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## Use of Biomedical Engineering for Rehabilitation of Patients with Disability Caused by Guillain-Barré Syndrome: a Systematic Review

### Uso de la Ingeniería Biomédica para Rehabilitación de Pacientes con Discapacidad Causada por el Síndrome de Guillain-Barré: Una Revisión Sistemática

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#### ABSTRACT

This systematic review aims to assess the extent to which biomedical engineering has been applied in the rehabilitation of patients suffering from Guillain-Barré Syndrome (GBS), given the scarcity of information on this topic. We conducted a thorough analysis of research articles, conference abstracts, and case reports published between 2000 and 2023, specifically from ScienceDirect, PubMed, IEEE Xplore, Springer, and Dimensions. 19 articles were extensively discussed, complemented by an additional 40 information sources providing supplementary information. Each paper underwent a meticulous review process by the four authors, where each separately examined the title and abstract of the papers and subsequently provided a thorough examination of the full text; when conflicts arose, a clear consensus was reached through discussion. The analysis of the articles revealed a notable improvement in upper and lower limb function of GBS patients that was facilitated by both custom-made and commercial devices. Likewise, a small handful of other devices have been used (e.g., to improve urinary retention issues). There is a clear opportunity for new research, innovation and applications.

**KEYWORDS:** Biomedical engineering, Guillain-Barré Syndrome, neurorehabilitation, rehabilitation device

## RESUMEN

Esta revisión sistemática tiene como objetivo evaluar hasta qué punto se ha aplicado la ingeniería biomédica en la rehabilitación de pacientes que padecen el Síndrome de Guillain-Barré (SGB), dada la escasez de información sobre este tema. Realizamos un análisis exhaustivo de artículos de investigación, resúmenes de conferencias e informes de casos publicados entre 2000 y 2023, específicamente de ScienceDirect, PubMed, IEEE Xplore, Springer y Dimensions. Se discutieron ampliamente 19 artículos, complementados con 40 fuentes de información adicionales. Cada artículo pasó por un meticuloso proceso de revisión por parte de los cuatro autores, donde cada uno examinó por separado el título y el resumen de los artículos y posteriormente proporcionó un examen exhaustivo del texto completo; cuando surgieron conflictos, se alcanzó un consenso mediante la discusión. El análisis de los artículos reveló una mejora notable en la función de las extremidades superiores e inferiores de los pacientes con SGB que fue facilitada por dispositivos tanto hechos a medida como comerciales. Asimismo, se han creado un pequeño puñado de otros dispositivos, (por ejemplo, para mejorar los problemas de retención urinaria). Existe una clara oportunidad para nueva investigación, innovación y aplicaciones.

**PALABRAS CLAVE:** dispositivo de rehabilitación, Ingeniería Biomédica, Síndrome de Guillain-Barré, neurorrehabilitación

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## INTRODUCTION

### Rationale

Guillain-Barré Syndrome (GBS) is a prevalent cause of acute flaccid paralysis, distinguished by symmetrical weakness of the limbs, and hyporeflexia or areflexia <sup>[1]</sup> <sup>[2]</sup><sup>[3]</sup><sup>[4]</sup>. Reports of GBS date back to the second half of the 19th century, and it has been formally investigated since 1916 <sup>[3]</sup>. Infection or other immune-related stimulation that causes an atypical autoimmune response that targets peripheral nerves and their spinal roots is often what precedes it <sup>[2]</sup><sup>[5]</sup>; more than 90 % of patients reach the peak of the disease severity between 2 and 4 weeks since the sickness debuts <sup>[6]</sup>. There are multiple clinically distinguishable subtypes of GBS: Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the most common; Miller-Fisher Syndrome (MFS); Acute motor axonal neuropathy (AMAN); Acute motor sensory axonal neuropathy (AMSAN); Bickerstaff's Encephalitis (EB); and Pharyngeal-cervical-brachial weakness <sup>[1]</sup><sup>[6]</sup><sup>[7]</sup><sup>[8]</sup>.

The symptoms of GBS vary depending on the subtype. Taking AIDP, for example, the aberrant immune response consists mainly in the degradation of the patient's myelin <sup>[9]</sup>, this reports in paresthesia in feet and fingertips followed by symmetrical or slightly asymmetrical weakness in lower limbs that can ascend to the upper limbs in a matter of hours or days, and even affect the respiratory system muscles in severe cases <sup>[1]</sup><sup>[6]</sup><sup>[10]</sup><sup>[11]</sup>.

GBS treatment generally combines multidisciplinary supportive medical care and immunotherapy. Recognized as the most effective treatments: Intravenous Immunoglobulin (IVIg) and plasma exchange are the most common and have proven to be very effective, especially if they are started within the first 2 weeks of the disease's debut <sup>[3]</sup><sup>[12]</sup>. Although the majority of cases report a complete or partial recovery of the patients, with very few resulting in death, many of the affected individuals obtain a residual deficit that

impacts their living conditions. For instance, 20 % of GBS patients still require assistance walking six months after their sickness first manifested. Reduced muscular strength, sensory indications, weariness, and discomfort are the most typical remaining deficiencies <sup>[1]</sup><sup>[13]</sup><sup>[14]</sup>.

Currently, the GBS rehabilitation process is based primarily in a multidisciplinary set of interventions, conducted mainly by neurologists and rehabilitation physicians. The main goal is to give the patient back a partial or complete autonomy and the ability to carry out normal life activities. According to the requirements of the particular patient, this may also include nursing care, nutritionist guidance, psychotherapy, speech therapy, and social rehabilitation in addition to physical or occupational therapy and exercise regimens. One of the main problems is that since multidisciplinary rehabilitation varies markedly between regions, it is challenging to design research trials to properly assess the effectiveness of the rehabilitation <sup>[10]</sup><sup>[11]</sup>.

Another common rehabilitation approach for GBS is exercise <sup>[15]</sup>. For example, in a Dutch study, 20 GBS patients who complaint mainly of fatigue had an intervention consisting of three 45-minute sessions weekly for 12 weeks, the target was to increase heart rate from 65 % to 90 % of maximal heart rate, and during that period the workload was gradually increased. As a consequence, there was less fatigue, more isokinetic muscular strength, and a higher peak oxygen uptake <sup>[10]</sup><sup>[15]</sup><sup>[16]</sup>.

Neuromuscular electrical stimulation has been a remarkable ally in GBS rehabilitation as well, especially for patients with a delicate state of health or an acute paralysis <sup>[10]</sup>. Without the patient's involvement, muscle contractions can be induced via neuromuscular electrical stimulation (NMES). In the acute stage of GBS, until patients have adequately recuperated to start a multidisciplinary rehabilitation effort, this may be an alternate treatment approach that can minimize inactivation and denervation waste <sup>[10]</sup><sup>[17]</sup>.

