Influence of Exercise on Patients with Guillain-Barré Syndrome: A Systematic Review

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ABSTRACT

Purpose: To evaluate the effects of exercise interventions on improving physical outcomes in patients with Guillain-Barré syndrome (GBS). **Methods:** The PubMed database was searched for articles published up to and including February 2015. Randomized controlled trials (RCTs), case reports, and quasi-experimental and single-subject designs published in English-language, peer-reviewed journals that assessed the impact of physical exercise on patients with GBS were included; study quality was assessed using Sackett's rules of evidence. Data are presented qualitatively and quantitatively using numerical values and percentages. **Results:** Seven articles were included in the systematic review. One RCT showed that high-intensity relative to lower intensity exercise significantly reduced disability in patients with GBS, as measured with the FIM ($p < 0.005$, $r = 0.71$). Overall, various types of exercise programmes improve physical outcomes such as functional mobility, cardiopulmonary function, isokinetic muscle strength, and work rate and reduce fatigue in patients with GBS. **Conclusion:** Because of insufficient high-quality literature, making confident conclusions about the effects of exercise interventions on physical outcomes in patients with GBS is not possible. Future research should consider using higher quality study designs to confirm the results outlined in this article.

Key Words: exercise; Guillain-Barré syndrome; physical exertion; rehabilitation; systematic review.

RÉSUMÉ

Objectif : évaluer les effets des programmes d'exercice sur l'amélioration des capacités physiques des patients atteints du syndrome de Guillain-Barré (SGB). **Méthode :** une recherche a été effectuée dans la base de données PubMed sur les articles publiés jusqu'en février 2015. Des essais contrôlés randomisés (ECR), des études de cas, des modèles quasi expérimentaux et des études individuelles publiés dans des revues anglophones révisées par les pairs qui évaluaient l'effet de l'exercice physique sur les patients atteints du SGB ont été inclus ; la qualité des études a été évaluée à l'aide de la règle des preuves de Sackett. Les données ont été présentées de manière qualitative et quantitative à l'aide de valeurs numériques et de pourcentages. **Résultats :** sept articles ont été inclus dans la revue systématique. Un ECR a montré que l'exercice à haute intensité par rapport à l'exercice à faible intensité réduisait de manière significative les incapacités des patients atteints du SGB, mesurées par la mesure d'indépendance fonctionnelle ($p < 0,005$, $r = 0,71$). Globalement, divers types de programmes d'exercice améliorent les capacités physiques, dont la mobilité fonctionnelle, la fonction cardiopulmonaire, la force musculaire isocinétique et le rythme de travail, et réduisent la fatigue chez les patients atteints du SGB. **Conclusion :** en raison du manque d'études de qualité, il n'est pas possible de tirer de conclusions définitives sur les effets des programmes d'exercice sur les capacités physiques des patients atteints du SGB. Des recherches futures se fondant sur des modèles d'études de qualité supérieure devraient être envisagées pour confirmer les résultats présentés dans cette revue.

Guillain-Barré syndrome (GBS) is an acute, inflammatory, post-infectious autoimmune polyneuropathy that causes demyelination of the peripheral and autonomic nerves and results in acute sensory and motor losses.^{1,2} The demyelination of peripheral nerve axons produces symmetrical motor paralysis, which progressively ascends from the lower extremities and causes tingling, burning sensations and areflexia.^{3–5} Altered soft-tissue length, muscle weakness, and sensory changes affect balance, posture, joint mobility, and gait.^{1,2,6,7}

Studies have shown that physical fitness can positively influence not only outcomes such as mobility and fatigue levels in GBS patients (GBSPs) but also mental functioning.⁸ Although some articles have noted beneficial effects of exercise on GBSPs, some have reported the contrary, stating that this population has had unfavourable responses to exercise.⁹ Accordingly, we sought to evaluate the available literature on the current exercise interventions used in the rehabilitation of GBSPs and to assess its usefulness in the maintenance of physical health in this population.

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METHODS

Systematic search strategy

Three authors (NSA, POV, RB) performed independent searches in PubMed (1951–present) and analyzed the reference lists in reviews of studies related to our topic of interest. Our search terms were *Guillain-Barré/GBS, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy/CIDP, acute inflammatory polyneuropathy, and acute idiopathic polyneuritis* combined with the results for *physical activity, exercise, rehabilitation, and physical therapy*. Our searches yielded one randomized controlled trial (RCT). The last electronic search was conducted on February 18, 2015.

Study selection and inclusion–exclusion criteria

Titles and abstracts obtained from the original search were reviewed independently by two authors (NSA, POV), who selected relevant articles for full-text analysis. These authors then read the full texts and included studies if (1) they were RCTs, single-subject studies, case reports, or quasi-experimental studies exploring GBS exercise intervention effects; (2) they were written in English; (3) they included only adult human subjects; (4) exercise was the main intervention studied; (5) the full text was available in print or electronic form; and (6) the outcomes of the exercise intervention were measured within 6 months of the onset of GBS or residual symptoms. Studies were excluded if they (1) included subjects with known adjunct diseases; (2) included multiple interventions and physical exercise was not the main intervention; (3) were written in a language other than English; (4) were older than 25 years and findings included knowledge from earlier articles; (5) were systematic reviews; (6) included animals or children; or (7) did not give explicit details about their exercise interventions. After reviewing the articles and applying the criteria independently, both reviewers met with a third reviewer (AS) to reach a final consensus.

