REVIEW ARTICLE

Exercise Therapy and Other Types of Physical Therapy for Patients With Neuromuscular Diseases: A Systematic Review

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ABSTRACT. Cup EH, Pieterse AJ, ten Broek-Pastoor JM, Munneke M, van Engelen BG, Hendricks HT, van der Wilt GJ, Oostendorp RA. Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review. Arch Phys Med Rehabil 2007;88:1452-64.

Objective: To summarize and critically appraise the available evidence on exercise therapy and other types of physical therapies for patients with neuromuscular diseases (NMD).

Data Sources: Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, Medline, CINAHL, EMBASE (Rehabilitation and Physical Medicine), and reference lists of reviews and articles.

Study Selection: Randomized clinical trials (RCTs), controlled clinical trials (CCTs), and other designs were included. Study participants had to have any of the following types of NMD: motoneuron diseases, disorders of the motor nerve roots or peripheral nerves, neuromuscular transmission disorders, or muscle diseases. All types of exercise therapy and other physical therapy modalities were included. Outcome measures had to be at the level of body functions, activities, or participation according to the definitions of the *International Classification of Functioning, Disability and Health* (ICF).

Data Extraction: Two reviewers independently decided on inclusion or exclusion of articles and rated the methodologic quality of the studies included. All RCTs, CCTs, and other designs only if of sufficient methodologic quality were included in a best evidence synthesis. A level of evidence was attributed for each subgroup of NMD and each type of intervention.

Data Synthesis: Initially 58 studies were included: 12 RCTs, 5 CCTs, and 41 other designs. After methodologic assessment, 19 other designs were excluded from further analysis. There is level II evidence ("likely to be effective") for strengthening exercises in combination with aerobic exercises for patients with muscle disorders. Level III evidence ("indications of effectiveness") was found for aerobic exercises in patients with muscle disorders and for the combination of muscle strengthening and aerobic exercises in a heterogeneous group of muscle disorders. Finally, there is level III evidence for breathing exercises for patients with myasthenia gravis and for patients with myotonic muscular dystrophy. Adverse effects of exercise therapy were negligible.

Conclusions: The available evidence is limited, but relevant for clinicians. Future studies should be preferably multicentered, and use an international classification of the variables of exercise therapy and an ICF core set for NMD in order to improve comparability of results.

Key Words: Exercise therapy; Neuromuscular diseases; Physical therapy modalities; Rehabilitation; Review literature.

NEUROMUSCULAR DISEASES (NMD) represent a heterogeneous group of disorders, including motoneuron diseases, disorders of motor nerve roots or peripheral nerves, neuromuscular transmission disorders, and muscle diseases.[1,2] The progression of the diseases varies considerably. The deficits can range from muscle weakness, sensory loss, pain, fatigue, and autonomic dysfunction in varying combinations. These deficits combine to lead to impairments of musculoskeletal and sensory functions, limitations in activities, and restrictions in participation.[2]

There are approximately 600 different NMDs with great variety in referral to physical therapy (PT).[3] There is no consensus regarding the type and intensity of PT.[4] PT often includes exercise therapy to improve or preserve muscle function (strength, endurance) and aerobic capacity to prevent or reduce secondary problems such as contractures, pain, or fatigue.[2,4] The benefits or injurious effects of exercises in NMD are unclear, and this uncertainty is particularly pertinent when the consideration of the "appropriate" level of intensity is addressed.[5-11]

Three Cochrane systematic reviews thus far focused on 1 type of NMD or a specific type of exercise therapy and were restricted to randomized clinical trials (RCTs) or controlled clinical trials (CCTs). In their Cochrane review on muscle strength training and aerobic exercise training for patients with muscle diseases, van der Kooi et al[12] concluded that moderate-intensity strength training in myotonic dystrophy and facioscapulohumeral muscular dystrophy appeared not to be harmful, but there was insufficient evidence to establish its benefit. This conclusion was based on 2 RCTs.[13,14] White et al[15] did a Cochrane review on exercise therapy for people with peripheral neuropathy and concluded that there is insufficient evidence to evaluate the effect of exercise therapy on functional ability in people with this condition. This was based on 1 RCT,[13] which was also included in the review by van der Kooi.[12] Ashworth et al,[16] reviewing treatment for spasticity in patients with amyotrophic lateral sclerosis (ALS), concluded

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that the available evidence was insufficient to determine whether individualized exercises for muscle endurance of the trunk and limbs with moderate intensity are beneficial or harmful for these patients. The conclusion was also based on 1 single RCT performed.[17]

When RCTs are scarce, evidence from nonrandomized studies and other designs, such as pre-post studies or case-control studies, may be particularly relevant.[18] There are previous reviews on exercise therapy for patients with NMD,[9,10] including other designs. However, these reviews lack a systematic approach.

Our aim here is to summarize and critically appraise the available evidence on exercise therapy and other modalities of physical therapies for patients with NMD to support neurologists, physicians, and physical therapists in their clinical decision-making for the individual patient with NMD. We conducted a comprehensive systematic review, including RCTs, CCTs, and other designs, all types of exercise and PT and all types of NMD.

METHODS

Search Strategy

We searched in the Cochrane Central Register of Controlled Trials (Cochrane Library 2005, Issue 3), Ovid Medline In-Process & Other Non-Indexed Citations and Ovid Medline (1966 through September 2005), CINAHL WebSPIRS 5.1 (1982 through September 2005), and EMBASE WebSPIRS 5.03 (Rehabilitation and Physical Medicine) (1995 through September 2005). We also searched in the Cochrane Database of Systematic Reviews to find articles indirectly by screening reference lists. Further, potentially relevant publications were searched manually through citation and author tracking.

Our broad search strategy was built on the following components: (1) RCTs and CCTs as recommended by the Cochrane Neuromuscular Disease Group; (2) other designs, such as pre-post designs; (3) types of NMD; and (4) PT modalities. For all search strategies Medical Subject Headings (MeSH) or indexed terms were used as well as free-text words. The full search strategy is available on request from the corresponding author.

Selection Criteria

Inclusion was restricted to articles with an abstract, and language had to be English, German, French, or Dutch. The following study designs were included: RCTs, CCTs, and other designs such as pre-post studies. Case studies were excluded.