Besides these approaches for GBS rehabilitation, there are some cases where biomedical engineering is applied in neurorehabilitation for this disease, however, these cases not only are scarce compared to the use of traditional rehabilitation but they are also little studied, hence the need for a systematic review for the analysis of the current state of the art.

### Objective

This systematic review targets to respond the question “How has biomedical engineering been used for the rehabilitation of patients with disability caused by Guillain-Barré?” and to provide a broad perspective on the knowledge that is presently available on the subject. It seeks to give a solid platform for decision-makers, therapists and future investigations for the development of better neurorehabilitation methods based on biomedical engineering in GBS.

## MATERIALS AND METHODS

### Review design and search strategy

This systematic review was developed in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement guidelines<sup>[18]</sup>, over three months: from April to June of 2023. Five databases were used in total: ScienceDirect, PubMed, IEEE Xplore, Springer and Dimensions. The guiding question for the review design and execution was: “How biomedical engineering has been used for the rehabilitation of patients with disability caused by Guillain-Barré?”.

The investigation was performed using a search equation combining Boolean operators and focused on three key terms, and was stated as follows: ("Guillain Barré" OR "Acute inflammatory demyelinating polyradiculoneuropathy" OR "Miller-Fisher Syndrome" OR "Acute motor sensory axonal neuropathy" OR "Acute motor axonal neuropathy") AND (rehabilitation OR recovery) AND ("biomedical engineering" OR "electronic device" OR "haptic device" OR “neuromodula-

tion” OR “virtual environment” OR “telemedicine” OR “artificial intelligence” OR “internet of things” OR “wearable device” OR “robot” OR “biomedical transducer”). The key terms related to biomedical engineering were selected by using the IEEE Taxonomy.

The overall procedure for recognizing relevant articles was: (I) literature search in designated databases applying eligibility criteria; (II) export of results in reference files and import to specialized software for literature reviews (Rayyan); (III) removal of duplicates; (IV) selection of articles by title and abstract; (V) selection of articles by full-text analysis; (VI) detection of any additional relevant papers using the snowball technique.

This academic work is exempt from Institutional Review Board clearance because it is a systematic review.

### Eligibility Criteria

#### Inclusion criteria:

- Research articles, conference abstracts and case reports released in full text between 2000 and 2023 in English.
- Articles published in peer-reviewed journals.
- Articles about rehabilitation of patients with disability caused by Guillain-Barré Syndrome using biomedical engineering.

#### Exclusion criteria:

- Review articles, mini-reviews, systematic reviews, books, editorials, encyclopedia, discussions and correspondence.

### Selection

After the database search, each article was subject to a manual filtration process by analyzing the title and abstract, followed by a full-text selection. Every article was scrutinized independently by the four authors, and when conflict arose, consensus was achieved through discussion.

The selection of papers, in both processes, was conducted considering the eligibility criteria and the focus of the research question.

### Data extraction

Data were obtained from eligible papers using a standardized format based on the PRISMA guidelines where a variety of key summarizing points of information were collected; this was carried out by the three reviewers. The variables determined useful to extract from each article were: Author(s), publication date, country (or region where the research was conducted), objective, patients, brief description of the biomedical engineering device, methodology, results and conclusions. The result of this extraction is exposed in Table 1.

### Quality assessment of the included articles

To assess the quality of the articles it was used the “Checklist for assessing the quality of quantitative studies” of the “Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields”, developed by Kmet, Lee and Cook in collaboration with the Alberta Heritage Foundation for Medical Research <sup>[19]</sup>. This checklist consists of 14 items stated as follows: I1: Question/objective sufficiently described. I2: Study design evident and appropriate. I3: Method of subject/comparison group selection or source of information/input variables described and appropriate. I4: Subject (and comparison group, if applicable) characteristics sufficiently described. I5: If interventional and random allocation was possible, was it described? I6: If interventional and blinding of investigators was possible, was it reported? I7: If interventional and blinding of subjects was possible, was it reported? I8: Outcome and (if applicable) exposure measure(s) well defined and robust to measurement/misclassification bias. Means of assessment reported. I9: Sample size appropriate. I10: Analytic methods described/justified and appropriate. I11: Some estimate of variance is reported for the main results. I12: Controlled for confounding. I13: Results reported in sufficient detail. I14: Conclusions supported by the

results. This checklist consists of 14 items. All the papers with 80% or more of positive results were included.

## RESULTS AND DISCUSSION

### Search results

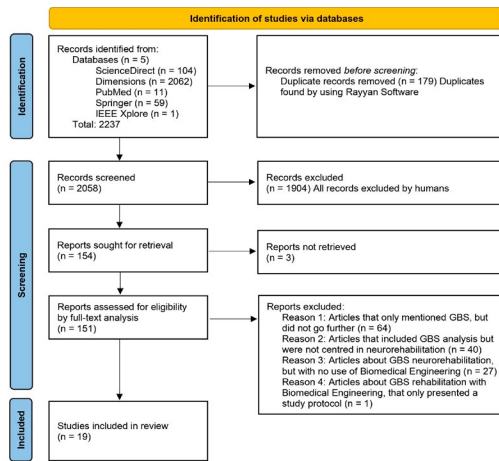
The database search using the Boolean equation yielded a total of 24,691 papers, with most articles found in Dimensions (23,818). However, after applying filtration based on the inclusion and exclusion criteria, only 2,237 remained. Of this total, 179 were duplicates, and the rest underwent analysis based on title and abstract, resulting in 154 papers. The next step involved a thorough examination of the full text of these articles to determine their usefulness for the review. Additionally, the snowball technique was employed by reviewing the references. Following this process, 19 articles were selected for inclusion in the systematic review. These selected articles were used to summarize the information using the pre-defined focus variables (refer to Table 1). The PRISMA flow diagram in Figure 1 illustrates the selection steps and results, providing reasons for excluding 135 out of the 154 articles.

### Quality and Reliability of Results

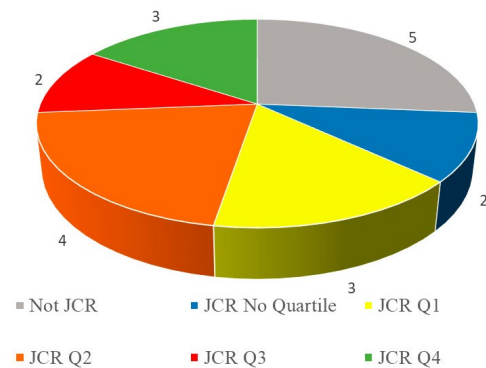
The included studies' quality was analyzed using the Checklist for assessing the quality of quantitative studies and the conclusions are reflected in Table 2. Figure 2 exhibits how many of the 19 articles are JCR and the number of articles that correspond to Quartile 1, 2, 3 or 4.

