Evidence-based guideline summary: Diagnosis and treatment of limb-girdle and distal dystrophies


ABSTRACT

Objective: To review the current evidence and make practice recommendations regarding the diagnosis and treatment of limb-girdle muscular dystrophies (LGMDs).

Methods: Systematic review and practice recommendation development using the American Academy of Neurology guideline development process.

Results: Most LGMDs are rare, with estimated prevalences ranging from 0.07 per 100,000 to 0.43 per 100,000. The frequency of some muscular dystrophies varies based on the ethnic background of the population studied. Some LGMD subtypes have distinguishing features, including pattern of muscle involvement, cardiac abnormalities, extramuscular involvement, and muscle biopsy findings. The few published therapeutic trials were not designed to establish clinical efficacy of any treatment.

Principal recommendations: For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on clinical phenotype, inheritance pattern, and associated manifestations (Level B). Clinicians should refer newly diagnosed patients with an LGMD subtype and high risk of cardiac complications for cardiology evaluation even if they are asymptomatic from a cardiac standpoint (Level B). In patients with LGMD with a known high risk of respiratory failure, clinicians should obtain periodic pulmonary function testing (Level B). Clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties designed specifically to care for patients with neuromuscular disorders (Level B). Clinicians should not offer patients with LGMD gene therapy, myoblast transplantation, neutralizing antibody to myostatin, or growth hormone outside of a research study designed to determine efficacy and safety of the treatment (Level R). Detailed results and recommendations are available on the Neurology® Web site at Neurology.org. Neurology® 2014;83:1453–1463

GLOSSARY

AAN = American Academy of Neurology; AAV = adeno-associated virus gene; ALS = amyotrophic lateral sclerosis; BMD = Becker muscular dystrophy; CK = creatine kinase; EDM = Emery-Dreifuss muscular dystrophy; hiBM = hereditary inclusion body myopathy; LGMD = limb-girdle muscular dystrophy; MFM = myofibrillar myopathies; sGH = subcutaneous growth hormone.

Limb-girdle muscular dystrophies (LGMDs) are a group of hereditary myopathies characterized by predominantly proximal muscle weakness (pelvic and shoulder girdles). Initially described as a clinical phenotype, they are now recognized as a heterogeneous group of myopathies that vary in severity and may affect persons at all ages from childhood through adulthood. The LGMDs are classified into 2 main...
Duchenne dystrophy, congenital muscular dystrophy, and myotonic dystrophy, and facioscapulohumeral dystrophy interchangeably to refer to the disorders referred to in this guideline. 

The principal audience for this guideline is clinicians caring for patients with muscular dystrophies. 

DESCRIPTION OF THE ANALYTIC PROCESS The systematic review and practice recommendations were developed according to the processes described in the 2004 and 2011 American Academy of Neurology (AAN) guideline development process manuals.5,6 Appendices e-1 through e-6 provide further background on development of this guideline. 

To inform recommendations regarding the diagnosis, management, and treatment of LGMD, the authors performed systematic reviews to answer the following questions: 

1. What is the frequency of genetically confirmed LGMD subtypes? 
2. How often do patients with muscular dystrophy and its specific subtypes have specific clinical features, including ethnic predilection, diagnostic patterns of weakness, respiratory and cardiac complications, laboratory abnormalities (e.g., elevated creatine kinase [CK]), specific patterns on imaging, and muscle biopsy features? 
3. Are there effective therapies for muscular dystrophies? 

The conclusions from the systematic reviews informed the practice recommendation development process. The author panel developed actionable practice recommendations following an explicit structured process. Levels of obligation associated with each recommendation were assigned using a modified Delphi process.5 

ANALYSIS OF EVIDENCE What is the frequency of genetically confirmed LGMD subtype? Overall, the LGMDs are uncommon disorders.6 The most common adult-onset muscular dystrophy presenting with limb-girdle weakness is BMD, with an estimated prevalence of 2.38–7.29 per 100,000.6,9–10 Most of the other specific LGMD disorders are rare, with estimated prevalences ranging from 0.07 per 100,000 (LGMD2D and LGMD2E) to 0.43 per 100,000 (LGMD2I).4 The frequency of some muscular dystrophies varies based on the ethnic background of the population (e.g., LGMD2C is more common in Roma and Tunisian populations, with a prevalence of 0.13 per 100,000).6,11–14 We found no studies estimating the frequency of disorders due to genetic defects in DNAJB6, TRIM32, FHL1, MYH7, filamin C, VCP, matrin-3, selenoprotein, cavin, nebulin, neprin, KLHL9, and Welander distal myopathies. 