Assessment of methodological quality

Assessment of methodological quality was completed using Sackett's rules of evidence, a modified version of the levels of evidence developed by the Centre for Evidence-Based Medicine (CEBM).¹⁰ The CEBM levels of evidence provide a classification of study designs, in which Level 1a indicates the highest quality design and Level 5 indicates the lowest quality design.¹¹ Two reviewers (RB, AS) independently extracted data from the studies. To minimize bias and errors, two reviewers (RB, AS) rated the levels of evidence independently, then met with a third reviewer (SZ) to discuss any discrepancy and reach consensus.

RESULTS

Articles retrieved

Our initial electronic search yielded 441 articles. We then included 88 abstracts using the reference lists of

the reviews found in that search. The resulting title and abstract review provided us with 84 relevant articles for full-text review. After we performed that review, we added 11 studies found in the reference lists of screened articles, yielding a total of 95 articles. After we implemented the inclusion and exclusion criteria, 7 articles remained. Figure 1 shows the steps in the search, along with the number of studies reviewed at each stage and the main reasons for their exclusion. We excluded 20 studies because they did not use an exercise protocol¹ and 13 articles because they provided an insufficient description of the exercise parameters. We removed 12 studies because they used a combination of interventions without clearly defining exercise as their main intervention. Eight literature reviews were withdrawn. Four excluded articles discussed the effects of exercise programmes on several diseases, without focusing on GBS. Three papers not translated into English were removed. We excluded 12 studies published before 1990 in favour of more recent papers that contained information from papers dating from before 1990 and implemented more current technologies and assessment tools. Eight papers without accessible electronic or printed full text were excluded. One study was excluded because children or animals were included, and 7 were excluded because they measured outcomes more than 6 months after intervention onset. Three researchers (RB, AS, SZ) analyzed the final 7 articles. Table 1 presents a summary of their study design, methods, and main results.

Interrater agreement in assessing levels of evidence was 100%. One single-subject design (Level 5),⁸ four case reports (Level 5),^{3,4,9,12} one quasi-experimental design (Level 5),² and one high-quality RCT (Level 1b) were reviewed.¹³ Overall, 133 patients were evaluated, 67 of whom were male. The subjects of five studies had median ages between 49 and 58 years.^{2,4,8,12,13} Two studies included severely fatigued patients,^{2,8} another included a 30-year-old former marathon runner,³ and one included chronic-phase patients.¹³ In general, the patients included in the review were all ambulatory; however, 1 subject showed residual difficulties in the ability to transfer, stand, and mobilize when the study began. That patient's score on a 10-metre walk test and timed up-and-go (TUG) test indicated some functional impairment.¹² See Table 2 (online) for an overview of the baseline levels of disability and the inclusion and exclusion criteria used by the studies included in our review.

Exercise protocol length varied between 1 and 25 weeks.^{2,4,8,9,13} See Table 3 (online) for a description of the exercise interventions used by the studies included in our review. Four studies that implemented cycling exercise showed significant improvements in the participants' respective outcomes,^{2,4,8,9} and three studies incorporating exercise programmes with physiotherapy treatments also showed improvements.^{3,12,13} Because of the heterogeneity of the study designs, each study is described individually.

Figure 1 Flow chart of the search process.

A single-subject design provided 12 weeks of bicycle training to 20 fatigued subjects and compared the relationships between physical fitness and domains of fatigue, mobility, and perceived physical or mental functioning.⁸ Cross-sectional data showed a strong relationship between physical fitness and perceived physical functioning (4/9; 44%; $p < 0.05$). Furthermore, baseline and post-intervention mean differences (MDs) indicated significant improvements in peak oxygen uptake (MD = 5.0 mL/kg/min, SD = 6.0 mL/kg/min); peak power output, measured in watts (MD = 38.6 W, SD = 28.5 W); and muscular fitness (MD = 7.2 W, SD = 7.9 W). Fatigue scores, rated using the Fatigue Severity Scale (FSS), decreased significantly from the baseline, showing fatigue reduction (MD = -1.0; 95% CI: -2.2, -0.3 (95% CI); $p < 0.05$).

A case report showed the effects of 7 days of exercise in a 10-month post-onset patient using the podiatron (described in Table 3 online).¹² The results showed improvements from baseline in walking confidence ($\geq 44\%$ using the VAS) and the surface area of the elevated left foot (63%) and right foot (92%). Furthermore, improvements were observed in the 10-metre walk (8%) and TUG (13%) tests, showing improvements in activity level and mobility. We concluded that the podiatron increased the subject's foot surface area, thereby acting as a support base.

A study with a quasi-experimental design examined the effects of bicycle training on functional outcomes in 20 patients.² The results showed that 12 weeks of training caused a 20% decrease in FSS scores in patients.