### Summarized results obtained from the articles

The analyzed 19 studies have been described in Table 1 reporting the chosen variables: Author(s), publication date, country (or region where the research was conducted), objective, patients, a brief description of the biomedical engineering device, methodology, results, and conclusions.



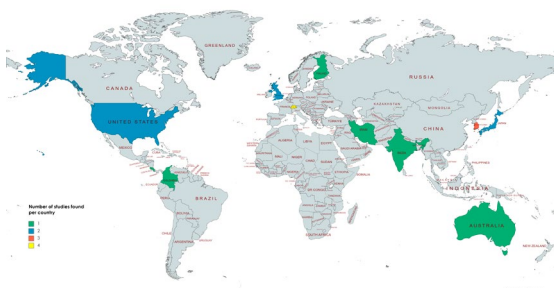
**FIGURE 1. PRISMA flow diagram for the steps followed to obtain the selection of eligible papers [18].**  
**JCR Articles**



**FIGURE 2. Pie chart of the JCR quartiles the journals of the presented articles belong to.**

**Global distribution of the studies**

The presented studies took place in 11 countries (Figure 3), although, in many cases, researchers of the same study came from different Universities, regions and even from different countries. The place where more studies were conducted was Zürich, Switzerland, with a total of 4.



**FIGURE 3. Map of the countries where the studies took place.**

**Discussion**

The need to organize information on GBS and its treatments is necessary for progress and future advances. This systematic review started with the of how biomedical engineering has been utilized towards the rehabilitation of patients with Guillain-Barré and the path to answer it start with a search equation divided into three parts: 1.- The disease and its most common subtypes (GBS), 2.- the key objective in relation to this disease (to rehabilitate) and 3.- the instruments to achieve it via biomedical technologies. A minor detail worth mentioning is that one of the used databases, Science Direct, has a limit of Boolean operators, but by repeating the search while rotating the terms the same result was achieved as if it did not have this restriction. It is plausible to criticize this search equation for being slightly general, however, the researchers have determined that there is not enough information about this topic, thus warranting a reasonably general search equation that translates into more results and meticulous screening.

Regarding search results, it is interesting how few eligible studies were obtained, despite the 22-year span that was examined. This could indicate, contextualized within this systematic review, a lack of development of this field and, therefore, a significant area of future study.

Concerning the reliability of the obtained articles, 14 of the journals are included in the Journal Citation Reports [39], half of them in quartiles 1 and 2, which is a recognized standard for research quality. This indicates that the articles probably contain reliable information, but it does not mean they are not subject to possible bias. The use of the Checklist developed by Kmet, Lee and Cook also revealed the excellent quality of the articles.

Only 5 articles provided complete information on the sex, age, height and weight of the patients [20][21][22][23][24].

Considering articles that provided data on the sex of the GBS patients, there were in total 13 male [20][21][22][23][24][25][26][27][28][29][30] and 2 female patients [31][33] examined throughout these investigations. Analyzing the articles that provided data about patient's ages, the age ranged from 7 to 86 years old, with the mean being 39.5 years.

The main area targeted by the studies was the lower limbs, eleven studies [20][21][22][23][24][26][27][28][30][33][34] worked with biomedical devices that helped patients' rehabilitation in this area. Six studies focused on the upper limbs [25][29][32][35][36][37]. Céspedes *et al.* [38] worked on a Socially Assistive Robot using a NAO platform, and even though the subjects were focused on lower-limb rehabilitation, the purpose of the platform is to be an assistant therapist that makes observations and gives feedback to the patient. Wosnitzer *et al.* [31] used neuro-modulation to attend urinary retention aiming the study at the sacral nerves. The area that more studies targeted was the lower limbs, which is consistent with the data that the most common disability amongst GBS patients is weakness or partial or complete paralysis in legs [5][7]. Most studies only included male GBS patients, solely two women were mentioned as subjects. This observation aligns with the fact that, unlike other autoimmune diseases, GBS is significantly more frequent in men than in women [11][40].

Of the 19 studies, 12 took place in countries that, according to the United Nations' "World Economic Situation and Prospects 2022" [41] are developed economies: Switzerland, Japan, United States of America (USA), Australia, Finland and United Kingdom (UK), the first one being the one where more investigations were conducted: four. The remaining 7 took place in countries with developing economies, all of which hosted one study, except for South Korea, where 3 took place. A possible connection between the number of studies for each continent and the density of incidences of GBS cases could be theorized, nonetheless, the data does not reveal one: The continents with more studies were Asia and Europe, each with 7, however,

the statistics show that in these regions the range of incidences per 100,000 habitants is 0.44-3.25 and 0.84-1.91, respectively. In South America, where only 2 researches were found, the range is 5.6-7.63 per 100,000 habitants [41]. Probably the real reason behind the differences in the number of studies are population and economic development: In Asia lives more than half of the planet's population [42], Japan is one of the world's leading economies and India, South Korea and Iran are thriving developing economies [41] that excel in technology and science; Europe's population is almost twice of that of South America [42], and Finland, UK and Switzerland are three formidable developed economies with high per capita income [41].

The variety excels in the presented studies in terms of the biomedical engineering devices utilized. Ten of the devices were custom-made systems, tested in the same article [20][21][22][24][25][29][32][35][36][37]. The other seven devices were acquired commercially [23][26][27][28][30][31][33][34][38]. Two of these devices were used in different studies: Morning Walk was the protagonist in two papers [33][34], and Lokomat was the main device in two studies as well [26][28]. However, it was also employed to test the NAO platform as a therapy assistance robot in a third study [38].

There were a total of four devices based on haptics and virtual reality, with one focusing on lower limb rehabilitation [20] and the other three concentrating on upper limb rehabilitation [29][32][36]. All of them paid close attention to the issue of patient motivation during therapy, particularly the PITS [29], which centered on pediatric rehabilitation. The developers applied principles of serious game development, as the main objective and the entire experience are designed to aid in rehabilitation while still maintaining motivation through an enjoyable gaming experience. The positive results obtained in the studies demonstrate the usefulness of specific-purpose video games in rehabilitation, a concept supported by research such as the one conducted by Ong *et al.* [43].

TABLE 1. Analyzed articles summarized. Note: Height is expressed in centimeters and weight in kilograms.

