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Review

Rehabilitation in Spinal Muscular Atrophy: A Narrative Review

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ABSTRACT

Spinal muscular atrophy (SMA) is a group of genetic diseases that cause muscle weakness and mobility problems. There are no clear clinical guidelines for assessing and rehabilitating individuals with SMA, despite its increasing prevalence. This study aimed to provide a comprehensive review of physical therapy's effectiveness in improving treatment outcomes for SMA by analyzing existing literature. A search was conducted in Pubmed, PEDro and Google scholar using relevant keywords. Studies on assessment, treatment, and rehabilitation for SMA were included in the review. The review found that assessment must be comprehensive, and rehabilitation approaches include exercise training, positioning, orthotics, and mobility aids, chest physiotherapy, contracture and scoliosis management, and aquatic exercises. Physical therapy improves the quality of life for children with SMA at every stage of the disease. However, there is still insufficient evidence on the effectiveness of physical therapy in managing people with SMA, and more high-quality studies are needed.

Keywords: Spinal muscular atrophy, exercise, rehabilitation, review

INTRODUCTION

Spinal muscular atrophy (SMA) is a hereditary disease that damages motor neurons in the spinal cord and brain stem, leading to muscle weakness and atrophy. This results in difficulty with essential skeletal muscle activities such as speaking, walking, breathing, and swallowing [1]. The condition, which was first described by Guido Werdnig and Johann Hoffsman in the 18th century is characterized by the degeneration of alpha motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis [2]. SMA is an autosomal recessive disorder that results from a homozygous deletion or mutation in the gene 5q13 survival motor neuron (SMN1) gene [3]. There are four known types of SMA, with decreasing severity from Type I, also known as the Werdnig-Hoffman disease to Type IV according to the age of onset, highest level of motor function and prognosis [4].

Literature on SMA's prevalence and incidence is rare. The National Organization of Rare Diseases reports that SMA has an overall incidence of approximately 1 in 10,000 live births, which means 10 in 100,000 live births. Despite the generally low prevalence of SMA, relatively high prevalence was observed in studies from Italy and Scandinavia with a prevalence of 6.56 per 100.000 persons under 20 years and 4.18 per 100.000 persons under 18 years respectively [5]. In Canada, no exact prevalent study has been reported, but it is estimated that 37.2 new cases of all SMA subtypes are reported annually [4]. There are higher estimates of the incidence of SMA among countries where consanguineous marriages are common [6, 7]. About 69% of people affected by SMA in Turkey had a history of consanguineous marriages [7]. Also in Saudi Arabia, a prevalence of 13.26 per 100.000 live births were reported [5].

SMA is second to cystic fibrosis on the list of common fatal autosome recessive disorder, and among children regarded as the most common genetic cause of death [5].

The complex nature of the clinical manifestation and associated difficulties in the diagnosis of SMA necessitates a multidisciplinary intervention that comprises of experts with the competencies in managing the pulmonary, gastroenterology or nutrition and orthopedic complications of the condition. SMA depending on the type and severity may be marked with severe hypotonia, symmetrical flaccid paralysis, respiratory insufficiencies, joint contractures, kyphoscoliosis, weakness in masticatory muscles which results in difficulties in chewing and swallowing[2]. Pharmacologically, disease-modifying drugs such as Nusinersen (Spinraza) which was the first to be approved in the United States by the FDA in 2016, Zolgensma in 2019 and Risdiplam (Evrisdy) in 2020 are used in the treatment of this incurable condition[8, 9]. Studies have showed the effectiveness of the Nusinersen through augmentation in the production of functional SMN protein [8, 10]. Physical therapy using exercise, electrotherapy, aqua-therapy, and other modalities may enhance outcomes such as quality of life, social integration, and independence of persons with SMA. The evidence regarding physical exercises for SMA type III is unclear, with only few studies [11].

The literature on assessment and treatment of SMA with physical therapy is insufficient. Therefore, there is a lack of clinical practice guidelines that guide physical therapists on the assessment or treatment of children and adolescents who survive SMA. The review aims to provide a comprehensive understanding of physical therapy in improving the treatment outcomes of children with SMA through assessment, best treatment, and evaluation by exploring the existing literature.