Table 1 Study Designs, Methods, and Main Results of Articles Reviewed

First author (design)	Sample population			Exercise			Outcome measures	Time	Main results
	LOE	Control	Intervention	Type	Characteristics	Control			
Bussman ⁸ (SS)	5	n/a	<i>n</i> = 20 F/M = 14/6 A = 49 y 16 GBS; 4 CIPD	Supervised cycle training session	D = 12 wk <i>F</i> = 3 × /wk	n/a	ICF: 1. Physical fitness (peak oxygen consumption, peak power output, muscular power) 2. Fatigue (FSS) 3. Actual mobility (activity monitor) 4. Perceived physical functioning (SF-36, FIS, RHS) 5. Perceived mental functioning	Baseline and post-training	2/30 significant physical fitness relationships (7%). Significant correlations between perceived mental functioning and actual mobility (4/9; 44%), between fatigue and perceived physical functioning (1/3; 33%), and between perceived mental functioning and perceived physical functioning. Physical fitness, FSS scores, and perceived physical functioning increased significantly.
Pitetti ⁴ (CR)	5	n/a	<i>n</i> = 1 F/M = 0/1 A = 57 y	GXT using SAE, BE, and ACE (5-min warm-up, 20 min at 75%–85% peak HR, 5 min cool-down)	D = 16 wk <i>F</i> = 3 × /wk 40 exercise sessions	n/a	ICF: Physical fitness (peak work levels, VO ₂ mL/min, mL/kg/min), ventilation, isokinetic leg strength (total work capacity)	Pre-training and post-training	Peak oxygen consumption increased with SAE (9%) and BE (11%); peak ventilation increased with SAE (23%), ACE (16%), and BE (11%). Total work capacity improved in BE (29%). For all three modes of exercise, sub-maximal HRs were reduced, and peak work level increased. Isokinetic leg strength in right leg saw improved peak torque (18%) and average power (24%), and the left leg also improved in peak torque (5%) and average power (13%).
Bulley ¹² (CR)	5	n/a	<i>n</i> = 1 F/M = 0/1 10 mo post-onset of severe GBS	Podiatron	D = 1 wk <i>F</i> = 10 min, 2 × /d	n/a	1. Body functions and structure level; measurement of activity level 2. General mobility 3. Confidence in walking	Baseline, post-training, and 6-wk follow-up	Surface areas of elevated left foot (63%) and elevated right foot (92%) improved as the feet were less elevated. Small improvements occurred in the 10-metre walk (8%) and TUG tests (13%). VAS (or confidence in walking) improved by more than 44%.
Garssen ² (QE)	5	<i>n</i> = 10 F/M = 6/4 A = 51	<i>n</i> = 20 F/M = 14/6 A = 49 y 16 GBS; 4 CIPD	Supervised and structured training sessions	D = 12 wk <i>F</i> = 3 × /wk	No exercise	1. Fatigue (FFS) 2. Cardiorespiratory fitness (cardiorespiratory cycle ergometer test) 3. Isokinetic muscle strength 4. Functional outcome of daily physical activity (RAM) 5. FIS (cognitive, physical, and social) 6. GBS disability score 7. HADS 8. RHS 9. QOL SF-36 10. VO ₂	Baseline, at 6 wk post-training; control group was only measured at baseline	Fatigue severity reduced by 20%. Isokinetic strength increased significantly at 12 wk. FIS decreased significantly at 6 and 12 wk. Physical domains of SF-36 improved significantly after 12 wk. HADS significantly improved at 12 wk. VO ₂ increased by 20% after 12 wk.

Table 1 Continued

First author (design)	Sample population			Exercise		Control	Outcome measures	Time	Main results
	LOE	Control	Intervention	Type	Characteristics				
Fisher ³ (CR)	5	n/a	n = 1 F/M = 0/1 A = 30 y	Progressive programme of functional exercise (including 1h/d of PT, OT, and group activities)	D = 3 wk F = 18 h/wk	n/a	1. Functional mobility (FIM) 2. Muscle performance (MMT)	Baseline (10 wk after onset of symptoms), post-training and follow-up at 19 wk after onset	Functional mobility improved significantly. Patient became independent doing all bed-mobility tasks. Muscle performance improved considerably. Strength gains continued after intervention, with improved MMT scores in all lower extremity muscle groups.
Khan ¹³ (RCT)	1b	n = 39 F/M = 15/24 A = 55.7	n = 40 F/M = 16/24 A = 54.9 y GBS duration: >1 y, ≤12 y	Individualized, high-intensity outpatient exercise, including strengthening, endurance training, gait training, and functional exercises	D = 12 wk F = 2–3 1-h sessions/wk Mean duration of treatment: 28 d	Lower intensity, home-based ambulatory exercise and a 30-min physical programme 2 × /wk (walking and stretching)	1. FIM with motor sub-scale 2. WHOQOL-BREF 3. DASS-21 and PIPP	Baseline at 12 mo and at 12 mo post-rehabilitation programme only for intervention group	Intervention significantly improved in FIM total score and in each motor sub-scale relative to control. Higher intensity rehabilitation compared with lower intensity rehabilitation reduced disability in later stages of recovery. Function improved more in the intervention group than in control. Intervention improved in domains of self-care and mobility compared with control. FIM splats showed a clinically relevant improvement in the intervention group for ability to transfer and walk.
Karper ⁹ (CR)	5	n/a	n = 1 F/M = 1/0 A = 23 y	Walking (20–37 min/session) Cycling (15–32 min/session)	D = 10 wk walking phase followed by 15 wk cycling phase F = 3 × /wk	n/a	1. Physical fitness (duration of exercise, distance walking, distance cycling, grip strength) 2. Pulmonary fitness (PEFR, FVC, FEV1)	Baseline, post-walking, and post-cycling	Walking time increased by 10 min (37%) and 1.25 km (88%) in distance. Cycling time increased by 17 min (over 100%). Body weight decreased by 1.35 kg, and PEFR was 0.7 L/s lower after walking and another 0.6 L/min lower after cycling. FEV1 increased by 0.2 L after walking, but increased by 0.1 L after cycling than before walking. FVC increased by 0.2 L after walking with no changes after cycling. Grip strength decreased after walking phase by 2.5 kg in the right hand and 1 kg in the left hand. Compared with pre-testing, grip strength improved after cycling by 0.5 kg in right hand and 2 kg in left hand.