How often do patients with muscular dystrophy and its specific subtypes have specific clinical features, including important respiratory and cardiac complications, laboratory abnormalities, and muscle biopsy features? Common features. 

Our systematic review identified features common to most patients with muscular dystrophy. Most patients present with slowly progressive asymmetrical weakness. The age at onset is usually adolescence to early adulthood but is highly variable, ranging from early childhood (LGMD2N, LGMD2P, LGMD1E, FHL1, BAG3)15–20,1,2 to late adult life (e.g., Welander myopathy, Udd distal myopathy).21–23 Although the limb-girdle pattern of weakness affecting proximal muscles of the arms and legs is the most common, other patterns, including scapuloperoneal weakness and distal weakness, are not rare. Indeed, a single genotypic variety can present with different patterns of weakness in different patients. For example, mutations in the titin gene can manifest with limb-girdle weakness, a distal myopathy affecting predominantly anterior leg compartment muscles (Udd distal myopathy), or early ventilatory/respiratory failure.24,25–33 Patients with desmin mutations can present with limb-girdle, scapuloperoneal, or distal pattern of muscle weakness.33,34,35,59–61 Lamin A/C mutations cause both limb-girdle and humeroperoneal phenotypes.34 Conversely, a single phenotype can result from more than one genotype. Miyoshi myopathy, manifesting with asymmetric leg weakness affecting posterior leg compartment muscles, can be seen in mutations in dysferlin (LGMD2B),25–30 and ANO5 (LGMD2L).31–34 The humeroperoneal pattern of weakness is seen in EDMD, which can be due to mutations in the emerin,35,36,37,43 lamin A/C,28–33 FHL1,20,22,45 TMEM43/LUMA,46 and neprin 1 and
2 genes (not reviewed in this guideline). Serum CK levels vary widely between patients with the same disorder, ranging from normal to greater than 10 times above normal levels, and can be as much as 100 times normal in some cases (e.g., LGMD2B). EMG shows short-duration, small-amplitude motor units with early recruitment in weak muscles; findings may be subtle in mild cases. Routine muscle biopsy often shows nonspecific myopathic features, but some dystrophies have specific diagnostic features (discussed below).

**Distinguishing features.** Although there are few pathognomonic features, many LGMD disorders have distinguishing features. These features for the major LGMD disorders are enumerated in table e-2. In addition to inheritance patterns and overall patterns of weakness, distinguishing clinical characteristics include the early development of foot drop (e.g., MFM; asymmetry in muscle weakness (e.g., LGMD1A,27,e47 LGMD2L,e39,e42, e66,e67 MFM; limb contractures (lamin A/C myopathies,e18,e23 EMD,e43,e60 BAG3,e35); prominent muscle cramps (LGMD1C); family or personal history of frontotemporal dementia, Paget disease of bone, or motor neuron disease (hIBM); ancytry (e.g., northern European for LGMD2F); scapular winging (e.g., sarcoglycanopathies,12,13,e92 LGMD2A,e35,e40); call hypertrophy (e.g., BMD,e101,e103,e104,e107,e108,e111,e113,e114,e116,e120,e122,e124,e126,e129,e132,e133,e137,e139,e151,e152); or cardiac conduction system abnormalities (e.g., laminopathy,e18,e175,e178 e185, desminopathy,e27,e29,e40,e42). Rippling muscle phenomenon and percussion-induced muscle contractions are noted in LGMD1C,e184,e185 Epidermolysis bullosa or congenital pyloric atresia suggest plectin mutations,e186,e191 Distinguishing EMG features include myotonic and pseudomyotonic discharges (the latter characterized by runs of decrescendo positive sharp-wave discharges without the typical waxing and waning of amplitudes and frequencies) in MFM. Muscle biopsy features that can distinguish muscular dystrophies include the presence of rimmed vacuoles (e.g., LGMD1D, hIBM,e67,e75,e79,ZASP,e221 MFM), reducing bodies/cytoplasmic bodies (FHL1,e193,e197), and derangement of myofibrils consistent with MFM (desmin,e222,e227 myotilin,e27,e47,e65,e52 αB-crystallin,e49,e55,e57 ZASP,e27,e49,e55,e228 BAG3,e25,e26 DNAJB6,e223 filamin C,e49,e60,e62). Nemaline rods may be seen in distal myopathies due to nebulin mutations.e220,e221 Reductions of specific proteins on immunohistochemistry suggest deficiencies of these proteins, although the diagnosis needs to be confirmed by genetic testing.