Participants included adults having one of the following types of NMD: (1) motoneuron diseases; (2) motor nerve root and peripheral nerve disorders; (3) neuromuscular transmission disorders; or (4) muscle disorders. Excluded were children or adolescents (<18y) with Duchenne's muscular dystrophy, spinal muscular atrophy, or Becker's muscular dystrophy. Also, patients having signs and symptoms of muscle weakness, pain, or fatigue not related to specific NMD were excluded, as well as diagnoses including chronic fatigue syndrome, spinal cord injuries, thoracic outlet syndrome, reflex sympathetic dystrophy or complex regional pain syndrome, cancer, or acquired immune deficiency syndrome. Although often classified as NMD, diabetic neuropathies, and entrapment neuropathies such as carpal tunnel syndrome and radiculopathies were not included in this review.

Regarding the type of interventions, we included different modalities of PT: (1) muscle strengthening exercises; (2) aerobic exercises; (3) breathing exercises; (4) other interventions such as relaxation techniques, exercises to improve mobility including transfers and walking, functional electric stimulation, education of the patient, family and caregivers; or (5) a combination of these interventions. Comprehensive rehabilitation programs were excluded, because it is impossible to isolate the effectiveness of PT in such programs.

Outcome measures had to be at the level of body functions, activities, or participation according to the definitions of the *International Classification of Functioning, Disability and Health* (ICF).[19] Outcome measures at the level of body functions included measures for muscle strength or muscle endurance, range of motion, aerobic capacity, pulmonary function, respiration, pain, or fatigue. Excluded were measures for blood pressure as well as blood parameters, such as lactate. Outcome measures at the level of activities and participation included indices for walking and moving around, self-care, work and employment, domestic life, leisure, quality of life, or general health.

Procedure for Inclusion

In all databases a preliminary selection, based on title and abstract, was carried out by 2 reviewers (EHC, AJP) independently. Studies that seemed to fit inclusion criteria were retrieved for more detailed evaluation (fig 1). In case of doubt, the reviewers collaboratively decided on retrieval of the full article.

Another pair of reviewers (EHC, JMB-P) independently decided on the inclusion or exclusion based on detailed information in the full articles. If disagreements persisted, a third reviewer (AJP) was consulted. The 2 reviewers (EHC, JMB-P) also independently scanned the reference lists of all articles and reviews for additional articles. Additional articles fulfilling the inclusion criteria, as well as relevant related articles and reviews found during the process of hand searching were retrieved for more detailed evaluation. Final inclusion or exclusion of the articles was always based on independent assessments of 2 reviewers (EHC, JMB-P).

Methodologic Quality

The methodologic quality of the RCTs, CCTs, and other designs was rated using the list recommended by van Tulder et al.[20] The quality of the internal validity was scored with 11 criteria (random assignment, allocation concealed, care provider blinded, cointerventions standardized, compliance ≥70%, patient blinded, outcome assessor blinded, outcome measures relevant, drop-out rate acceptable, timing of outcome assessment comparable, intention-to-treat analysis). Descriptive quality was scored with 8 criteria (eligibility criteria, similarity of groups at baseline, interventions, adverse effects, short-term follow-up, long-term follow-up, sample size, point estimates, measures of variability). All criteria were scored as yes, no, or unclear. Equal weight was given to all items. For the other designs, only the criteria that were applicable (7 criteria for internal validity and 7 criteria for descriptive quality) were used.

RCTs and CCTs were considered to be of sufficient quality if at least 6 of 11 criteria for internal validity and 4 of 8 descriptive criteria were scored positively. The other designs were considered to be of sufficient quality if at least 4 of 7 criteria for internal validity and 4 of 7 descriptive criteria were scored positively. Two reviewers (EHC, JMB-P) independently rated the methodologic quality of the trials. Disagreements were resolved by discussion.

We decided to exclude other designs of insufficient methodologic quality from further analysis because of their lack of value for the best evidence synthesis.