LOE = level of evidence; SS = single subject; n/a = not applicable; M = male; F = female; A = median age; GBS = Guillain-Barré syndrome; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; D = duration; F = frequency; ICF = *International Classification of Functioning, Disability and Health*; FSS = Fatigue Severity Scale; SF-36 = 36-item Short Form Health Survey; FIS = Fatigue Impact Scale; RHS = Rotterdam Handicap Scale; CR = case report; GXT = graded exercise test; SAE = Schwinn Airdyne ergometer; BE = bicycle ergometer; ACE = arm cranked ergometer; HR = heart rate; VO₂ = maximal oxygen consumption; TUG = timed up-and-go; VAS = visual analogue scale; QE = quasi-experimental design; RAM = Rotterdam Activity Monitor; HADS = Hospital Anxiety and Depression Scale; QOL = quality of life; PT = physical therapy; OT = occupational therapy; MMT = manual muscle testing; RCT = randomized controlled trial; WHOQOL-BREF = World Health Organization Quality of Life abbreviated version of original instrument; DASS-21 = Depression, Anxiety and Stress Scale (21 items); PIPP = Perceived Impact of Problem Profile; PEFR = peak expiratory flow rate; FVC = forced vital capacity; FEV1 = forced expiratory volume (in 1 s).

Table 2 Summary of Inclusion and Exclusion Criteria for the Studies Reviewed and the Baseline Measures of Disability of the Patients with GBS Who Participated

First author (no. of subjects)	Inclusion criteria	Exclusion criteria	Baseline measures of disability
Bussman ⁸ (<i>n</i> = 16)	Severe fatigue, defined as mean FSS of at least 5.0/7.0 Neurologically stable, defined as no change in GBS disability score in 3 mo before baseline Onset of GBS/CIDP: >6 mo, <15 y earlier Age: ≥18 y GBS disability score: ≥3 (able to walk 3 m)	Severe fatigue before GBS/CIDP Concomitant conditions (e.g., CVD and diabetes) Use of medications (<4 wk before study began) that might cause or influence fatigue	MRC SS (range 0–60): 52–57, <i>n</i> = 2; 58–59, <i>n</i> = 4; 60, <i>n</i> = 14 GBS disability score (range 0–6): <i>F</i> = 0, <i>n</i> = 0; <i>F</i> = 1, <i>n</i> = 15; <i>F</i> = 2, <i>n</i> = 5 RHS (median value [25–75 percentile]): 3.56 (3.44–3.89) FSS (mean, range): 6.1 (5.8–6.4)
Pitetti ⁴ (<i>n</i> = 1)	Observations when study began: 3 y after onset Able to walk with one crutch Minimal weakness of hands and feet	n/a	Peak torque R/L knee flexion (ft/lb): 32/29 Peak torque R/L knee extension (ft/lb): 56/65
Bulley ¹² (<i>n</i> = 1)	Observations when study began: 10 mo after onset Decreased central mobility and stability Pelvis postured in anterior tilt Weakness Decreased sensation Decreased ankle ROM No visual evidence of ankle strategy for balance	n/a	10-metre walk test: 15.45 s TUG test: 25.405 s
Garssen ² (<i>n</i> = 20)	Severe fatigue, defined as mean FSS of at least 5.0/7.0 Neurologically stable, defined as no change in GBS disability score in 3 mo before baseline Onset of GBS/CIDP: >6 mo, <15 years earlier Age: ≥18 y GBS disability score: ≥3 (able to walk 3 m)	Severe fatigue before GBS/CIDP Concomitant conditions (e.g., CVD and diabetes) Use of medications (<4 wk before study began) that might cause or influence fatigue	MRC SS (score range 0–60): 52–57, <i>n</i> = 2 58–59, <i>n</i> = 4 60, <i>n</i> = 14 GBS disability score (range 0–6): <i>F</i> = 0, <i>n</i> = 0; <i>F</i> = 1, <i>n</i> = 15; <i>F</i> = 2, <i>n</i> = 5 RHS (median value [25–75 percentile]): 3.56 (3.44–3.89) FSS (mean, range): 6.1 (5.8–6.4)
Fisher ³ (<i>n</i> = 1)	Observations when study began: Above-average pre-existing level of fitness before onset of GBS Atypical presentation and course of GBS	n/a	FIM score: Total score, 80/126; Motor sub-score, 45/91 MMT score: upper limbs, 2–3+/5; lower limbs, 1–2+/5
Khan ¹³ (<i>n</i> = 40, treatment; <i>n</i> = 39, control)	Admitted to Royal Melbourne Hospital for acute care between 1996 and 2008, with WHO ICD code (G61.0) for GBS as primary diagnosis: Age: ≥18 y Definite GBS diagnosis Stable medical course Ability to participate in therapy	GBS diagnosis not confirmed Deceased or record destroyed Not contactable or had relocated Refused to participate in previous rehabilitation	FIM score (inter-quartile range): median score of treatment group, 86/126 (78, 90); median score of control group, 82/126 (78, 86)
Karper ⁹ (<i>n</i> = 1)	Observations when study began (self-reported): Handgrip weakness in both hands Ankle weakness in both ankles Balance problems Chronic fatigue Diagnosed with osteoporosis	n/a	PEFR: 4.5 L/s FVC: 2.5 L FEV: 2.1 L