Reference	Author(s) and year	Goal	Patient(s)	Brief description of the biomedical engineering system	Methodology	Results	Conclusions
[20]	Albiol-Pérez S., Forcano-García M., Muñoz-Tomás M., Manzano-Fernández P., Solsona-Hernández S., Mashat M. A., Gil-Gómez J. A. 2014.	Try out a virtual motor rehabilitation program to boost patient compliance and enhance therapeutic outcomes.	<b>Patient one:</b> Male, (Subtype) MFS, (Age) 54, (Height) 174.9, (Weight) 75.5, (Time since hospitalization) 5 months. <b>Patient two:</b> Male, (Age) 33, (Height) 168.8, (Weight) 94, (Time since hospitalization) 4 months.	<b>Active Balance Rehabilitation (ABAR):</b> Various virtual settings emphasizing weight transference and specific motions. It includes two difficulty levels and six interactive games. The budget-friendly hardware comprises a 47-inch TV, a PC, a WBB, and a Bluetooth dongle.	Twenty sessions, thrice weekly: 30 minutes for conventional rehab, 30 minutes for VMR (Virtual Motor Rehabilitation) with ABAR. Static balance work involves lateral and forward-backward weight shifts. Dynamic balance work includes single-leg stance and sit-to-stand movements. Patients began with cognitive and functional tests, along with static and dynamic balance assessments; these tests were repeated at the final and follow-up stages.	<b>Patient one</b> demonstrates autonomous ambulation under therapist supervision, ascending and descending stairs, and traversing slopes, with notable enhancements in shoulder muscle mass and joint range. Persistent upper limb motor coordination disorders are observed. <b>Patient two</b> attains independent ambulation, negotiating stairs and slopes, displaying augmented muscle strength in the left ankle. Despite progress, persistent hypoesthesia is noted in fingertips, foot soles, and heels.	VMR presents a groundbreaking contribution to GBS patient rehabilitation, demonstrating suitability and effectiveness. However, a notable limitation is the diminished sample size. Clinical experts advocate the exploration of additional modules to augment the dynamic recovery process.
[21]	Fang Y., Lerner Z.. 2021.	(1) To compare the influence of bilateral ankle exoskeleton support with assistance limited to the paretic limb on walking performance. (2) To validate the effectiveness of a real-time ankle-moment-adaptive exoskeleton control system for assisting hemiparetic gait.	* (1 GBS out of 3 subjects) GBS patient: Male, (Age) 65, (Weight) 93.5, (Height) 173, (Time since injury) 5 years. Disability scale: 2. Primarily unilateral gait deficit due to hemiparesis.	An unattached ankle exoskeleton weighing 2.6 kg, powered by a 2 Ah Li-ion battery. It delivers plantar and dorsiflexor ankle support through brushless DC motors (Maxon) situated in a waist assembly, utilizing Bowden cable transmission. The system incorporates a custom PCB housing motor driver, a microcontroller, signal processing components, and a Bluetooth transceiver.	Each session comprises initial acclimatization and a rest period exceeding 20 minutes. Formal data collection involves three 6-minute randomized walking scenarios: baseline walking with shoes lacking the mechanism, walking with exoskeleton support limited to the paretic limb, and bilateral walking with the device supporting both sides. Participants subsequently undergo 6-minute walk test trials in each circumstance within a 25-meter corridor.	GBS patients exhibited a preference for exoskeletal assistance limited to the paretic limb on the treadmill, with no discernible preference on solid ground. The adaptive system demonstrated efficacy in facilitating walking. In enhancing clinically pertinent treadmill and over-ground walking performance, bilateral support frequently exhibited greater reliability than unilateral assistance.	Three individuals exhibiting hemiparetic gait underwent validation of the ankle-moment-adaptive exoskeleton controller. The results underscored the safety and efficacy of both bilateral and paretic-limb-only support in enhancing overall ankle function, overground walking speed, and treadmill performance.
[25]	Lee K., Park J., Beom J., Park H. 2018	To create and assess a passive shoulder joint tracking system that accounts for gravity and enables three-DOF shoulder joint movement.	* (1 GBS out of 19 subjects, 8 healthy) One male GBS patient.	<b>Shoulder Joint Tracker:</b> Primarily comprises a horizontal tracker featuring a two-link mechanism and a vertically oriented tracker supported by a compressive spring composed of interconnected small spring segments.	The tracker underwent evaluation through two key shoulder movements—flexion/extension and abduction/adduction—via a three-DOF motion capture experiment utilizing the J-Wrex and CPM rehabilitation systems. The experiments were conducted in three setups: unrestricted motion without any device, motion aided by the device alongside the tracker, and motion assisted solely by the existing device.	The tracker exhibited high efficacy in tracking arm movements. Analysis of the Glenohumeral (GH) joint's Range of Motion (ROM) focused on determining the arm elevation ROM common to all three conditions. The range of motion in the inferior-superior direction was more extensive in both healthy individuals and patients compared to the transversal direction. Although the ROM in the absence of the tracker was generally minimal, it was nearly identical for both the unrestricted and tracker-assisted conditions.	GH joint tracking performance was experimentally validated. The tracking module, by achieving increased range of motion with reduced power consumption for the same rehabilitation tasks, has the potential to enhance the comfort and efficacy of shoulder rehabilitation.
[35]	Kauhanen L., Jylänki P., Lehtonen J., Rantanen P., Alaranta H., Sams M. 2007.	Developing a Brain-Computer Interface (BCI) enabling tetraplegic individuals to operate it within a brief thirty-minute timeframe.	* (1 GBS out of 6 subjects) Subject S2: (Age) 59, (Time since injury) 1.5 years	<b>TKK-BCI system:</b> The client obtained EEG signals via TCP/IP, with the server collecting them in 20-ms data packets. Upon accumulating sufficient packets for feature extraction, MATLAB was employed for analysis. Post-categorization of the data, the client received the results and provided user feedback.	Subjects used EEG signals to guide a circle from the screen center to specific locations on each side by performing rapid movements with their right or left hands. Movements included fist closure, finger raising, and pinching. Participants were instructed to choose a specific movement and maintain it throughout the trial (S2 chose fist closure).	S2 was able to perform 10 correct games vs 1 mistake. The other subjects had a ratio correct/incorrect of: 15/0, 8/1, 3/0, 1/2, 9/5.	Participant S2 successfully acquired the ability to use a BCI during a series of five to seven training sessions, each lasting four minutes.