Are there effective therapies for muscular dystrophies? The systematic review identified only 12 studies evaluating treatments for patients with LGMD. These are summarized below.

**Gene therapy.** In 2 randomized double-blind trials,232,235 adeno-associated virus gene (AAV) transfer to the extensor digitorum brevis muscle in 6 patients with LGMD2D (α-sarcoglycanopathy) demonstrated that AAV gene therapy probably increases the expression of α-sarcoglycan gene. The clinical relevance of this effect is unknown.

A case series of patients with LGMD2C who received escalating doses of AAV-vector-expressed human γ-sarcoglycan genes into the extensor digitorum communis provided insufficient evidence to determine the clinical effect of AAV-vector-expressed γ-sarcoglycan gene.234

**Myoblast transplantation.** A case series evaluating myoblast transplantation into the tibialis anterior in 3 male participants with BMD pretreated with cyclosporine A provided insufficient evidence to determine the efficacy of myoblast transfer in BMD.235

**Neutralizing antibody to myostatin.** A phase 1 randomized controlled study of a neutralizing antibody (MYO-029) to an endogenous inhibitor of muscle growth (myostatin) performed in 116 participants with different types of muscular dystrophies provided evidence that MYO-029 is probably safe and tolerable in patients with BMD, LGMD2A–E, and LGMD2I. The study was not designed to assess efficacy or long-term safety.236

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**Corticosteroids for BMD.** A 12-month randomized crossover study237 in 4 boys with BMD provided evidence that prednisolone 0.35 g/kg/day is probably effective in improving isometric muscle strength in patients with BMD after 3 months of treatment.

**Growth hormone for BMD.** A randomized study238 evaluating the effects of subcutaneous growth hormone (sGH) in 10 patients with BMD provided insufficient evidence to support or refute the use of sGH to improve cardiac and pulmonary function in patients with BMD.

**Hand training program in Welander distal myopathy.** A case series of a hand training program in 12 patients with Welander distal myopathy provided insufficient evidence to support or refute the benefit of the exercise program.239

**Endurance training.** Two case series studying the effect of endurance training in 9 ambulatory patients with LGMD2F and 11 men with BMD236 provided insufficient evidence to determine the benefit of endurance training to improve maximal oxygen uptake, maximal workload, and other patient-reported outcomes. Two additional case series240,241 evaluating the effects of exercise on hIBM secondary to a defect in the MYH2 gene provided insufficient evidence to assess the effect of endurance training on maximum workload, muscle strength, or change in the expression of...
myosin isoforms on muscle biopsy after statistical corrections for multiple outcome measures.

**MAJOR PRACTICE RECOMMENDATIONS** The recommendations below encompass 3 major areas: diagnosis, evaluation, and management of muscular dystrophies. The full recommendation set is available online.

**Diagnosis of muscular dystrophies. The case for genetic diagnosis.** Accurate diagnosis of the muscular dystrophies is important for patients, their families, and efficient and cost-effective use of medical resources.