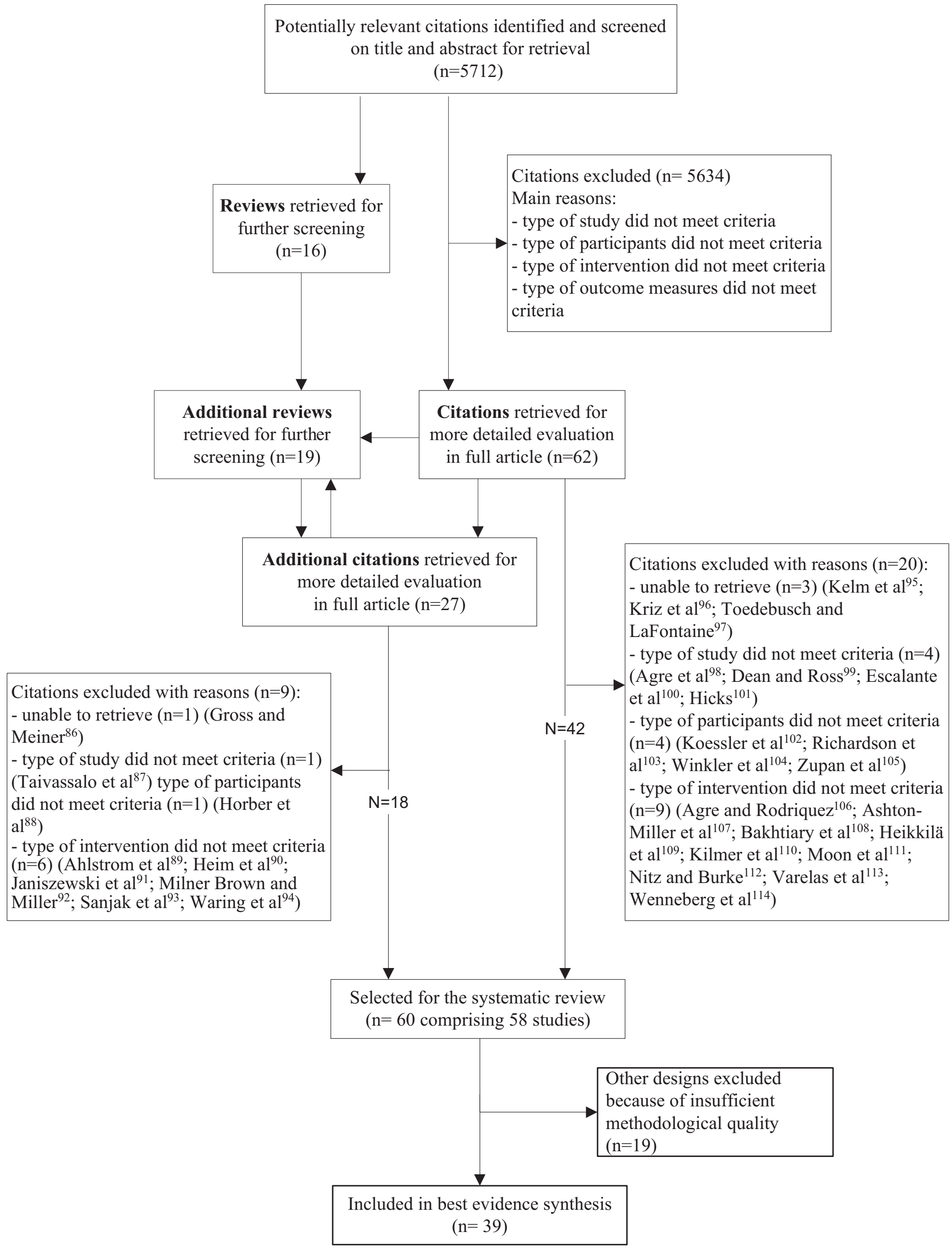

Fig 1. Flowchart showing the selection of studies for PT for patients with NMD.

Classification of Included Studies

The studies were classified based on type of NMD and type of intervention. For each study, the design, the methodologic quality, the number of participants, the diagnosis, the exercise intensity, frequency and duration, and outcome was presented (table 1).

Studies comparing a group of patients with a reference group of healthy persons were categorized as other designs. Also studies in which 1 side of the body was exercised and the contralateral side of the body served as control were treated as other designs.

The type of intervention was categorized into the different modalities of PT: (1) muscle strengthening exercises; (2) aerobic exercises; (3) breathing exercises; (4) other interventions; or (5) a combination of these modalities. For the different types of exercise therapy, the intensity was described, if the article provided enough details.

We divided the outcome variables into 2 categories: 1 category with outcome variables at the level of body functions and a second category including outcome variables at the level of activities and participation. This is based on the corresponding components in the ICF.[19] Adverse effects were presented separately. The aim was to present primary and secondary outcomes for each study. However, only few studies defined primary and secondary outcome measures.[14,21] We then decided to include all outcome variables fulfilling the inclusion criteria and considered them of equal importance. Within each category (body functions or activities/participation, respectively), the number of variables that showed a statistically significant ($P<.05$) effect in a study was divided by the total number of outcome variables in the study. If presented in the article, different subscales of an instrument were treated as different outcome variables. A study was considered to provide evidence of effectiveness if more than half of the variables showed a significant effect.

Best Evidence Synthesis

The comprehensive scope of our review and the heterogeneity in patient populations, interventions, and outcome measures precludes quantitative analysis (meta-analysis) of the data. We used a best evidence synthesis based on a classification of the Dutch Institute for Healthcare Improvement.[22] The following levels of evidence were attributed based on the hierarchy of evidence. Recommendations were formulated accordingly.

Level I evidence is based on (a systematic review of) at least 2 independent RCTs of sufficient methodologic quality and leads to the conclusion: "It has been shown that. . . ." Level II evidence is based on 1 good quality RCT or at least 2 independent controlled studies (RCTs or CCTs) of less methodologic quality and leads to the conclusion: "It is likely that. . . ." Level III evidence is based on an RCT or CCT of low methodologic quality or at least 1 other design of sufficient methodologic quality. The conclusion is formulated as "There are indications that. . . ." In case of inconsistent findings in studies of similar design and methodologic quality (studies with and without evidence), the conclusion is formulated as "There is insufficient evidence that. . . ." If studies showed consistent significant findings, a level of evidence was attributed for each subgroup of NMD and each type of intervention.

RESULTS

Selection of Studies

The search resulted in 5712 citations (see fig 1). Of these, 5634 articles were excluded because the type of study, the participants, the intervention, or outcome measures did not meet the predefined criteria.

The preliminary selection resulted in 62 articles and 16 reviews that were retrieved for more detailed evaluation. Citation tracking resulted in 19 additional reviews and 27 additional articles to be retrieved. The final selection resulted in a total of 60 articles, comprising 58 different studies, because 2 studies were published twice.[13,23-25] Among these studies were 12 RCTs, 5 CCTs, and 41 other designs.

Methodologic Quality

Five of 12 RCTs[13,14,21,26,27] and 1 of 5 CCTs[28] had sufficient methodologic quality (a score of ≥6/11 for internal validity and ≥4/8 for descriptive quality). Of the other designs, 22 studies had sufficient methodologic quality (a score of ≥4/7 for internal validity and ≥4/7 for descriptive quality). Nineteen other designs had insufficient methodologic quality and were excluded from further analysis.[29-47]

Two RCTs[17,48] had a lower score on the validity criteria than we accepted from other designs.

Four RCTs[48-51] and 4 CCTs[28,52-54] presented only within-group analysis, but no between-groups comparisons. These studies were treated as other designs in the best evidence synthesis.

The methodologic quality of all studies included in the best evidence synthesis is presented in table 1.

Best Evidence Synthesis

The best evidence synthesis is based on the information presented in table 1. For each subgroup of NMD and each type of intervention, the evidence is summarized.

Motoneuron Disorders

Muscle strengthening exercises. Four RCTs[17,48,50,55] and 4 other designs[56-59] studied muscle strengthening exercises in NMD. None of the RCTs had sufficient methodologic quality. One RCT[17] included patients with ALS and all other studies included patients with postpoliomyelitis syndrome (PPS).

The low quality RCT[17] on muscle strengthening exercises in patients with ALS reported significant findings in 1 of 8 variables on body functions and 1 of 4 variables on activities and participation. According to the criteria used in this review, this implies that there is insufficient evidence for the effectiveness of muscle strengthening exercises for patients with ALS.