[33]	Choi S., Kim S. W., Jeon H. R., Lee J. S., Kim D. Y. 2019.	To evaluate the viability and effectiveness of utilizing Robot-Assisted Gait Training (RAGT)	* (7 GBS out of 189 subjects) 7 GBS patients (Ages) Between 31.6 and 71.6 years,	<b>Morning Walk®:</b> is an end-effector robot featuring a saddle seat for body support. Its autonomous end-effector footplates	RAGT consisted of three phases: (1) a screening trial involving 5 minutes each of walking in "flat surface," "stair-up," and "stair-down" modes, (2) an initial assessment where physiatrists stratified patients	In the Hard group, one GBS patient discontinued training due to saddle discomfort, and the remaining patients in the Possible group completed all sessions. None of the patients in the Hard	This study indicates that individuals with various neurological conditions, including GBS, can safely and effectively utilize an end-effector-type automated gait machine with saddle support.
		employing the Morning Walk®, an end-effector robot with footplate and saddle seat support, for the improvement of functional capabilities.	Inclusion criteria: Patients who could sustain an upright seated position without external assistance, despite having a spinal cord damage classified as grade C or D. Exclusion criteria: patients <120 cm in height and with >120 kg of body mass.	replicate motion behavior in the longitudinal plane, guiding the feet to recreate natural gait patterns.	into prediction groups (Hard, Difficult, and Possible) based on the expected capacity to complete RAGT, and (3) the main treatment involving RAGT conducted five times a week for thirty minutes per session, with successful completion requiring 24 sessions.	group completed RAGT, while 66.7% of the Difficult group successfully finished, with only three abandoning. In the Possible group, only 4.2% (7 out of 168) patients were unable to complete RAGT.	
[26]	Meyer-Heim A., Borggraefe L., Ammann-Reiffer C., Berweck S., Sennhauser F. H., Colombo G., Knecht B., Heinen F. 2007.	To evaluate the feasibility of employing robotic-assisted treadmill training as a therapeutic intervention for children with central gait impairment.	* (2 GBS out of 26 subjects) 2 male GBS patients of 7 and 10 years. Inclusion criteria: impairment of the central gait caused by inherited or acquired brain or spinal disorders. The femur needed to be at least 21 cm long.	<b>Driven Gait Orthosis (DGO) Lokomat:</b> Comprising two leg orthoses, adjustable features include the span of the hip orthosis, upper and lower leg lengths of the DGO, and the position and dimensions of the leg braces. Both adult and pediatric versions were utilized.	In-patient group training for GBS patients consisted of two to five weekly 45-minute DGO sessions, totaling 20 sessions. The training included various therapeutic modalities such as occupational therapy, speech and language therapy, neuropsychology, orthopedagogy, circuit training, and preschool activities. Occupational therapy sessions covered balance training, joint mobility and stretching, COGT, and functional exercises.	24 patients successfully underwent DGO training. Among the in-patient group, 13 out of 15 children demonstrated enhanced gait speed. Of the thirteen children capable of performing the 6-Meter Walking Test, 11 exhibited improvements in walking distance. In terms of the Functional Ambulation Categories (FACs), six out of sixteen children showed enhanced walking ability, nine remained stable, and one regressed to a previous category.	The clinical rehabilitation regimen for children, implemented in both inpatient and outpatient settings, efficiently incorporated DGO training. Throughout the training period, the vast majority of children consistently exhibited a heightened motivation to participate in the DGO program.
[36]	Takahashi Y, Terada T, Inoue K, Ito Y, Ikeda Y, Lee H. 2007.	to seamlessly integrate motion and sensory interventions to sustain a quantitative assessment of the degree of disorder in the patient.	* (2 GBS out of 133 subjects, 126 healthy).	<b>Haptic Device System Rehabilitation:</b> Involving a haptic device equipped with two servomotors featuring reduction gears, link rods, a grip, and a flat panel, this system also integrates a display and a computer. The link rods establish a linkage between the grip and servomotors.	Patients can perform two-dimensional upper limb motions by manipulating their grip on the surface of the flat panel. In the WAVE game, patients strive to maintain the cursor within circles while navigating along a line. Adjustments can be made to the height and cycle of the wave. The system records the grip's location and velocity when subjected to diverse forces, including load, assistance, viscosity, and friction. The wave cycle is set to two during these experiments.	Patients exhibited reduced effectiveness in movement, struggling to maintain a consistent grip speed as it frequently dropped to zero. Nevertheless, an improvement in performance was observed when applying viscosity force.	Experimental results suggest the potential utility of this approach for effective patient training, providing data for evaluating dysfunction severity and training program efficacy. Moreover, it can sustain patients' engagement throughout the recovery process.
[22]	Tanida S, Kikuchi T, Kakehashi T, Otsuki K, Ozawa T, Fujikawa T. 2009	To prove the effectiveness of an intelligently Controllable Ankle Foot Orthosis (I-AFO) for a GBS patient.	One GBS subject: Male, (Age) 34, (Height) 183, (Weight) 83.1. The subject had difficulties moving their lower limbs voluntarily, particularly their ankle and toe joints on both sides.	<b>I-AFO:</b> An attachable laptop equipped with a versatile card (A/D and D/A) serves as a controller, providing the reference signal for regulating braking torque through amplified electric current. Input signals from a potentiometer and foot switches are conveyed to the controller via the A/D card.	Gait studies were conducted on a level surface, with results recorded using a response force plate and a three-dimensional movement analysis device. The participant underwent walking trials under three conditions: (1) barefoot walk, (2) walk with I-AFO, and (3) walk with plastic orthosis (P-AFO walk). Each test was performed at three distinct walking speeds: normal (1.30 seconds, 92 steps per minute), fast (1.03 seconds, 116 steps per minute), and slow (1.72 seconds, 69 steps per minute).	In the I-AFO walk, there was a noticeable increase in the flexural angle of the hip joint during the swing phase compared to the barefoot walk. Both the barefoot and P-AFO walks exhibited a distinct elevation in the knee joint angle at the onset of the stance phase. Despite dorsiflexion observed in both P-AFO and barefoot walks, the I-AFO walk demonstrated clear plantarflexion during the initial portion of the stance phase. In contrast to the other walking conditions, the rapid increase following foot contact with the floor surface diminished in the I-AFO walk.	The noticeable improvements led to suggestions on the effectiveness of the I-AFO's ankle joint control.