Pathophysiology

The precise function of the SMN protein in neuronal function and development is unknown, and its absence causes such severe impairments that detailed pathophysiological explanations have evaded us thus far. In youngsters, the severity of SMA varies. Only a tiny portion of the SMN messenger RNA (mRNA) transcript produced by the SMN1 gene is composed of the SMN2 gene. The severity of the condition is inversely related to the number of copies of the SMN2 gene [12]. Individuals with severe SMA type I who had sural nerve biopsy had significant sensory nerve pathology, but patients with milder SMA types II or III had no sensory nerve abnormalities clinically or morphologically [13]. The SMN protein is found in all eukaryotic cells and has proven to serve a critical function in homeostatic cellular pathways in all cells. SMA is divided into four phenotypes based on the age of onset and the level of the motor function obtained [3] (Table 1).

Table 1. The SMA phenotypes

Type	Definition
SMA type 0	This is a rare type. Early respiratory failure, significant weakness, and often decreased fetal movements accompanying arthrogryposis can be seen in the neonatal period. Death occurs most frequently during birth or within the first month of life.
SMA type I	Is the most prevalent, and children may never be able to sit independently. Hypotonia and areflexia are present in the first six months of infancy, and their cognitive development is normal, and their expressive gaze contrasts with their paralytic attitude. Intercostal muscle involvement predominates, and brainstem involvement can also occur, which are significant characteristics of the condition.
SMA type II	Symptoms emerge between the ages of 6 and 18 months; children may sit, and some can even stand, but they will not be able to walk independently and suffer from a gradual proximal weakness that disproportionately affects the legs rather than the arms. Restrictive lung disease may be caused by progressive scoliosis and the weakening of the intercostal muscles. Patients may live to 25 years, a few live till their third decade; respiratory failure is the leading cause of death.
SMA type III	Usually achieve all the major motor milestones, including independent walking. **Patients will have muscle exhaustion, progressive weakening, and atrophy of the lower limbs.** Visceral involvement is more common in this type. Hypotonia, hyperlaxity, and the lack of osteo-tendinous reflexes are all common symptoms. Patients rarely develop restrictive lung disease, and their life expectancy is unaffected
SMA type IV	Patients who can walk in adulthood and have no respiratory or dietary issues fall into this category. The last category includes SMA type IV, which represents a mild course, and adult-onset (> 18 years) patients. This category includes patients who can walk in adulthood and have no respiratory or nutritional problems. This phenotype of SMA affects adults (over 21 years of age) and is the mildest of the SMA phenotypes. The patients are ambulatory and have mild leg weakness that progresses to proximal weakness. In most cases, life expectancy is unchanged.

Diagnosis

Clinically, patients with SMA have significant hypotonia and proximal weakness. The weakness is usually symmetrical and affect the legs more than the arms. There is also weakness in the bulbar, intercostal, and fascial muscles. Weakness of the intercostal muscles results in the typical bell-shaped chest and paradoxical breathing pattern. In addition, these patients have absent or decreased tendon reflexes [14]. The standard tool for diagnosing SMA is molecular genetic testing. Molecular testing is highly efficient and SMA is observed frequently in hypotonic or "floppy" infants [15]. Creatine Kinase (CK) and electromyography (EMG) are used in the diagnosis of SMA. For a patient suspected of having SMA, the initial diagnostic test to look out for is the homozygous deletion of the SMN1 gene. There is a characteristic homozygous absence of exons 7 and 8 of the SMN1 gene, or in some instances, only exon 7 in majority of patients with SMA [16].

The results of electro-diagnostic studies display diverse characteristics of motor neuron or axon loss, which are in accordance with the impairment of motor neuron function. EMG is typically unnecessary for children with type I and II SMA; however, it can be useful for chronic forms in which the phenotype may not be as noticeable. While CK serum levels are generally normal or only slightly elevated in SMA, there have been a few cases where levels were significantly elevated (up to 10 times). As a result, a normal CK level does not necessarily rule out a diagnosis of SMA [17].

Complications

The focus of treating and managing SMA is to prevent or treat complications caused by weakness while also maintaining the individual's quality of life. Weakness can affect various body systems, including the respiratory system, leading to breathing problems, the gastrointestinal system, causing difficulty swallowing and constipation, and the musculoskeletal system, resulting in mobility issues [18]. Respiratory insufficiency is the primary cause of morbidity and mortality in patients with SMA type II. Primary complications include ineffective coughing causing reduced airway clearance, impaired lung and chest wall development, and an increased risk of pulmonary infections. Nocturnal hypoventilation is also a common problem [19]. In the absence of ventilation assistance, children with SMA type I typically do not survive beyond the first two years of life. However, for type IIa and IIb, the estimated survival rates are 81% and 67.7%, respectively, without the need for ventilation assistance [20]. Patients also experience a diminished health-related quality of life that is lower when compared to the general healthy population [21, 22]. Caregivers also report the need for respite care, physiotherapy from injuries, sleep disturbances and work adjustments [22].