Three RCTs[48,50,55] of insufficient methodologic quality and 4 other designs[56-59] studied muscle strengthening exercises in PPS. The type and intensity of strengthening exercises and the outcome variables differed in all studies. Although 4 studies (1 RCT, 3 other designs) showed significant effects in most outcome variables at the level of body functions, the other 3 studies (2 RCTs, 1 other design) resulted in insufficient evidence of effectiveness. Hence, according to our criteria, there is insufficient evidence for the effectiveness of muscle strengthening exercises for patients with PPS.

Aerobic exercises. One RCT[60] and 1 CCT,[53] both of limited methodologic quality, studied the effectiveness of aerobic exercise in PPS. The RCT showed a significant effect in 4 of 7 outcome variables in the category body functions. The CCT showed no significant results in the between-groups analysis. In the within-group analysis, significant results were found for 2 of 7 variables on body functions and in 1 of 2 variables on activities and participation level. Our conclusion is that there is insufficient evidence for the effectiveness of aerobic exercises for patients with PPS.

A combination of muscle strengthening and aerobic exercises. One CCT[61] of insufficient methodologic quality evaluated the combination of muscle strengthening exercises and aerobic exercises in patients with PPS. Three of 20 variables on body functions and none of the outcome variables on activities and participation showed a significant effect. Hence, there is insufficient evidence for the effectiveness of a combination of muscle strengthening exercises and aerobic exercises for patients with PPS.

Lifestyle modification with or without muscle strengthening exercises. One study with a randomized parallel group design evaluated the effectiveness of lifestyle modification alone and in combination with muscle strengthening exercise in PPS.[50] The methodologic quality of the study was insufficient. There was a significant effect in 1 of 5 variables on body functions in the group receiving the lifestyle modification. The group combining the 2 intervention strategies showed no significant findings. In conclusion, there is insufficient evidence for the effectiveness of lifestyle modification techniques, with or without muscle strengthening exercises for patients with PPS.

Table 1: Classification of PT Studies in Type of NMD

Study	Design	V	D	N	Diagnosis	Type of Intervention (type of exercises, type of muscles, load, number of repetitions, sets, progression)	Frequency and Duration	Body Functions	Activities/ Participation
1. Motoneuron disorders									
Muscle strengthening exercises									
Drory et al[17]	RCT†	3	7	25	ALS	AROM exercises for muscles of limbs and trunk against modest loads	Twice a day 15min for 12mo	1/8†	1/4†
Klein et al[50]	RCT*	4	4	29	PPS	3–5 AROM exercises for hip and knee extensors against gravity. RPE 12–14, increasing number of repetitions	Daily 30min for 16wk	2/5*	NV
Prins et al[55]	RCT†	4	5	16	PPS	Aquatic exercise: swimming and exercises for arms and legs using fins and paddles	3×/wk 45–70min for 8wk	7/39†	NV
Chan et al[48]	RCT*	3	7	10	PPS	3 sets of eight 3–5s 50% MVC of thenar muscle. If possible increase of 10% a week until 70% MVC level	3×/wk for 12wk	2/2*‖	NV
Fillyaw et al[59]	OD‡	4	5	17	PPS	Full AROM exercises for knee or elbow: 3 sets of 10 repetitions with weights. 1st set weight of 50% of 10-RM; 2nd set 75% and 3rd set 100% of 10-RM. 10-RM weight was evaluated every 2 weeks	Every other day up to 2y	2/3‖	NV
Einarsson[58]	OD§	4	7	12	PPS	12 sets of 8 maximal isokinetic knee extensors contractions at 180°/s angular speed interposed with 12 sets of isolated 4-s isometric contractions	3×/wk (96s) for 6wk	5/7‖	NV
Agre et al[56]	OD	5	6	12	PPS	6 repetitions (30s each) of knee extension with weight of 1–1.5kg until RPE 17 or until 10 reps. If RPE <17 weight was increased (.23 kg)	Every other day up to 12wk	0/5	NV
Agre et al[57]	OD	5	6	7	PPS	Tuesday and Friday: 3 sets of 12 reps with ankle weights (1–1.5 kg). If RPE <19, the weight increased (.23kg) the next session. Monday and Thursday: 3 sets of 4 max effort isometric quadriceps contractions (5s)	4d/wk for 12wk	6/6‖	NV
Aerobic exercises									
Jones et al[60]	RCT†	5	7	37	PPS	Cycle ergometer at intensity of 70%–75% of HRR plus resting HR. Bouts of 2–5min, 1-min rest	3×/wk 15–30min for 16wk	4/7†‖	NV
Dean and Ross[53]	CCT*†	4	6	20	PPS	Treadmill walking at comfortable speed, RPE ≤5 (somewhat heavy)	3×/wk 20–40min for 6wk	0/1† 2/7*	1/2*
Muscle strengthening and aerobic exercises									
Willen et al[61]	CCT†	4	5	28	PPS	Fitness in water: resistance and endurance activities, balance, stretching and relaxation, avoiding muscle fatigue	2×/wk 40min for 8mo	3/20†	0/4†
Lifestyle modification									
Klein et al[50]	RCT*	4	4	29	PPS	Lifestyle modification to avoid shoulder overuse	Monthly for 16wk	1/5*	NV
Muscle strengthening exercise and lifestyle modification									
Klein et al[50]	RCT*	4	4	29	PPS	3–5 AROM exercises for hip and knee extensors against gravity, increasing number of repetitions. RPE 12–14	Daily 30min for 16wk	0/5*	NV
2. Motor nerve root disorders and peripheral nerve disorders									
Muscle strengthening exercises									
Lindeman et al[13,25]	RCT†	6	7	29	HMSN	Exercises of muscles of hip and knee. Weeks 1–8: 3 sets of 25 repetitions of 60% of 1-RM; weeks 9–16: 3 sets of 15 repetitions of 70% of 1-RM; from week 18: 10 repetitions of 80% of 1-RM	3×/wk 30min for 24wk	1/4†	1/6†
Chetlin et al[23,24]	OD	5	6	20	HMSN	3 sets of varying repetitions for flexion and extension at 40% to 50% MVIS for knee and 20% to 30% MVIS for elbow. Every 4 weeks, resistance increased. Reps increased weekly from 4 to 6 to 8 to 10	Daily for 12wk	3/9	4/4‖
Muscle strengthening and aerobic exercises									
Ruhland and Shields[51]	RCT*	4	5	28	CPN	Exercises with Theraband with no resistance and progressing to light and medium resistance with 10 repetitions. Aerobic conditioning at 60%–70% of estimated maximal HR or "somewhat hard" on Borg RPE Scale	Daily 20min for 6wk	2/4*	1/11*