GBS = Guillain-Barré syndrome; FSS = Fatigue Severity Score; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CVD = cardiovascular disease; MRC SS = Medical Research Council Strength Score; *F* = frequency; RHS = Rotterdam Handicap Scale; n/a = not applicable; R = right; L = left; ROM = range of motion; TUG = timed up-and-go; MMT = manual muscle testing; WHO ICD = World Health Organization *International Classification of Diseases*; PEFR = peak expiratory flow rate; FVC = forced vital capacity; FEV = forced expiratory volume.

Table 3 Exercise Interventions Used in the Studies Reviewed

First Author (date)	Exercise type	Description
Bussman (2007) ⁸	Cycle ergometer (cycle training)	Exercise consisted of 3 supervised cycle-training sessions/wk over 12 wk. Details of exercise protocol during sessions were not disclosed.
Pitetti (1993) ⁴	Graded exercise testing using SAE, BE, or ACE	For the SAE and BE tests, subjects began exercising at a workload of 25 W for 2 min. Workload was increased every 2 min until volitional exhaustion (defined as the work level at which a subject believed that he or she could no longer continue). For the ACE test, the subject began by arm cranking at 10 W for 2 min. Work rate was increased by 10 W every 2 min.
Bulley (2003) ¹²	Podiatron	The podiatron is a motorized, variable-pitch wobble board, with a control panel and handrails, designed to mobilize and strengthen the ankles, knees, hips, and back. It was used for 10 min in the morning and afternoon at an incline of 5° (Level 1). The incline was built up over the first 30 s to top speed, at which point the podiatron performs rotational exercises.
Garssen (2004) ²	Cycle ergometer	Participants performed three supervised training sessions/wk for 12 wk, consisting of 5 min of warm-up at an intensity of 65% of their maximal HR and lasting for 30 min. Over the 12 wk, training intensity was increased from 70% to 90% of maximal HR. The load was increased from 0 to 10 W or 20 W, depending on the patient's physical ability. All sessions finished with a 5- to 10-min cool-down.
Fisher (2008) ³	Physical therapy session	A progressive programme using functional exercises was used. Exercise progressed from passive ROM through gravity-eliminated AROM and antigravity AROM to resisted functional exercises. Exercises were performed for the upper extremity, lower extremity, and trunk and for 5–10 repetitions. Exercise was terminated before the patient reported fatigue. Sessions typically lasted 60 min.
Khan (2011) ¹³	Rehabilitation programme	Participants received an individualized, higher intensity outpatient rehabilitation programme for <12 wk. Sessions lasted 1 h and occurred 3 × /wk. PT was used for strengthening, endurance, and gait training, and OT was used to improve everyday functioning (i.e., domestic and community tasks).
Karper (1991) ⁹	Walking and cycling	Walking was performed for 10 wk, followed by 15 wk of cycling. Walking was performed 3 × /wk for 20–37 min; cycling was performed 3 × /wk for 15–32 min. The subject was not permitted to work above a workload of 45% of predicted maximal HR reserve. Walking was performed in an indoor hallway; the subject repeatedly walked the length of the hallway (36 lengths = 1.6 km). Cycling consisted of the subject riding an exercise bicycle, pedalling at 60 revolutions/min with no resistance. The subject rode at an average of 5-min intervals, with 2 min between rides.

SAE = Schwinn Airdyne ergometer; BE = bicycle ergometer; ACE = arm-crank ergometer; HR = heart rate; ROM = range of motion; AROM = active range of motion; PT = physical therapy; OT = occupational therapy.

Cardiopulmonary functions for maximal oxygen consumption (20%), maximum partial pressure of oxygen (29%), and maximal heart rate (6%) improved significantly from the baseline, as did isokinetic muscle strength in elbow flexion, elbow extension, and knee extension ($p < 0.05$). Researchers concluded that exercise was positively associated with improvements in disability scores, strength, and fatigue in GBSPs.

A case report observed the effects of aerobic exercise (10 wk of walking followed by 15 wk of cycling) on a 23-year-old woman.⁹ Baseline and post-intervention results showed increased walking time (10 min; 37%) and distance (1.25 km; 88%) while maintaining a faster forced cadence and eliminating rest intervals. Cycling time increased by 17 minutes. Furthermore, improved pulmonary function was observed, with decreased peak expiratory flow rate and increased forced vital capacity and forced expiratory volume. Researchers concluded that low-level aerobic exercise provided safe and positive clinical benefits for this GBSP.

Another case report observed the effects of a progressive functional exercise programme on functional mobility

and muscle performance in a male marathon runner.³ The subject underwent 1 hour/day of daily physiotherapy exercises, described in Table 3 (online). Total FIM score increased between the baseline and post-intervention (from 80/126 to 113/126), as did muscle performance sub-scores (from 45/91 to 78/91). Manual muscle testing showed improved scores, although the distal muscles remained more affected. Researchers observed the patient's post-intervention independent mobility and reported a positive influence of exercise on this GBSP's muscle performance.