Functional Assessment

To assess patients with SMA, a comprehensive physical examination is recommended to evaluate structural and physical impairments or disabilities, social participation, and environmental integration, as well as participation in basic functional and instrumental activities of daily living. This assessment should follow the International Classification for Functioning Disability and Health (ICF) guidelines to cover all relevant aspects based on the patient's age and level of severity. Clinical evaluation in SMA patients should include the musculoskeletal, neuromuscular, and pulmonary systems. This may include assessments for strength and range of joint motion, as well as the use of relevant motor functional scales and timed tests to monitor the aspects of function that reflect the patient's ability to carry out daily activities [23]. To assess hypoventilation in patients with SMA, a range of techniques can be used, including spirometry, forced oscillation technique (FOT), lung clearance index (LCI), evaluation of signs of nocturnal hypoventilation and respiratory muscle strength, swallow function assessment, chest x-ray, and sleep study. Volitional or non-volitional spirometry tests are commonly used in clinical practice to assess respiratory muscles. These tests include vital capacity (VC), maximal static pressures, sniff nasal inspiratory pressure (SNIP), peak expiratory flow (PEF), and peak cough flow (PCF) [24]. Spirometry and FOT testing are applicable in children with SMA as young as three years old. Vital capacity (VC) is the primary test used to assess respiratory function in children with SMA. Peak cough flow (PCF) and maximal static inspiratory and expiratory pressures are used to monitor cough efficiency and respiratory strength. Polysomnography (PSG) is used to evaluate sleep patterns, breathing, and the use of non-invasive ventilation (NIV) in pediatric SMA patients [25]. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Functional Motor Scale (HFMSE), Revised Upper Limb Module (RULM), and Hammersmith Infant Neurological Examination (HINE) are commonly used scales for assessing the functional status of children with SMA. These scales are used based on the patient's level of function, which can be classified as non-sitters, sitters, and ambulant [26].

Rehabilitative Approaches to Managing SMA

Exercise Training

Exercise training is important in managing SMA to protect muscles from wasting, improve cardiorespiratory function and physical fitness, and prevent contractures. A study demonstrated that progressive resistance training exercise is safe and well tolerated in children with SMA. The study involved nine children with SMA who completed 12 weeks of home-based progressive resistance training with supervision. Significant improvements were observed in the total composite score of manual muscle testing (MMT), but no significant changes were reported in quantitative muscle analysis and hand-held dynamometry (HHD) measures [27]. A study involving 14 patients with SMA found that a home-based cycling and strength training program could be tolerated and performed safely by children with SMA and had the potential to increase their maximum aerobic capacity (VO2 max) within six months. However, no significant changes were observed in measures such as fatigue, quality of life, strength or motor function, or distance walked on the six-minute-walk-test (6MWT) after the six-month period [28]. A study involving six SMA III patients who underwent 12 weeks of cycle ergometer training reported an improvement in VO2 max, but there were no significant changes in muscle strength or increased activities of daily living [29]. All these studies involved relatively fewer numbers of patients with SMA.

A recent Cochrane review found no significant difference in improvement of walking distance or quality of life between an exercise group and a usual care group. Additionally, there was no significant difference in VO2 max between the two groups [30]. A study showed that 92.4% of the respondents recommended stretching interventions. Among the modalities to encourage stretching, standers or standing frames, passive stretching, daytime splinting/bracing, nighttime splinting/bracing, active-assisted stretching, positioning in prone/on a wedge and active stretching were the most prevalent [31]. The recommended duration of stretching to improve length is up to 60 minutes and should be held at an end range greater than 60 degrees. The recommended frequency of stretching varies based on the functional status of the patient, with a minimum of three to five times per week for non-sitters, five to seven times per week for sitters, two to three times per week for ambulators, and three to five times per week for optimal ambulators [23]. Furthermore, the combination of pharmacotherapy Nusinersen, with exercise training in patients with SMA is more effective in improving motor skills than using only pharmacological treatments [32].