Table 1 (Cont'd): Classification of PT Studies in Type of NMD

Study	Design	V	D	N	Diagnosis	Type of Intervention (type of exercises, type of muscles, load, number of repetitions, sets, progression)	Frequency and Duration	Body Functions	Activities/ Participation
3. Neuromuscular transmission disorders									
Breathing exercises									
Fregonezi et al[26]	RCT†*	6	6	27	MG	Ten minutes of diaphragmatic breathing, followed by 10-min interval-based inspiratory muscle training and 10min of pursed lips breathing. Initial load 20% of PImax, increased to 30% in week 3, 45% in the fifth week, and 60% in week 7.	3×/wk 45min for 8wk	4/19† 10/19*‖	1/9† 1/9*
4. Muscle disorders									
Muscle strengthening exercises									
Van der Kooi et al[14]	RCT†	7	7	65	FSHD	Dynamic and isometric exercises for elbow flexors and ankle dorsiflexors, weeks 1–8: 2 sets of 5–10 repetitions with 10-RM weights, interspersed with 30s isometric exercise with 10-RM; weeks 9–17: sets of 8 reps with 8-RM weights; from week 18: 5 reps of 5-RM.	3×/wk for 52wk	2/12†	0/3†
Lindeman et al[13,25]	RCT†	6	7	33	MMD	Exercises of muscles of hip and knee. Weeks 1–8: 3 sets of 25 reps of 60% of 1-RM; weeks 9–16: 3 sets of 15 reps of 70% of 1-RM; from week 18: 10 reps of 80% of 1-RM	3×/wk 30min for 24wk	0/4†	0/6†
Belanger and Noel[52]	CCT*	4	6	6	MMD (5) LGD (1)	Maximal contractions of dorsiflexors and plantarflexors with ankle exerciser. Two sets of 10 MVC of 3–5s for dorsiflexors and for plantarflexors	Daily for 4mo	0/2*	0/4*
Alexanderson et al[63]	OD	6	6	11	PM (7) DM (4)	Warming up. Exercises for shoulder mobility and grip strength with a pulley apparatus, exercises for quadriceps and hip muscles, sit ups, and stretching. If FI score >38 exercises with weights (.25–2.0kg) were included. Also 15-min walking at self-selected speed	5×/wk 15min for 12wk	4/5‖	3/8
Arnadottir et al[64]	OD	6	5	7	sIBM	Exercises for shoulder mobility with a pulley apparatus, resistive exercises for shoulder and hip muscles, quadriceps and neck and trunk muscles. (10 reps of each exercise); weight cuffs (.25–2.0kg) depending on FI score (>38) and self-paced walking (15min)	5×/wk for 12wk	0/3	NV
Aldehag et al[62]	OD	6	6	5	MMD 1	Hand exercises with silicone-based putty with isolated (1-2-3 sets of 3 reps or 1-2-3 sets of 5 reps) and mass (1-2-3 sets of 10 reps or 1-2-3 sets of 15 reps) movements, starting with 1 set of 3–5 reps in isolated movements and 1 set of 10–15 reps in mass movements. Number of sets increased every 4 weeks. Stretching was also included	3×/wk 4min for 12wk	7/12‖	3/4‖
Sandin and Jonsson[65]	OD	5	5	12	WM	Hand exercises with silicone-based putty with isolated (1-2-3 sets of 3 reps or 1-2-3 sets of 5 reps) and mass (1-2-3 sets of 10 reps or 1-2-3 sets of 15 reps) movements, starting with 1 set of 3–5 reps in isolated movements and 1 set of 10–15 reps in mass movements. Number of sets increased every 4 weeks. Stretching was also included	3×/wk 45min for 12wk	4/14	1/2
Tollbäck et al[66]	OD‡	4	6	9	MMD	Maximal AROM exercises for knee extensors with weights on an iron shoe with increasing load. Week 1: 60% of 1-RM; week 2: 70% of 1-RM; thereafter 80% of 1-RM. 3 sets of 8 reps were performed	3×/wk for 12wk	1/4	NV
Aerobic exercises									
Taivassalo et al[70]	OD§	4	5	24	MM (14) NMM (10)	Treadmill exercise 70% to 85% of HRR	3–4×/wk 20–30min for 8wk	2/2‖	1/1‖
Taivassalo et al[69]	OD	5	5	10	MM	Treadmill exercise at 60%–80% of HRR Exercise until reaching the RPE of 15 ("hard")	3–4×/wk 20–30min for 8wk	4/4‖	1/1‖
Taivassalo et al[71]	OD	5	5	10	MM	Cycling at 70%–80% of maximal HR	3–4×/wk 30–40min for 14wk	4/6‖	NV
Trenell et al[72]	OD§	5	5	10	MM	Cycling at 70%–80% of maximal HR	3×/wk 30min for 12wk	2/3‖	1/1‖