					freedom was applied to compute momentum in the dynamic model.		
[37]	Nehrujee A. Andrew H, Reethajane tsurekha, Patricia A, Samuelka maleshkumar S, Prakash H. 2021.	To evaluate the usability of PLUTO: robot with one Degree of Freedom (DoF) that can train many joints simultaneously.	(1 GBS patient out of 45 subjects, 30 healthy).	<b>PLUG and Train rObot (PLUTO):</b> A portable, lightweight, and versatile hand rehabilitation robot utilizes a single actuator with an open/free output shaft. This design enables training for various wrist and hand functions, allowing easy coupling with alternative passive single-DOF mechanisms.	To evaluate the outcome, the authors employed a System Usability Scale (SUS) as the standard for categorizing system usability. Additionally, a User Experience Questionnaire (UEQ) assessed usability across six subscales: perspicuity, attractiveness, novelty, stimulation, efficiency, and dependability. The training with the robot was gamified using three performance-adaptive games.	With an average score of 73.84 among the 45 participants, the system demonstrated acceptable usability (SUS > 70, t = 1.81, p = 0.038). According to UEQ findings, both patients and doctors evaluated all six subscales positively, with no negative scores observed in either group.	The system's immediate efficacy is outstanding. Subsequent research is required to evaluate the feasibility of implementing minimally supervised treatment, along with its long-term (beyond two weeks) usability and effectiveness.
[27]	Tuckey J., Greenwood R. 2004	To assess the GBS patient's response to treadmill training using Partial Body Weight Support (PBWS).	One male GBS patient: (Age) 44, (Height) 188.9, (Time since injury) 4 years.	<b>Biodex Unweighting Support System:</b> Enables calibration of the supported bodyweight proportion, utilizing a conventional rehabilitation treadmill.	During the hospitalization, the patient engaged in 4-5 weekly 45-minute physical therapy sessions, pursued a daily independent progressive muscular strength training program, and joined 4-5 physical therapy groups. The utilization of the PBWS system was incorporated into his therapy sessions.	The PBWS system contributed to the patient's notable improvement in treadmill walking distance, progressing from 3 meters to 100 meters. On the floor, within a week, the walking distance increased from 15 meters to 40 meters.	This study demonstrates the effectiveness of a PBWS system, functioning as a safety tool for high-risk weight-bearing exercises and gait retraining.
[38]	Céspedes N, Múnera M, Gómez C, Cifuentes CA. 2020	To assess the Socially Assistive Robot's (SAR) efficacy in neurorehabilitation.	* (1 GBS out of 4 subjects) One GBS patient.	<b>NAO:</b> A 58 cm humanoid robot with 25 DOF, 7 tactile sensors, 4 microphones, speakers, two 2D cameras, and voice recognition in 20 languages, featuring open-source programmable code.	Programmed routines include cervical posture feedback, thoracic posture feedback, heart rate alert, Borg scale inquiry fulfilled by the robot, and motivational feedback routines. The robot provides feedback to either the patient or the therapist in all routines. Eight 45-minute Lokomat sessions were completed.	Under the robot condition, all patients exhibited enhanced posture. The GBS patient's poor cervical posture time decreased from 22% to 5.15%, and poor thoracic posture time reduced from 2.66% to 2.00%. All therapists agreed that the robot was a valuable tool for providing feedback to patients and reducing workload.	The study revealed the positive and well-received influence of the robot on companionship, social contact, and cervical and thoracic postural behavior.
[28]	Bolliger M, Banz R, Dietz V, Lünenburger L. 2008.	To test a novel measuring technique's ability to quantify isometric muscle force in the DGO Lokomat.	(1 GBS out of 14 subjects) One male GBS patient (P13): (Age) 53, (Time since injury) 6 months	<b>Driven Gait Orthosis (DGO) Lokomat: (Described in article 6)</b>	The DGO Lokomat combines a dynamic body weight support device and a treadmill. In the sagittal plane, the DGO directs the patient's leg trajectory, utilizing linear back-drivable actuators within an exoskeleton framework to move the knee and hip joints. Actual joint angles are measured by potentiometers, while force transducers gauge linear forces in each actuator.	To assess inter- and intra-rater reliability, a total of 672 measurements were taken, comprising 84 for each joint and movement direction. Intra-rater reliability was lower compared to inter-rater reliability. Utilizing the average of two trials instead of a single measurement increased the reliability when calculating Intraclass Correlation Coefficients.	The DGO Lokomat provided precise results when assessing the maximum voluntary muscular force of hip and knee flexors and extensors in individuals with neurological movement disorders (NMD).
[34]	Rhee SY, Jeon H, Kim SW, Lee JS. 2020.	To assess the impact of gait training on GBS patients with a robotic end-effector type device.	15 GBS patients. Inclusion criteria: (1) 19 years or older, (2) first GBS diagnosis. (Mean age) 55.7 ± 15.3. (Mean time since injury) 3.9 ± 3.6 months.	<b>Morning Walk®: (Described in article 5).</b>	Subjects underwent 24 thirty-minute sessions of gait training supported by Morning Walk®. Evaluation of participants included the Modified Barthel Index Score (MBI) for activities of daily living, the Medical Research Council (MRC) scale for muscle strength, the Functional Ambulation Categories (FAC) for functional gait, the Rivermead Mobility Index (RMI) for functional abilities, and the 2-minute walk test (2MWT) for endurance of walking distance.	After Morning Walk®-assisted gait training, all outcome measures demonstrated improvements compared to baseline data. There were significant enhancements in ankle, knee, and hip muscular power, as well as improvements in FAC, MBI, 2MWT, and RMI.	After Morning Walk®-assisted gait training, individuals with GBS exhibited notable improvements in daily living activities, gait endurance, and lower limb motor power.