Diagnosis assists in defining the long-term prognosis, since some dystrophies are more rapidly progressive, involve the cardiorespiratory systems more frequently, or are associated with other disorders. The identification of these dystrophies through genetic testing will not only inform long-term prognosis but will also assist in directing care more efficiently (e.g., more frequent cardiorespiratory monitoring and prophylactic treatments such as pacemaker/defibrillator placement for those disorders known to be associated with cardiac involvement). Precise identification of the disorder also eliminates the need for repeated testing for an acquired, treatable disorder such as an inflammatory myopathy, because some dystrophies have inflammation on muscle biopsy, making diagnosis difficult on the basis of routine biopsy findings. In addition, the temptation to try immunosuppressive agents repeatedly, looking for a therapeutic response, is not unusual when there is no diagnosis and the patient is worsening. This exposes patients to potentially serious side effects of immunosuppressive medications. Patients on immunosuppressants need regular monitoring, adding logistical difficulties to a population that may have significantly impaired mobility. Health care costs are increased by repeated investigations, immunosuppressive treatments, and laboratory monitoring. Although establishing a genetic diagnosis is expensive on the front end, the costs of continued investigation for other causes and the risks and expenses associated with empiric trials of immunosuppressants make a strong case for establishing a genetic diagnosis, which often provides patients a sense of closure. Establishing a genetic diagnosis is crucial for genetic counseling to inform decision-making about having children and for screening of offspring. Treatment of cardiomyopathy, arrhythmias, and ventilatory failure prolongs life and improves quality of life in patients with other neuromuscular diseases.

The approach to genetic diagnosis. The wide variation in phenotypic expression of the LGMDs makes establishing a clinical diagnosis a challenge. Our systematic review found that muscular dystrophies have few features that are pathognomonic of a specific disorder. An algorithmic approach emphasizing the pattern of weakness, the inheritance pattern, and the presence of distinguishing clinical and muscle biopsy features can efficiently narrow the differential diagnosis to a few disorders. The overall conceptual approach is outlined in figure 1. See figures 2–5 and figures e-1 and e-2 for more detailed algorithms based on the specific pattern of weakness and suspected inheritance patterns.

**Recommendations.** For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on the

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**Figure 1** Conceptual approach to a patient with a suspected limb-girdle muscular dystrophy

1. Determine pattern of weakness
   - Limb-girdle
   - Humoperceneal
   - Distal

2. Determine the likely inheritance pattern
   - X-linked
   - Autosomal dominant
   - Autosomal recessive

3. Identify distinguishing features. For example:
   - Ethnicity (e.g., northern European)
   - Clinical features (e.g., calf hypertrophy)
   - Complications (e.g., cardiomyopathy)
   - Specific EMG features (e.g., myotonic or pseudomyotonic discharges)

4. Order targeted genetic testing

5. Muscle biopsy for distinguishing features. For example:
   - Rimmed vacuoles
   - Nonrimmed vacuoles
   - Myofibrillar myopathic changes

6. Order targeted genetic testing

7. Consider genome- or exome-wide screening or next-generation sequencing
clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (e.g., early contractures, cardiac or respiratory involvement) (Level B).

In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality (Level C).

Evaluation and medical management of muscular dystrophies. Cardiac involvement. Our systematic review
reveals that many (e.g., LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P, BMD, EDMD, and MFM), though not all (e.g., LGMD1C, LGMD2A, LGMD2B, and LGMD2L), muscular dystrophy subtypes have associated cardiac involvement. Muscular dystrophy patients with cardiac involvement often do not have symptoms such as chest pain, pedal edema, or palpitations that precede cardiac morbidity or sudden cardiac death. Serious cardiac manifestations in patients with muscular dystrophy are often identified only with cardiology testing. The detection and appropriate management of cardiac dysfunction are important to reduce morbidity and mortality. Patients with muscular dystrophy often have improved quality of life following appropriate pharmacologic treatment, device placement, or surgical intervention for their cardiac involvement.\textsuperscript{1246}

**Recommendations.** Clinicians should refer newly diagnosed patients with (1) LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P, BMD, EDMD, and MFM or (2) muscular dystrophy without a specific genetic diagnosis for cardiology evaluation, including ECG and structural evaluation (echocardiography or cardiac MRI), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management (Level B).

If ECG or structural cardiac evaluation (e.g., echocardiography) has abnormal results, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (e.g., Holter monitor or event monitor) to guide appropriate management (Level B).

Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation (Level B).

It is not obligatory for clinicians to refer patients with LGMD2A, LGMD2B, and LGMD2L for cardiac evaluation unless they develop overt cardiac signs or symptoms (Level B).