Table 1 (Cont'd): Classification of PT Studies in Type of NMD

Study	Design	V	D	N	Diagnosis	Type of Intervention (type of exercises, type of muscles, load, number of repetitions, sets, progression)	Frequency and Duration	Body Functions	Activities/ Participation
Haller et al[67]	OD	4	5	8	MD	Cycling at 60%–70% of maximal HR	4×/wk 30–40min for 14wk	3/3‖	NV
Olsen et al[68]	OD	5	5	8	FSHD	Cycling at 65% of $\dot{V}O_2$max	5×/wk 35min for 12wk	2/2‖	NV
Sunnerhagen et al[73]	OD	5	5	8	HM	Cycling at 70% of maximal workload Subjective workload with a target of 5 (Borg category scale with exponential increments from 0–10)	5×/wk 30min for 8wk	1/3	1/4
Muscle strengthening and aerobic exercises									
Cejudo et al[49]	RCT*	4	7	20	MM	Cycling 30min at 70% of peak work rate; and 3 dynamic isotonic arm weight (50% 1-RM, repeated every 2wk) lifting procedures through full ROM; shoulder press (shoulder, upper back, arm muscles), butterfly (pectoralis major) and biceps curls (biceps brachii, brachialis). Week 1 and 2: 1 set of 10–15 reps; next weeks: 2–3 sets	3×/wk 60min for 12wk	13/18*‖	2/4*
Wiesinger et al[27]	RCT†	6	7	14	DM/PM	Cycling: 3–5min warming up; resistance increased until 60% of maximal HR. Step aerobics 30min at different rate levels adjusting load of exercises. Last 5min cooling down and stretching exercises First 2 weeks, 2×/wk; remaining 4 weeks, 3×/wk	2–3×/wk 60min for 6wk	2/2†‖	1/1†‖
Wiesinger et al[54]	CCT*	5	7	8	DM/PM	Cycling: 3–5min warm-up; resistance increased until 60% of maximal HR. Step aerobics 30min at different rate levels adjusting load of exercises. Last 5min, cooling down and stretching exercises First 2wk, 2×/wk; 4wk, 3×/wk; remaining 18wk, 1×/wk	1–3×/wk 60min for 6mo	6/8*‖	1/1*‖
Muscle strengthening exercises, respiratory exercises and mud/massage/bath									
Varju et al[74]	OD	4	5	21	DM/PM	Assisted bending and stretching of all joints; isotonic muscle training until fatigue. Movements were repeated until 65%–70% of max reps, then rest for 3min. If muscles were too weak, a sling was used. Breathing exercises included instructions how to put hands on abdomen and rib cage and feeling and controlling movements, mud/massage/bath	5×/wk 40–60min for 3wk	9/18	2/4
Breathing exercises									
Ugalde et al[75]	OD§	4	5	11	MMD	Pursed lips breathing as voluntary expiratory blowing through partially closed lips to create a resistance at the mouth compared to matched volume breathing (exhaling without pursing lips) and tidal breathing (comfortable breathing without pursing lips)	120s of each breathing condition	6/9‖	NV
5. Heterogeneous neuromuscular disorders									
Strengthening exercises									
Aitkens et al[76]	OD‡§	4	4	27	MMD (n=12) HMSN (n=8) LGD (n=3) SMA (n=2) FSHD (n=2)	Initially 3 sets of 4 reps with speed of 30/s for knee extensor with ankle weights of 30% of max isometric knee extension force; and also for elbow flexors with weight of 10% of max elbow flexion force. Also 3 sets of 4 reps for hand grip exercises. Increasing resistance and reps	3×/wk 15–20min for 12wk	7/11‖	NV
Kilmer et al[77]	OD‡§	6	5	10	MMD (n=5) LGD (n=3) HMSN (n=2)	Knee extensors and elbow flexors with ankle and wrist cuff weights, 1 set of 10 reps with 12-RM, gradually increasing until 5 sets of 10 reps during 4d/wk. After week 5, resistance was increased by .45kg/wk (1lb/wk) if feasible. After week 9, from 4 to 5 sets	3–4×/wk for 12wk	3/10	NV

Table 1 (Cont'd): Classification of PT Studies in Type of NMD

Study	Design	V	D	N	Diagnosis	Type of Intervention (type of exercises, type of muscles, load, number of repetitions, sets, progression)	Frequency and Duration	Body Functions	Activities/ Participation
Aerobic exercises									
Florence and Hagberg[28]	CCT*	6	5	12	CCD (n=1) NM (n=1) MyM (n=1) SMA (n=1) CMD (n=2) LGD (n=3) CMT (n=2) FSHD (n=1)	Cycling on cycle ergometer 5-min exercise bouts, 2-min rest at 70% of $\dot{V}O_2max$: resistance was adjusted to continually elicit 70% of $\dot{V}O_2max$	3×/wk for 12wk	3/5*‖	0/2*
Wright et al[78]	OD	4	5	11	MMD (n=7); HMSN (n=3) LGD (n=1)	Walking with training at HR of 50%−60% HRR Weeks 1 and 2: 3×/wk 15min; week 3: 20−30min; week 5–9 options to increase frequency to 4×/wk	3−4×/wk 15−20−30min 12wk	1/33	NV
Muscle strengthening and aerobic exercises									
Dawes et al[21]	RCT†*	7	6	18	Becker MD (n=4) MMD (n=4) PM (n=1) FSHD (n=3) IMB (n=1) LGD (n=4) CM (n=1)	Walking for as long as possible at light subjective exercise intensity up to 20min, then increase toward a moderate intensity (Borg CR-10 scale). Two exercises for each leg muscle endurance and core stability increasing the number of repetitions and range until 2.5min for each exercise. Then increasing difficulty with gravity as resistance, increasing number of repetitions	Alternate days for 8wk	1/7† 6/7*‖	0/6† 0/6*

Abbreviations: Activities/participation, number of variables at the level of activities or participation with significant change divided by total number of variables at the level of activities or participation; AROM, active range of motion; Becker MD, Becker muscular dystrophy; Body functions, number of variables at the level of body functions with a significant change divided by the total number of variables at the level of body functions; Borg CR-10 scale, exercise symptom rating scale; CCD, central core disease; CM, congenital myopathy; CMD, congenital muscular dystrophy; CMT, Charcot-Marie-Tooth; CPN, chronic peripheral neuropathy; D, descriptive criteria (maximum, 8); DM, dermatomyositis; FI, functional index in myositis; FSHD, facioscapulohumeral muscular dystrophy; HM, hereditary myopathy; HMSN, hereditary motor and sensory neuropathy; HR, heart rate; HRR, heart rate reserve; IBM, inclusion body myositis; LGD, limb girdle dystrophy; MD, McArdle's disease; MG, myasthenia gravis; MM, mitochondrial myopathy; MMD, myotonic muscular dystrophy; MVC, maximum voluntary contraction; MVIS, maximal voluntary isometric strength; MyM, myotubular myopathy; N, number of patients included in the study; NM, nemaline myopathy; NMM, nonmetabolic myopathy; NV, no variables in this area; OD, other design; PM, polymyositis; PPS, postpoliomyelitis syndrome; reps, repetitions; RPE, rating of perceived exertion; sIBM, sporadic inclusion body myositis; SMA, spinal muscular atrophy; V, criteria for internal validity (maximum, 11); $\dot{V}O_2max$, maximum oxygen uptake; WM, Welander myopathy; xRM, repeated maximum (maximum weight, which can be lifted *x* repetitions).
*Analysis within groups; †analysis between groups.
‡One side of the body randomly chosen for exercise, contralateral side of the body served as control.
§Comparison with a reference group of healthy subjects.
‖Results significant ($P<.05$) for more than half of the variables.