One RCT assessed the differences between high- and low-intensity exercise programmes on FIM motor scores in 79 chronic-phase patients, including 31 women, and concluded that high-intensity rehabilitation reduces disability significantly more than low-intensity rehabilitation.¹³ Significantly greater increases in total FIM and motor sub-scale scores occurred in the intervention group compared with the controls; 80% of the treatment subjects achieved clinically meaningful improvements in FIM motor scores compared with 8% of the controls ($p < 0.001$). Compared with the controls, intervention

patients also showed more improvement in other FIM domains (mobility and transfers, sphincter control, and locomotion) and Perceived Impact of Problem Profile “relationship” scores. More controls (41%) than intervention patients (3%) reported function deterioration. Finally, the treatment patients significantly improved in self-care and mobility domains compared with the controls.

Last, one case report⁴ evaluated the effects of cycling (described in Table 3 online) on an acute-onset GBS with residual complications. Forty 20-minute exercise sessions at 75%–80% of peak heart rate occurred over 16 weeks. Two interventions, cycling (using the Schwinn Airdyne ergometer, or SAE) and bicycle ergometer (BE) testing, showed increases in peak aerobic fitness (9% and 11%, respectively) and peak ventilation (23% and 11%, respectively). Furthermore, total work capacity increased with BE testing (29%), and submaximal heart rate was reduced and peak work levels increased in all testing modes. Finally, both legs’ peak torque and average power improved from the baseline.

DISCUSSION

Overall, our analysis shows that exercise is linked to improved GBS physical outcomes. Only one study demonstrated non-direct associations between physical fitness and GBS progression.⁸ However, it showed significant and clinically meaningful post-intervention improvements relative to baseline physical fitness. That study also highlighted how exercise could improve both physical fitness and mental functioning, but selecting severely fatigued patients might have increased the potential for improved FSS scores and caused confounding bias.

The remaining articles showed that exercise positively influenced physical outcomes for subjects recovering from GBS. However, four studies involved single patients and therefore lacked representativeness.^{3,4,9,11,12} Most study subjects were older adults (aged >50 y), which may have systematically skewed our results.^{2,4,8,12,13}

A 12-week bicycle intervention with severely fatigued patients with GBS and CIDP showed a significant increase in physical and isokinetic muscle strength and reduced fatigue scores.² That study provided higher methodological quality, internal validity with variability measures, and sex- and age-matched controls.² However, those controls were not randomized and were measured only at baseline. Despite significant improvements on almost all measures after cycling training, the results for GBS subjects remained worse than those for healthy controls. Moreover, daily physical activity Rotterdam Activity Monitor measurements did not show significant increases in activity, suggesting that changing daily physical activity levels is not an important adaptation strategy in fatigued patients.

In the study that used the podiatron, the patient showed mobility and activity improvements after 1 week

of intervention. Nevertheless, the devised outcome measure of area under the elevated foot may prove invalid and create information bias by not reflecting the body-function domains necessary for our analysis.¹² Another limitation of this study was that it did not consider any significant or clinically meaningful changes of the intervention.

Similarly, another study showed that low-aerobic exercise with walking (10 wk) followed by cycling (15 wk) increased exercise capacity, pulmonary functions, and grip strength to enhance functional capacity.⁹ However, using consecutive interventions prevented independent assessment of cycling effectiveness with carry-over effects from walking, thereby creating confounding bias. In addition, having a single subject with chronic-relapsing GBS may have altered exercise outcomes compared with other patients, thereby creating selection bias.

In another study, progressive functional exercise rapidly improved muscle performance and FIM scores in a former marathon runner over the course of a 3-week intervention.³ However, the patient’s atypical disease progression and previous high exercise capacity limited generalization of the study’s results. Before the intervention, the patient was being treated with a combination of immunoglobulins, plasmapheresis, and corticosteroids, all of which affected patient scores. Also, a superimposed axonal injury may have altered functional prognosis and created confounding bias.

The only RCT included in our analysis had a high evidence level (1b) and should be given greater consideration. That study showed greater improvements in FIM motor sub-scale scores with high-intensity exercise compared with lower intensity exercise.¹³ Furthermore, the study suggested implementing a second rehabilitation therapy phase in later GBS stages to support reconditioning and improve patients’ function and participation.¹³ Although an exercise programme was the main intervention, some patients received adjunct treatments, possibly creating confounding bias. Moreover, although this study suggested using high-intensity exercise with GBSPs, other studies have shown that rapid increases in exercise intensity can result in strength reversals; consequently, exercise intensity should be closely monitored.¹⁴ Also, significant differences exist in post-onset years between the controls (8.8 y) and high-intensity patients (4.4 y), possibly creating confounding bias. Moreover, high variability in treatment duration (21–84 d) may hinder the assessment of appropriate treatment length.