Positioning and Orthotics

Muscle strength and mobility are common difficulties in children with SMA. Pediatric orthotics can assist these children in moving around and performing other duties. Orthotic treatment is crucial in dealing with muscle weakness. Ankle foot orthoses (AFOs), knee-ankle-foot orthoses (KAFOs) and hip-ankle-knee-foot orthoses (HKAFOs) enable children to maintain proper joint alignment during walking or standing. Corset braces, thoracolumbarsacral orthosis (TLSO), and cervical-thoracolumbarsacral orthosis (CTLSO) provide postural support to reduce undesired movements and deformities. Neck immobilization is important for transportation safety. Orthotics should be worn at least five times a week and removed 60 minutes before bedtime. The patient's vertical position should be maintained for no more than 60 minutes, with a minimum of 3–5 times per week and a maximum of 5–7 times per week [33, 34]. Different methods, such as orthoses, splints, active or passive positioning, and phased gypsum casting procedures, can be used to retract the muscles of the axial skeleton and limbs. Verticalization can be achieved with the use of TLSO corsets, KAFO splints, or individual HKAFO devices. A Shant's collar is often used to fix the neck in an upright position to reduce the risk of suffocation and regulate the head [28]. Seating and orthostatic support systems should include components for maintaining a proper sitting position such as molded cushions and supports. Individualized wheelchairs and sleeping arrangements are advised. Wheelchairs with a falling/tilting back, customized seats, and neck braces may be used for daily movement and transit. TLSO corsets with an abdominal window are recommended for respiratory support [33].

Use of Mobility Aids

For patients with limited stamina, lightweight manual wheelchairs or motorized wheelchairs can be used to facilitate mobility. Power wheelchairs or motorized scooters may be used for long distances. Patients who can only be verticalized in a sitting position should have motorized wheelchairs or a tailored chair. Motorized wheelchair usage should be evaluated in patients above two years of age [35]. Lightweight manual or power wheelchairs may be recommended for patients with preserved upper limb function and muscular strength. Patients with SMA Type I and Type II may require an adaptable stroller or electric wheelchair, depending on their age. These wheelchairs and strollers can be equipped with critical medical equipment and have customizable controls [23, 36]. To enhance mobility and functional independence in children and adolescents

with SMA, activities such as swimming, hippotherapy, and wheelchair sports should be used in rehabilitation. Aerobics, general exercises, and other activities like walking, cycling, yoga, rowing, and elliptical/cross trainers may also be included under the supervision of a therapist. Horseback riding and wheelchair games can also be used to engage core muscles and promote sitting upright [33].

Chest Physiotherapy

Pulmonary dysfunction and respiratory impairment are the primary cause of mortality in SMA patients, especially in those with types I and II [37]. Patients with type III have a lower incidence of pulmonary failure and better lung function. Regular monitoring of respiratory muscle function is crucial to prevent and treat acute and chronic respiratory failure, as respiratory muscle involvement is a significant factor in children with SMA [38]. Patients with SMA often experience proximal muscular weakness, which may cause a decline in the function of the muscles that control breathing. The progression of scoliosis and chest wall deformity can also lead to a decrease in pulmonary function. However, advancements in spinal/chest wall implant systems, peri-operative critical care management, medical treatments, and physiotherapy/respiratory therapy offer promising outcomes for patients [39].

The main pulmonary approach for patients with neuromuscular disease is mechanical airway-secretion mobilization and clearance, assisted by coughing or mechanical insufflation-insufflation. Airway clearance techniques for congenital muscle disorders involve cough augmentation and mucus mobilization. To protect the airways, techniques such as oral suction and side-lying are indicated [38]. The mechanical in-exsufflator (MI-E) has been found to effectively stimulate normal cough in adults with SMA by providing positive-pressure insufflation with expulsive exsufflation. However, there is insufficient evidence to support its effectiveness in children [40]. Interest is growing in the utility of maximal inspiratory pressure (MIP) as both a therapeutic clinical trial endpoint and an early evaluation tool for assessing respiratory muscle strength in patients with SMA [41]. In non-sitting patients, utilizing a mechanical suction pump and a catheter for oral suctioning is a crucial element of airway clearance [42].

A study involving 34 children (18 SMA and 16 Duchenne Muscular Disease) found that functional vital capacity (FVC) reduction varied across age groups, and scoliosis was present in a significant proportion of patients with both subtypes. Surgery for scoliosis was required for a substantial number of patients. The study also found that FVC was associated with scores on the HFMS and RULM scales, and that noninvasive positive-pressure ventilator support was effective in managing respiratory function in SMA patients undergoing spinal surgery [43]. Continuous Positive Airway Pressure (CPAP) and Bilevel Positive Airway Pressure Support (BIPAP) can be acquired via respiratory aids depending on the severity of the breathing difficulty [44].