Motor Nerve Root Disorders and Peripheral Nerve Disorders

Muscle strengthening exercises. One RCT[13] of sufficient methodologic quality studied the effect of muscle strengthening exercises for patients with hereditary motor and sensory neuropathy (HMSN). Significant findings were found in 1 of 4 variables on body functions and 1 of 6 variables on activities and participation.[13,25] One other design[23,24] showed significant findings in 3 of 9 variables on body function and all 4 variables on activities and participation. Based on these findings, the conclusion is that there is insufficient evidence for the effectiveness of muscle strengthening exercises in patients with HMSN.

A combination of muscle strengthening and aerobic exercises. One RCT[51] of insufficient methodologic quality studied the effectiveness of muscle strengthening and aerobic exercises in chronic peripheral neuropathy (CPN). There were significant findings in 2 of 4 variables on body functions and in 1 of 11 variables on activities and participation. Our conclusion is that there is insufficient evidence for the effectiveness of strengthening exercises in combination with aerobic exercises in patients with CPN.

Neuromuscular Transmission Disorders

Breathing exercises. One RCT with sufficient methodologic quality studied the effectiveness of inspiratory muscle training and diaphragmatic breathing and pursed lips breathing in patients with myasthenia gravis (MG).[26] Four of 19 variables on body functions and 1 of 9 variables on activities and participation showed a significant effect in the analysis between groups. The within-group analysis showed a significant effect in 10 of 19 variables on body function. If we consider this study as another design, then the conclusion is that there are indications for the effectiveness of breathing exercises in patients with MG (level III evidence).

Muscle Disorders

Muscle strengthening exercises. Two RCTs[13,14,25] of sufficient methodologic quality, 1 CCT[52] with insufficient methodologic quality and 5 other designs[62-66] studied strengthening exercises for patients with muscle disorders. Different types of muscle disorders and different muscle groups were studied. There was also much variety in type and intensity of strengthening exercises and in the outcome variables. The RCTs and CCTs showed hardly significant findings, either at the level of body functions or at the level of activities and participation. The findings of the other designs were inconsistent. In conclusion, there is insufficient evidence for the effectiveness of muscle strengthening exercises for patients with muscle disorders.

Aerobic exercises. Seven other designs[67-73] studied aerobic exercises for patients with muscle disorders. Six other designs[67-72] showed consistent significant findings at the level of body functions and at the level of activities and participation. One other design[73] showed significant findings in only 1 of 3 outcome variables on body function. The outcome variable that showed a significant effect was a measure of aerobic capacity; the other 2 were strength measures. In conclusion, there are indications that aerobic exercises have a positive effect on body functions as well as activities and participation in patients with muscle disorders (level III evidence).

A combination of muscle strengthening and aerobic exercises. Two RCTs[27,49] and 1 CCT[54] studied the combination of muscle strengthening exercises and aerobic exercises in patients with muscle disorders. One RCT[27] had sufficient methodologic quality, whereas the methodologic quality of the other RCT[49] and the CCT[54] was insufficient. The good quality RCT[27] showed significant findings in all 2 variables at the level of body functions and in the only variable measured at the level of activities and participation. The low quality RCT[49] and CCT[54] showed significant findings consistent with the good quality RCT. In conclusion, it is likely that strengthening exercises in combination with aerobic exercises have a positive effect on body functions as well as on activities and participation in patients with muscle disorders (level II evidence).

A combination of muscle strengthening and breathing exercises and mud/massage/bath. One other design[74] showed significant findings in 9 of 18 variables at the level of body functions and 2 of 4 variables at the level of activities and participation. In conclusion, there is insufficient evidence for the effectiveness of the combination of strengthening and respiratory exercises and mud/massage/bath for patients with muscle disorders.

Breathing exercises. One other design[75] on pursed lips breathing in myotonic muscular dystrophy (MMD) showed significant findings on 6 of 9 variables on body functions. In conclusion: there are indications that pursed lips breathing is effective in patients with MMD (level III evidence).

Heterogeneous Group of Patients With NMD

Muscle strengthening exercises. Two other designs[76,77] studied muscle strengthening exercises in a heterogeneous group of patients with NMD. The findings were inconsistent. In conclusion, there is insufficient evidence for the effectiveness of muscle strengthening exercises for a heterogeneous group of NMD.

Aerobic exercises. One CCT[28] and other design[78] studied aerobic exercises in a heterogeneous group of patients with NMD. The CCT was of sufficient methodologic quality and presented significant findings in 3 of 5 variables on body function.[28] There were no significant findings at the level of activities and participation. Only within-group findings were presented, which means that we cannot consider this study to be a truly controlled trial. The other design[78] showed a significant effect in only 1 of 33 variables on body functions. In conclusion, there is insufficient evidence for the effectiveness of aerobic exercises for a heterogeneous group of NMD.

Muscle strengthening and aerobic exercises. One RCT[21] of sufficient methodologic quality studied muscle strengthening and aerobic exercises in a heterogeneous group of NMD. The between-groups analysis showed a significant effect in 1 of 7 variables on body functions and none of the variables at the level of activities and participation. The within-group analysis showed a significant effect in 6 of 7 strength measures in the intervention group. If we consider this study as another design, then the best evidence synthesis leads to the conclusion that there are indications that a combination of muscle strengthening and aerobic exercises is effective in increasing muscle strength (level III evidence).