Another single-subject design,⁴ an endurance stationary cycling exercise using the SAE, noted improved physiological adaptations in cardiopulmonary outcomes, physical work capacity, and leg strength. Peak oxygen consumption, ventilation, and work levels increased, showing improved patient fitness. We included that study in our analysis despite the fact that it had lasted longer than 6 months post-onset (3 y), and there may

be confounding effects from a remittance of symptoms. The indirectness of the measures, such as with volitional exhaustion, decreased the quality of the study.^{2,4,8}

It is worth repeating that exercise intensity should be closely monitored. Although patients usually recover from GBS with muscle re-innervation, it has been shown that overworking partially denervated muscles can cause further damage, including a loss of functioning motor units.¹⁴ Furthermore, having a decreased number of remaining motor units has been linked to central fatigue. Recent studies have indicated that central fatigue might be the cause of the chronic fatigue that patients experience many years after they recover from GBS.¹⁵ It is thus imperative to be cautious and avoid over-exercising diseased motor units in this population.^{3,16}

CONCLUSION

Overall, various types of exercise programmes improve physical outcomes such as functional mobility, cardio-pulmonary function, isokinetic muscle strength, and work rate and reduce fatigue in GBSPs, although the low quality of evidence of most studies decreases their external validity. Cycling training seems the most warranted type of program, although strengthening exercises and physiotherapy interventions, including physical activity, can also target physical outcomes.^{2,4,8,9} The frequency, intensity, and duration of exercise vary among studies, but programmes tend to last around 12 weeks and include 30–60 minutes of exercise intervention three times per week at 70%–90% of maximal heart rate. For optimal recovery, a two-phase rehabilitation process should take place—the first in the early stages of recovery to diminish the disability burden and the second in the later stages of the disease to support reconditioning.¹³ Because over-exercising GBSPs generates immediate and irreversible relapse, optimal treatment methods should quantitatively maximize therapy while minimizing the chance of fatigue.¹⁷

Preliminary research evaluating the effects of exercise in this population has shown negative outcomes when patients are pushed into a state of fatigue. Vigorous physical exercise, performed even after the disease has stabilized, has been shown to elicit a temporary loss of function.¹⁸ Furthermore, there is evidence that over-fatiguing the respiratory muscles during the initial period of motor unit recovery may induce respiratory failure.¹⁹

It is imperative that patients and nursing staff be alert for symptoms of fatigue to prevent a patient's rehabilitation from regressing and to promote long-term functional independence. Therefore, patients should be taught to recognize the symptoms of fatigue so that they can live independently without harm.¹⁸

This study has several limitations that should be kept in mind when interpreting the results. First, because there was little high-quality literature, only seven articles were included in the final review. Second, the hetero-

geneity of the study designs described in those articles made it difficult to compare the studies. In addition, although PubMed encompasses all Medline articles, we may have used too narrow a focus by searching for English-language articles in only the PubMed database, rather than including other databases such as Embase, PEDro, Synapse, and SPORTDiscus.

The absence of CIs, in conjunction with the heterogeneity of both the outcome measures and the exercise interventions of the studies, limited our ability to compare the effectiveness of the interventions. Of the seven articles that we reviewed, only two attempted to separate patients with chronic GBS from those with acute or recovering GBS,^{2,8} and both found similar results in those two categories. However, most studies had no standardized baseline assessment of GBS variety, thereby making the interpretations of treatment effectiveness difficult to compare.

The lack of randomization in non-RCT studies may prevent balancing confounders such as age and disease severity. Furthermore, most studies omitted assessor, trainer, and subject blinding, thereby weakening methodological quality. In addition, one article violated an exclusion criterion for using other treatments conjointly with exercise, which may have acted as a confounder.⁹ However, because of the detailed description of its intervention and outcome measures and the limited number of available articles, this article was retained.

The absence of control groups in most studies reduced internal validity and prevented them from determining whether temporal factors caused GBS symptoms to improve from spontaneous remittance. However, this limitation cannot be avoided because it is unethical to implement control groups with sub-optimal care in the initial stages of GBS.²⁰ Furthermore, poor descriptions of the intervention modalities used and their duration, frequency, and intensity may have led to information bias.^{8,13} Finally, finding articles about patients who showed symptoms for less than 6 months was not possible in the sparse literature; we therefore broadened our search to include patients who were more than 6 months post-onset or with relapse.^{2,9,13} Even using this modified inclusion criterion, the sample size for analysis was limited and, in conjunction with the heterogeneous study designs of the articles included in the review, limited the validity of our findings.

Gaps and directions for further research

To build on our findings, higher quality studies with high levels of evidence, such as RCTs and clinical controlled trials, are required. Standardized, valid, reliable, and sensitive rehabilitation outcome measures should be established to determine effectiveness and facilitate comparisons among studies. Because patients show marked clinical heterogeneity, it may be necessary to use standardised tools to assess GBS severity at baseline

and prevent confounding bias. Providing clinically meaningful change values or effect sizes for outcome measures is also warranted to help clinicians better understand the magnitude of intervention effects. Indeed, studies have yet to establish the optimal modalities for treating GBSPs, and a multidisciplinary team may be required to improve future outcomes.¹

KEY MESSAGES

What is already known on this topic

Exercise is prescribed to patients with Guillain-Barré syndrome (GBSPs) to improve their health outcomes.

What this study adds

This systematic review aimed to examine recent research on the effects of exercise on GBSPs. Although studies published on this topic are sparse, the present evidence suggests that physical exercise shows a positive association with improved health outcomes in this population and that cycling appears to be the most effective type of exercise. However, the literature is not without gaps, and this area requires more studies with higher methodological quality to increase the validity of our findings.