Contracture Management

Patients with SMA often experience orthopedic issues like contractures, hip instability, chest deformities, fractures, and scoliosis. Muscle weakness, decreased range of motion, and prolonged static positioning contribute to the development of contractures, which are more common in non-ambulatory individuals with SMA, particularly in the lower extremities [33]. Contractures can result in limited function and pain, significantly affecting daily lives. ROM exercises are crucial in maintaining joint flexibility, reducing the risk of permanent joint shortening and tightening, and ultimately reducing contractures. It is recommended that all SMA patients engage in flexibility and ROM exercises regardless of their level of mobility to improve mobility and reduce pain [45].

Scoliosis Management

More than half of children with SMA develop scoliosis, which is most frequently observed in those who are non-ambulatory or have lost their ability to walk. Approximately 50% of individuals with type III SMA will develop scoliosis, while almost all children with types I and II SMA are affected by scoliosis. Children with SMA frequently develop scoliosis at a young age, often before the age of four [46]. Most children with the disease develop thoracolumbar scoliosis that is C-shaped and progresses at a rate of 5°-15° in Cobb angle [33]. The conservative management of scoliosis in patients with SMA is difficult and the outcomes are typically not satisfactory. Corset therapy is not recommended for ambulatory patients as it can reduce trunk mobility and lead to a potential loss of walking ability. Spinal fusion and bracing are commonly used treatments for scoliosis, but there is no clear consensus on their efficacy [45]. In children with SMA type II, there is a correlation between achieving assisted walking through orthotics and bracing and a decreased risk of developing scoliosis. If scoliosis is left untreated, it can worsen the prognosis for the respiratory system [46].

Aquatherapy

Aquatic therapy or hydrotherapy is recommended as a treatment for SMA patients who can sit or walk, according to the International Standard of Care Committee for SMA [47]. Individuals with SMA type III may partake in aquatic therapy that encompasses exercises aimed at improving their balance, flexibility, strength, posture, and walking. On the other hand, individuals diagnosed with SMA type I may engage in activities that target their respiratory function, such as blowing pingpong balls in the water. Water has unique qualities that enable weight relief and postural support, enhance antigravity movements, and offer children the ability to execute activities that may be beyond their capabilities on land [48]. The importance of aquatherapy in the rehabilitation of children with SMA is provided below (Figure 1).