Adverse Effects

Thirty-three studies reported absent or negligible adverse effects. Chetlin et al[24] reported that 3 of 20 patients decreased their training for 1 or 2 sessions due to delayed-onset soreness. Six studies did not report whether exercise therapy resulted in adverse effects.

Other PT Modalities

No studies were found on the application of functional electric stimulation or interventions to improve mobility including transfers and walking or education of the patient, family, and caregivers.

DISCUSSION

Methodology

The extensive search used in this review with MeSH terms exploded without restrictions and free-text words such as activities of daily living or physical activity, which resulted in a large database of citations. However, 90% of the citations did not fulfill our predefined inclusion criteria regarding the study design, the participants, the intervention, or the outcome measures. Surprisingly, hand searching of the reference lists of the articles and reviews revealed a substantial number of additional citations. Hopewell et al[79] compared hand searches with Medline searching and found that 25% of reports of randomized trials with a Medline record were missed by the electronic search, because they did not have either of the publication type terms *randomized controlled trial* or *controlled clinical trial*. This was especially the case for reports of RCTs published prior to 1991. It shows the limitations of electronic searches and suggests the need to combine electronic searches and manual searches.[18] Another explanation is that the indexing of other designs is less precise and reliable compared with RCTs.[18]

We included all RCTs and CCTs in our best evidence synthesis, regardless of their methodologic quality, and only the other designs of sufficient methodologic quality. Although RCTs are usually regarded as the highest level of evidence for judging the efficacy of therapeutic interventions, randomization should not be seen as a reliable proxy for overall quality.[18] Well-conducted nonrandomized studies may be more valid than poorly conducted RCTs. In this review we found 2 RCTs[17,48] with a lower score on the criteria for internal validity than we accepted from other designs. Another unexpected finding was that 4 RCTs[48-51] and 4 CCTs[28,52-54] did not present between-groups comparisons. We recommend the presentation of between-group comparisons to be an additional criterion in the future rating of methodologic quality.

The various types of NMD and PT interventions in combination with the use of a variety of outcome measures required that decisions were made on classifications and cutoff points. We decided that more than half of the outcome variables in a given study had to show a significant effect in order to provide evidence. We presumed that all outcome variables were of similar importance, but this is arbitrary. It may have resulted in loss of evidence when effects of important variables were overruled by other variables without an effect. However, when we checked the actual variables, they were generally in agreement with our assumptions.

Finally, in our method, a study that provided evidence of effectiveness could be neutralized by studies without evidence.

One can argue that this is too strict, considering the fact that a study could only provide evidence if more than half of the variables showed a significant effect. On the other hand, we were not strict in including all RCTs and CCTs, regardless of their methodologic quality and other designs of sufficient methodologic quality.

Exercise Intensity

Most studies evaluated muscle strengthening exercises, aerobic exercises, or a combination of these. The intensity of strengthening exercises can be manipulated by varying the resistance or weight, the number of repetitions, the length of the rest interval, or the number of sets of exercises completed. The American College of Sports Medicine (ACSM) formulated minimal requirements to evaluate the quality of training programs for effective muscle strength training in healthy adults.[80] The ACSM recommends a progressive individualized program, for all major muscle groups with at least 1 set of 8 to 12 repetitions and a frequency of 2 to 3 days a week. Obviously, these requirements for healthy persons cannot simply be applied to persons with NMD, because of lack of evidence regarding the effect of physical exertion on the diseased neuromuscular system. Overexerting muscles might accelerate disease progression.[12] Still, the intervention should be of enough intensity to provide a training stimulus.

Nearly all studies on muscle strengthening exercises included in this review met the requirements of an individualized and progressive program. However, there was considerable variation in the muscles exercised, type of exercises given, and type of resistance, number of repetitions, and number of sets. Most investigators used a moderate level of intensity in order to prevent adverse effects. Indeed, a very important finding was the absence of adverse effects. If, however, the intensity is too low, one cannot expect an effect of training other than physiologic adaptations due to activation of muscles that might have been inactive before.

For aerobic exercises, ACSM recommends the use of large muscle groups in a rhythmic, aerobic, and continuous manner.[18,81] For most people, intensities within the range of 70% to 85% of maximum heart rate, or 60% to 80% of oxygen uptake reserve or heart rate reserve are sufficient to achieve improvements in cardiorespiratory fitness, when combined with an optimal frequency of 3 to 5 days a week.[81] This review has shown that these intensities can be recommended for patients with NMD without adverse effects. Most of the included studies used cycling or treadmill exercise with a frequency of at least 3 times a week and exercise intensity around 70% of heart rate reserve or estimated maximum heart rate.

For both muscle strengthening and aerobic exercises the entire program should last at least 10 weeks and regular supervision optimizes the effect of training and improves safety and compliance.[12] Yet, in only 30% of all studies on muscle strengthening and aerobic exercises, the duration of the interventions was less than 10 weeks, and in approximately 50% of the studies, the training was under regular supervision.

Uniformity

To facilitate meaningful comparisons among studies and statistical power by effective pooling of study results, more uniformity is needed in type of interventions, intensity of exercise therapy, and type of outcome measures. To achieve more uniform terminology, we recommend the development of an international classification for PT modalities. In the Netherlands, such a classification has been developed for allied health care professionals.[82] In this study, the ICF[19] was used to make a distinction between outcome variables at the level of body functions and at the level of activities and participation. We recommend the development of ICF core sets specifically for NMD, like ICF core sets developed for other chronic diseases.[83-85] This would provide professionals and researchers with a framework for the selection of assessment and outcome measures on body functions, activities and participation and on environmental factors for research as well as for clinical purposes.

CONCLUSIONS

Our best evidence synthesis resulted in level II evidence (likely to be effective) for strengthening exercises in combination with aerobic exercises for patients with muscle disorders. Level III evidence (indications of effectiveness) was found for aerobic exercises in patients with muscle disorders and for the combination of muscle strengthening and aerobic exercises in a heterogeneous group of patients with muscle disorders. Finally, there is level III evidence for breathing exercises for patients with MG and for patients with MMD. There was insufficient evidence for strengthening exercises due to insignificant or inconsistent effects. Most studies reported the absence of adverse effects.

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