the searches to clinical trials registries.

We used a random-effects meta-analysis throughout, regardless of the presence of heterogeneity.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [administration & dosage; adverse effects; *therapeutic use]; Glucocorticoids [administration & dosage; adverse effects; *therapeutic use]; Muscle Strength [*drug effects]; Muscular Dystrophy, Duchenne [*drug therapy]; Prednisolone [therapeutic use]; Prednisone [therapeutic use]; Pregnenediones [administration & dosage; therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Walking

MeSH check words

Humans; Male