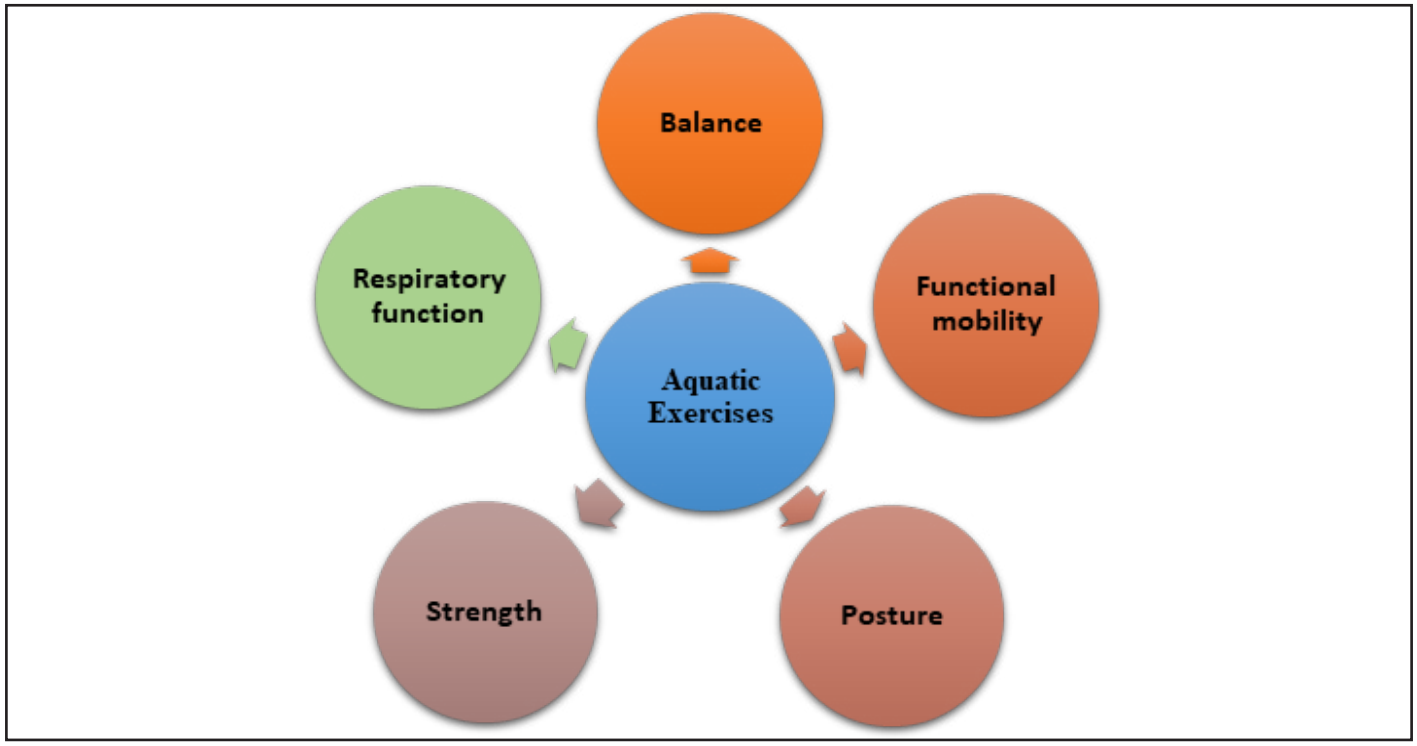

Figure 1. The importance of aquatic therapy for treatment in persons with SMA.

Technology and Ergometric Management

Robot-assisted gait training (RAGT) is a physiotherapy approach that combines robotics and intense repetitive workouts to enhance mobility, but there is insufficient evidence to support its effectiveness in individuals with SMA [49]. The Hybrid Assistive Limb (HAL) is a treatment device that utilizes cybernics to assist walking exercise, and has shown to be more effective than traditional walking approaches in patients with incurable neuromuscular diseases [50]. Cybernics technology integrates the human nervous system and a robot using bioelectric signals. This results in a dynamic state where the wearer and the device are physically and functionally linked, and the device operates based on the wearer's motor intentions and internal ideal movement patterns [51]. The use of Hybrid Assistive Limp (HAL) device, which integrates the human nervous system and a robot through bioelectric signals, resulted in a significant improvement in the distance covered during the two-minute-walk test and cadence total scores during the ten-minute-walk test. The study reported mild adverse effects such as myalgia, back pain, and skin contact issues, which were easily resolved [52].

The Yumen Arm is a new dynamic arm support that can improve the performance of upper extremity tasks in patients with neuromuscular diseases. Studies show that using the Yumen Arm can lead to improvements in active range of motion and functional ability and can make exercise performance less tiring. However, individual subject variability was high, highlighting the importance of tailoring dynamic arm supports to each patient's specific needs [49]. A new approach to evaluate

upper limb function in patients with SMA has been created using the Kinect 3-D sensor. The sensor is portable and cost-effective, and the assessment is designed as a game-like test. The Kinect-based assessment offers a comprehensive and objective movement analysis, while being a low-cost, portable, and child-friendly solution compared to traditional clinical rating scales or marker-based video systems [53].

The Wilmington Robotic Exoskeleton (WREX) is a modular body-powered orthosis that can be easily attached to a wheelchair to enable antigravity, three-dimensional arm movements. Patients who use the WREX and their families reported a substantial improvement in self-feeding. However, the current apparatus does not allow or assist in pronation or supination, which are necessary for the feeding process, and this extra degree of flexibility is being planned for a future version of the WREX [54].

Conclusion and Recommendations

This review provides a comprehensive overview of the management of SMA through physical therapy modalities spanning from conventional physical therapy such as exercise, chest physiotherapy, aqua-therapy and the use of mobility aids, through technological advancements that enhance performance in functional and recreational activities of living. It also provides an update on holistic assessment of deficits and other conditions related to SMA with reference to the ICF system. Physical therapy at every stage of SMA enhances the participation of various life activities, ensures social integration, and thus promote the quality of life of children and adolescents affected by SMA. The evidence supporting the effectives of physical therapy in management of persons with SMA is still inadequate, and therefore we recommend the need for more high quality randomized controlled trials of physical therapy interventions among this population.

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