[24]	Chrif F, Van Hedel HJA, Vivian M, Nef T, Hunt KJ. 2022.	To assess the usability and technical viability of an interactive leg-press training robot designed to help children with neuromuscular deficits improve their leg muscle strength and control.	* (1 GBS out of 5 patients) One male GBS patient: (Age) 14.8, (Height) 165, (Weight) 65.5.	<b>Interactive leg press training device:</b> A seat module that can be adjusted, separate footplates connected to two pneumatic linear actuators by lever mechanisms, and an LCD screen that faces the user. Two exergames were developed in Unity for the training environment: Space Shooter and Ping-Pong.	Supervised by two therapists, patients underwent a single training session with the therapeutic apparatus. Before each session, therapists received an equipment introduction. Sessions lasted 40-45 minutes, incorporating active resistance training where patients maintained desired position profiles against resistive forces applied to the footplates. Exergames, conducted in active resistance mode, were part of the training.	All patients found the interactive device instruction satisfactory. Therapists gave a SUS score of $61.2 \pm 18.4$ . In active resistance training, every patient completed the exercise without any adverse effects. During exergames, high motivation and engagement were observed, with all patients successfully navigating the games.	Users have embraced and deemed the pediatric system practical. Experimental results quantitatively affirm the effectiveness of the proposed training modes, yielding satisfactory numerical outcomes.
[32]	Laver K, Lim F, Reynolds K, George S, Ratcliffe J, Sim S, et al. 2012.	To assess whether a grocery shopping simulator based on virtual reality is useful for neurological rehabilitation.	(1 GBS out of 15 patients) One female GBS patient: (Age) 86. Patients who met the eligibility requirements were undergoing therapy for a neurological ailment and had the necessary cognitive, emotional, physical, and visual abilities to try out the simulator.	<b>Virtual Reality Grocery Shopping Simulator:</b> Designed to be versatile, realistic, and flexible, the hardware includes a large touch screen displaying the supermarket surroundings and a specially designed shopping cart handle. The virtual supermarket comprises three aisles displaying food products and their corresponding pricing, along with a manned checkout area.	The session commenced with an introduction, followed by a practical demonstration. Participants then had practice time before undertaking a predetermined task within a specific timeframe. The task involved starting at the supermarket entrance, selecting four items from a shopping list, and proceeding to the checkout. This test was repeated with consenting participants to assess learning and potential improvement in speed over time. Subsequently, participants answered a questionnaire to gauge their level of interest and enjoyment.	Out of the participants, 14 believed the program would be beneficial for recovery, with only 6 directly considering it helpful for rehabilitation. Regarding the software's ease of use, nine participants found it easy to learn, and twelve individuals described it as straightforward, although four found it somewhat frustrating to use.	The shopping simulator demonstrated utility for individuals undergoing neurological rehabilitation. Further investigation is required to validate the program.
[29]	Wille D, Eng K, Holper L, Chevrier E, Hauser Y, Kiper D, et al. 2009.	To assess how well a Pediatric Interactive Treatment System (PITS) based on virtual reality may help children with motor impairments improve their arm and hand function.	(1 GBS out of 5 patients) One male GBS patient with both arms affected: (Age) 13 years, 10 months.	<b>Paediatric Interactive Therapy System (PITS):</b> Comprising a height-adjustable custom table on wheels, a speaker-equipped display, a personal computer, and tailor-made data gloves for measuring forearm 3D orientation and finger flexion/extension, it includes a vibration motor for haptic feedback.	The Melbourne Assessment (MA), Box and Block Test (BBT), and Nine Hole Peg Test (NHPT) were used as outcome measures, administered before and after treatment. Additionally, patients rated their level of enjoyment on a subjective 0–10 scale (0 = no fun at all; 10 = lots of fun) after each session.	The GBS patient was excluded from the group evaluation in the Melbourne Assessment due to the lack of a pre-assessment. However, in both the Box and Block Test (BBT) and Nine Hole Peg Test (NHPT), both arms of the GBS patient exhibited improvement. Overall, all five patients demonstrated improved results in each test compared to their pre-therapy sessions.	Successfully integrating PITS into the clinical rehabilitation program, despite occasional technical challenges affecting motivation, all children remained highly motivated due to engaging gaming challenges, unpredictability, indirect competitiveness through the high-score function, and immediate feedback on their motor progress.
[30]	Bulley P.	To test The Podiatron as a rehabilitation tool for a patient with GBS.	One male GBS patient: (Age) 58 years, (Time since injury) 10 months.	<b>The Podiatron:</b> A motorized wobbling board with adjustable pitch, featuring handrails and a control panel, designed specifically for enhancing and mobilizing the back, hips, knees, and ankles.	The podiatron was incorporated alongside the patient's regular physiotherapy. Sessions, held twice a day for 10 minutes at Level 1 (a 5° incline), gradually increased to maximum speed over the initial 30 seconds. Initially supervised to ensure body alignment, the patient later self-monitored using a mirror. This visual compensation addressed reduced somatosensory input, promoting extension and stimulating the vestibulospinal tract.	The patient exhibited improvement in all assessments following Podiatron use: 10-m walk (15.45 s to 14.11 s, 8.67% improvement); “up and go” (25.40 s to 22.07 s, 13.13% improvement); Confidence in walking (2.5 to 4.5, 44.44% improvement); Surface area of elevated left foot (17.68 cm <sup>2</sup> to 6.52 cm <sup>2</sup> , 63.12% improvement); Surface area of elevated right foot (88.8 cm <sup>2</sup> to 6.28 cm <sup>2</sup> , 92.93% improvement).	The implementation of the Podiatron expanded the surface area of the patient's feet for enhanced support. While progress seemed stagnant initially, two months later, substantial improvement in functional ability was observed, although not immediately evident in the first-week assessment.

**TABLE 2. Checklist for assessing the quality of quantitative studies. "2" = Yes, "1" = Partially, "0" = No, "-" = Does not apply**

Studies	ITEMS														Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
[20]	2	2	2	2	2	-	-	2	1	2	-	-	2	2	19/20
[21]	2	2	2	2	2	-	-	2	1	2	-	-	2	2	19/20
[22]	1	2	2	2	2	-	-	1	2	2	-	-	2	2	18/20
[23]	1	1	2	2	2	-	-	2	1	2	-	-	1	2	16/20
[24]	1	2	2	2	2	-	-	2	2	2	-	-	2	2	19/20
[25]	1	2	2	2	2	-	-	2	2	2	-	-	2	2	19/20
[26]	2	2	2	1	2	-	-	1	2	2	-	-	2	2	18/20
[27]	1	2	2	1	2	-	-	2	2	2	-	-	2	2	18/20
[28]	2	2	2	1	1	-	-	2	2	2	-	-	2	2	18/20
[29]	1	1	1	2	2	-	-	2	2	2	-	-	2	2	17/20
[30]	0	1	2	1	2	-	-	2	2	2	-	-	2	2	16/20
[31]	1	1	2	1	2	-	-	1	2	2	-	-	2	2	16/20
[32]	1	2	2	1	2	-	-	2	2	2	-	-	2	1	17/20
[33]	2	2	2	1	2	-	-	2	2	2	-	-	2	2	19/20
[34]	1	2	2	1	2	-	-	2	2	2	-	-	2	0	16/20
[35]	2	2	2	1	2	-	-	2	2	2	-	-	2	2	19/20
[36]	1	2	2	1	1	-	-	2	2	2	-	-	2	2	17/20
[37]	1	2	2	0	2	-	-	2	2	2	-	-	2	2	17/20
[38]	1	2	2	0	2	-	-	2	2	2	-	-	2	2	17/20

Three devices were orthoses: two of them were wearables designed for the ankle-foot area <sup>[21][22]</sup>. Contrary to most orthoses, these devices had integrated electronic systems that improved the patients' ability to move their feet. The third one is the Lokomat <sup>[26][28]</sup>, which functions as an integrated system providing body weight support and rehabilitating gait by driving both legs. The Biodex Unweighting Support System <sup>[27]</sup> only provides weight support but is adjustable, aiding in gait rehabilitation. The Morning Walk device <sup>[33][34]</sup> had great relevance in gait rehabilitation. Even though, in some cases, the saddle caused discomfort, the use of the end-effector footplates has proven to be beneficial for the patients.