**Dysphagia and nutrition.** Patients with muscular dystrophy may have difficulty receiving adequate oral

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*Autosomal dominant, autosomal recessive, or X-linked inheritance may be responsible in sporadic cases. EDMD = Emery-Dreifuss muscular dystrophy; hIBMPFD = hereditary inclusion body myopathy with Paget disease and frontotemporal dementia; LGMD = limb-girdle muscular dystrophy; VCP = valosin-containing protein.*
intake due to dysphagia or inability to feed themselves due to arm weakness. Maintaining adequate nutrition and body weight is important for optimizing strength, function, and quality of life. When oral intake is inadequate, other means of maintaining intake (e.g., gastrostomy or jejunostomy feeding tubes) may be needed to maintain optimal nutrition. There is evidence from related conditions (amyotrophic lateral sclerosis [ALS]) that maintenance of nutrition and body weight prolongs survival.

**Recommendation.** Clinicians should refer muscular dystrophy patients with dysphagia, frequent aspiration, or weight loss for swallowing evaluation or gastroenterology evaluation to assess and manage swallowing function and aspiration risk, to teach patients techniques for safe and effective swallowing (e.g., chin tuck maneuver, altered food consistencies), and to consider placement of a gastrostomy/jejunostomy tube for nutritional support (Level B).

**Pulmonary complications.** Our systematic review demonstrates that some forms of muscular dystrophy (e.g., LGMD2I or MFM) are associated with oropharyngeal or ventilatory muscle weakness and that patients with these forms are at high risk for developing respiratory failure during the course of their disease. Patients with other forms of muscular dystrophy (e.g., LGMD2B and LGMD2L) rarely, if ever, have symptomatic respiratory involvement from their disease. Patients with respiratory failure from neuromuscular-related weakness often do not have symptoms, such as dyspnea, that precede the onset of respiratory failure. Impending respiratory failure in these patients is often identified only with pulmonary function tests. Respiratory failure constitutes a major source of morbidity, interfering with daytime cognitive function and negatively affecting quality of life. In addition, ventilatory and oropharyngeal weakness can threaten survival through the risk of upper airway obstruction or bellows failure (or both). Patients with respiratory failure secondary to muscle weakness often have improved quality of life with noninvasive pulmonary ventilation.

*Autosomal dominant, autosomal recessive, or X-linked inheritance may be responsible in sporadic cases. LGMD = limb-girdle muscular dystrophy.*
Recommendations. Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course (Level B).

In patients with a known high risk of respiratory failure (e.g., those with LGMD2I or MFM), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency (Level B).

It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic (Level C).

Clinicians should refer muscular dystrophy patients with excessive daytime somnolence, nonrestorative sleep (e.g., frequent nocturnal arousals, morning headaches, excessive daytime fatigue), or respiratory insufficiency based on pulmonary function tests for pulmonary or sleep medicine consultation for consideration of noninvasive ventilation to improve quality of life (Level B).

Spin deformities. Our systematic review has revealed the risk of evolving musculoskeletal spine deformities, such as scoliosis, kyphosis, or rigid spine syndrome, in various muscular dystrophies (EDMD, rigid spine syndrome). These deformities can result in discomfort and functional impairment, interfering with gait, activities of daily living, and pulmonary function. Their management is important in order to...
reduce discomfort, preserve mobility or ability to sit in a wheelchair, and reduce pulmonary complications.\textsuperscript{248}

\textbf{Recommendations.} Clinicians should monitor patients with muscular dystrophy for the development of spinal deformities to prevent resultant complications and preserve function (Level B).

Clinicians should refer muscular dystrophy patients with musculoskeletal spine deformities to an orthopedic spine surgeon for monitoring and surgical intervention if it is deemed necessary in order to maintain normal posture, assist mobility, maintain cardiopulmonary function, and optimize quality of life (Level B).