REFERENCES

- Albiol-Pérez S, Forcano-García M, Muñoz-Tomás MT, et al. A novel virtual motor rehabilitation system for Guillain-Barré syndrome: two single case studies. *Methods Inf Med*. 2015;54(2):127–34. <http://dx.doi.org/10.3414/ME14-02-0002>. Medline:25609504
- Garssen MP, Bussmann JB, Schmitz PI, et al. Physical training and fatigue, fitness, and quality of life in Guillain-Barré syndrome and CIDP. *Neurology*. 2004;63(12):2393–5. <http://dx.doi.org/10.1212/01.WNL.0000148589.87107.9C>. Medline:15623709
- Fisher TB, Stevens JE. Rehabilitation of a marathon runner with Guillain-Barré syndrome. *J Neurol Phys Ther*. 2008;32(4):203–9. <http://dx.doi.org/10.1097/NPT.0b013e31818e0882>. Medline:19265762
- Pitetti KH, Barrett PJ, Abbas D. Endurance exercise training in Guillain-Barre syndrome. *Arch Phys Med Rehabil*. 1993;74(7):761–5. [http://dx.doi.org/10.1016/0003-9993\(93\)90039-D](http://dx.doi.org/10.1016/0003-9993(93)90039-D). Medline:8328900
- Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*. 1989;95(2 Suppl):2S–4S. http://dx.doi.org/10.1378/chest.95.2_Supplement.2S. Medline:2914516
- El Mhandi L, Calmels P, Camdessanché JP, et al. Muscle strength recovery in treated Guillain-Barré syndrome: a prospective study for the first 18 months after onset. *Am J Phys Med Rehabil*. 2007;86(9):716–24. <http://dx.doi.org/10.1097/PHM.0b013e31813e0b67>. Medline:17709995
- Ydemann M, Eddelien HS, Lauritsen AO. Treatment of critical illness polyneuropathy and/or myopathy—a systematic review. *Dan Med J*. 2012;59(10):A4511. Medline:23158890
- Bussmann JB, Garssen MP, van Doorn PA, et al. Analysing the favourable effects of physical exercise: relationships between physical fitness, fatigue and functioning in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. *J Rehabil Med*. 2007;39(2):121–5. <http://dx.doi.org/10.2340/16501977-0007>. Medline:17351693
- Karper WB. Effects of low-intensity aerobic exercise on one subject with chronic-relapsing Guillain-Barré syndrome. *Rehabil Nurs*. 1991;16(2):96–8. <http://dx.doi.org/10.1002/j.2048-7940.1991.tb01189.x>. Medline:2000470
- Phillips B, Ball C, Sackett D, et al. (2009). Oxford Centre for Evidence-based Medicine—levels of evidence. Oxford, UK: Centre for Evidence-Based Medicine; 2016 [cited 2016 Feb 18]. Available from: <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>.
- Soryal I, Sinclair E, Hornby J, et al. Impaired joint mobility in Guillain-Barré syndrome: a primary or a secondary phenomenon? *J Neurol Neurosurg Psychiatry*. 1992;55(11):1014–7.
- Bulley P. The podiatron: an adjunct to physiotherapy treatment for Guillain-Barré syndrome? *Physiother Res Int*. 2003;8(4):210–5. <http://dx.doi.org/10.1002/pri.291>. Medline:14730725
- Khan F, Pallant JF, Amatya B, et al. Outcomes of high- and low-intensity rehabilitation programme for persons in chronic phase after Guillain-Barré syndrome: a randomized controlled trial. *J Rehabil Med*. 2011;43(7):638–46. <http://dx.doi.org/10.2340/16501977-0826>. Medline:21667009
- Herbison GJ, Jaweed MM, Ditunno JF Jr. Exercise therapies in peripheral neuropathies. *Arch Phys Med Rehabil*. 1983;64(5):201–5. Medline:6303270
- Garssen MP, Schillings ML, Van Doorn PA, et al. Contribution of central and peripheral factors to residual fatigue in Guillain-Barré syndrome. *Muscle Nerve*. 2007;36(1):93–9. <http://dx.doi.org/10.1002/mus.20739>. Medline:17238173
- Drory VE, Bronipolsky T, Bluvshstein V, et al. Occurrence of fatigue over 20 years after recovery from Guillain-Barré syndrome. *J Neurol Sci*. 2012;316(1–2):72–5. <http://dx.doi.org/10.1016/j.jns.2012.01.024>. Medline:22336700
- Cohen BA, Crouch RH, Thompson SN. Electromyographic biofeedback as a physical therapeutic adjunct in Guillain-Barré syndrome. *Arch Phys Med Rehabil*. 1977;58(12):582–4. Medline:597026
- Bensman A. Strenuous exercise may impair muscle function in Guillain-Barré patients. *JAMA*. 1970;214(3):468–9.
- Meythaler JM, DeVivo MJ, Braswell WC. Rehabilitation outcomes of patients who have developed Guillain-Barré syndrome. *Am J Phys Med Rehabil*. 1997;76(5):411–9. <http://dx.doi.org/10.1097/00002060-199709000-00012>. Medline:9354496
- Demir SO, Köseoğlu F. Factors associated with health-related quality of life in patients with severe Guillain-Barré syndrome. *Disabil Rehabil*. 2008;30(8):593–9. <http://dx.doi.org/10.1080/09638280701352626>. Medline:17852306