It is worth mentioning that four of the studies addressed limb-related issues indirectly. Jamshidi *et al.* <sup>[23]</sup> developed a computerized model using the SimMechanics toolbox to simulate human gait, aiming to contribute to the improvement of leg orthosis.

Céspedes *et al.* <sup>[38]</sup> designed their experiment around patients using the Lokomat for gait rehabilitation, with the main focus on developing an automated assistant for rehabilitation. Kauhanen *et al.* <sup>[35]</sup> addressed upper limb rehabilitation, targeting tetraplegic patients. The EEG device 'TTK-BCI' provided screen feedback based on left-hand or right-hand movement attempts. Lastly, Lee *et al.* <sup>[25]</sup> created a passive shoulder joint tracker that can be integrated into various rehabilitation mechanisms to aid in upper limb rehabilitation. An outlier in the investigations was conducted by Wosnitzer *et al.* <sup>[31]</sup>; they did not focus on arm or leg rehabilitation but successfully applied sacral nerve neuromodulation to treat urinary retention.

Almost every GBS patient treated showed positive rehabilitation results; one of the few exceptions occurred in the study conducted by Choi *et al.* <sup>[33]</sup>, where one patient was unable to complete the process due to discomfort with the saddle. The biomedical

engineering devices proved to be useful, although, in most cases, further analysis and validation are required, especially in the long term.

A wide variety of parameters, scales, and methods were used to measure the patients' evolution during research directly dedicated to rehabilitation. The most commonly used tests [20][26][28][30] included the 10-meter walk test, which is essentially a speed evaluation measuring the time it takes for the patient to walk 10 meters [43][44][45][46]. The 'timed up and go test' also calculates speed but involves additional activities such as standing up, turning around, and sitting down [45][46][47]. A related test designed to estimate endurance is the 6-minute walk test [21][26][28], which records the distance the patient walks in 6 minutes [48][49][50].

The Medical Research Council Scale for Muscle Strength was also applied [27][33][34]. This scale focuses on muscle strength, encompassing 6 muscle systems in total [51][52][53]. However, since these studies were focused on the lower limbs, only 3 systems were considered: hip flexors, knee extensors, and foot dorsiflexors. Typically, therapists used the Functional Ambulation Categories [26][33][34] in conjunction with this form of examination.

Besides velocity and endurance, equilibrium is a crucial parameter to observe. For this purpose, the Berg Balance Scale [21], Tinetti test, and Unipedal stance time were employed [20]. These methods were useful in assessing patients' improvement, and all objectively revealed a correlation between the use of biomedical devices and the subjects' progression.

Multiple studies reveal the importance of motivation and comfortability during the neurorehabilitation process [54][55][56][57][58]. In order to take in consideration this topic, both the physical and psychological acceptance of the devices were taken in consideration in the studies, two of them used scales like the Suitability Evaluation Questionnaire [20] or the User Experience

Questionnaire [37], but most authors reported subjective observations made by the therapists. In the bulk of the studies, the authors observed that the improvement of the patient's autonomy and motor abilities had a remarkable incidence in their motivation and psychological well-being.

The usability of biomedical devices was tested in two studies by means of the System Usability Scale [24][37], which is a highly reliable tool for measuring the usability of a system or device. While this scale can be somewhat subjective, it is also very versatile [58][59]. However, in most research, authors opted for custom-made scales.

Living with the disabilities caused by GBS can be a significant challenge, as basic day-to-day activities become much harder to execute. Both patients and caregivers are psychologically affected, and their quality of life is reduced. This impact can be even more challenging for those who don't have good economic conditions.

Biomedical engineering devices are being used as auxiliary technologies that serve as extensions of human capacities. They enhance traditional rehabilitation methods, and the benefits for the patients multiply. There is a vast range of possibilities with this equipment, from wearables capable of providing firmness to steps to haptic devices that train fine motor abilities. Additionally, there are very complex mechanical systems that can take a patient from not being able to walk 4 meters to almost complete independence.

We must highlight the importance of studying the long-term effects of these rehabilitation methods. There should be more follow-up studies to understand the consequences in the long term and how well patients have evolved, in order to pursue a holistic comprehension of the benefits of these devices.

## CONCLUSIONS

This systematic review has answered the question 'How has biomedical engineering been used for the rehabilitation of patients with disabilities caused by Guillain-Barré?' and, at the same time, has made contributions to the field. The targeted areas for rehabilitation were identified, revealing where current devices tend to focus. The review illustrated the global distribution of studies using this approach for GBS rehabilitation and provided an analysis of the probable reasons why some continents have more studies than others. The biomedical engineering devices were described, and a general analysis was provided, considering whether they were custom-made or commercially acquired, and classifying them based on the engineering principle they operate on (haptics, orthosis, unweighting support systems, etc.). Another contribution is a brief description of the scales used to assess the status development of patients before and after rehabilitation with the devices. All of these contributions, along with the main objective of the investigation, help to create a solid platform for future research in this field.

We can conclude that, even though most studies lack an understanding of long-term effects, biomedical engineering devices are a useful ally in the rehabilitation process, serving both as the main therapy and as an auxiliary one. There are opportunities for new research based on the foundations provided by the pioneers in these studies. The authors would like to encourage biomedical engineers, therapists, and physicians to explore this avenue.

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## LIMITATIONS OF THE ARTICLE

One of the main problems encountered is that many of the studies did not have the GBS patients as the center of the investigation, this made it difficult, and sometimes impossible to obtain specific information on their development. Another general limitation is that most studies included a very reduced number of patients, and the great majority were samples from a single rehabilitation center, which caused a lack of heterogeneity.

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## DECLARATION OF COMPETING INTERESTS

All authors declare there are no conflicts of interests.

## AUTHOR CONTRIBUTIONS

A. B. T. R. Conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing original draft, writing review and editing, visualization, resources. I. R. H. Conceptualization, methodology, supervision, validation, writing review and editing. O. A. D. R. Conceptualization, project administration, supervision, validation, investigation, funding acquisition, writing review and editing. A. M. T. L. Methodology, validation, resources, supervision, writing review and editing.

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