\textbf{Rehabilitative management and treatment of muscular dystrophies. Clinical rehabilitative management.} Our evidence-based review of the literature on rehabilitative management of muscular dystrophies consisted primarily of single Class III studies. Thus, the currently available data are not adequate to assess the effect of any rehabilitation modality (endurance and strength training, bracing, assistive devices, new computer-based technology). However, the principles of long-term management emphasize maintaining mobility and functional independence for as long as possible, with a focus on maximizing quality of life. The prevention and management of comorbidities, both expected and acquired, is a major part of such management. Another important aspect of management includes proactively preparing patients and their families for the long-term consequences of muscular dystrophies and engaging in discussions regarding end-of-life care. There is evidence from studies in other neuromuscular diseases, including ALS, that a multidisciplinary approach is the most effective way to deliver care.\textsuperscript{249}

\textbf{Recommendations.} Clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties (e.g., physical therapy, occupational therapy, respiratory therapy, speech and swallowing therapy, cardiology, pulmonology, orthopedics, and genetics) designed specifically to care for patients with muscular dystrophy and other neuromuscular disorders in order to provide efficient and effective long-term care (Level B).

Clinicians should recommend that patients with muscular dystrophy have periodic assessments by a physical and occupational therapist for symptomatic and preventive screening (Level B).

While respecting and protecting patient autonomy, clinicians should proactively anticipate and facilitate patient and family decision-making as the disease progresses, including decisions regarding loss of mobility, need for assistance with activities of daily living, medical complications, and end-of-life care (Level B).

For patients with muscular dystrophy, clinicians should prescribe physical and occupational therapy, as well as bracing and assistive devices that are adapted specifically to the patient’s deficiencies and contractures, in order to preserve mobility and function and prevent contractures (Level B).

\textbf{Strength training and aerobic exercise training.} The evidence base regarding the effectiveness of rehabilitation management of muscular dystrophies is limited. However, the available evidence suggests that this population would benefit from strengthening and aerobic fitness training programs. Due to the muscle degeneration in muscular dystrophy, there may be some risk of exercise-induced muscle damage, myoglobinuria, and subsequent overwork weakness following supramaximal, high-intensity exercise. There have been several randomized or quasi-randomized controlled trials comparing strength training programs, aerobic exercise programs, or both to nontraining controls in patients with a variety of neuromuscular disorders.\textsuperscript{230}–\textsuperscript{232} On the basis of this literature, both strength training and aerobic exercise programs appear to be safe, without any notable deleterious effects.

\textbf{Recommendations.} Clinicians may advise patients with muscular dystrophy that aerobic exercise combined with a supervised submaximal strength training program is probably safe (Level C).

Clinicians may advise patients with muscular dystrophy that gentle, low-impact aerobic exercise (swimming, stationary bicycling) improves cardiovascular performance, increases muscle efficiency, and lessens fatigue (Level C).

Clinicians may counsel patients with muscular dystrophy to hydrate adequately, not to exercise to exhaustion, and to avoid supramaximal, high-intensity exercise (Level C).

Clinicians should educate patients with muscular dystrophy who are participating in an exercise program about the warning signs of overwork weakness and myoglobinuria, which include feeling weaker rather than stronger within 30 minutes after exercise, excessive muscle soreness 24–48 hours following exercise, severe muscle cramping, heaviness in the extremities, and prolonged shortness of breath (Level B).

\textbf{Medical treatments.} The systematic review demonstrated that effects on the clinical course and the long-term safety of gene transfer,\textsuperscript{234}–\textsuperscript{235} myoblast transplantation,\textsuperscript{235} neutralizing antibody to myostatin,\textsuperscript{235} myostatin, or growth hormone\textsuperscript{235} are yet to be determined.

\textbf{Recommendation.} Clinicians should not currently offer patients with muscular dystrophy gene therapy, myoblast transplantation, neutralizing antibody to myostatin, or growth hormone outside of a research study designed to determine the efficacy and safety of the treatment (Level R).
AUTHOR CONTRIBUTIONS

Pushpa Narayanaswami: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

Michael Weiss: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Duygu Selcen: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Elizabeth Raynor: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Gregory Carter: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN and AANEM recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guidelines into perspective with current practice habits and challenges. Formal practice recommendations are not intended to replace clinical judgment.

CONFLICT OF INTEREST

The American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine are committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and AANEM keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN and AANEM limit the participation of authors with substantial conflicts of interest. The AAN and AANEM forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, at least 1 AANEM committee, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.

Received February 21, 2014. Accepted in final form June 23, 2014.

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Pushpa Narayanaswami, Michael Weiss, Duygu Selcen, et al.
Neurology 2014;83:1453-1463
DOI 10.1212/WNL.0000000000000892
This information is current as of October 13, 2014