Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER327
Topic:	Powered lower limb exoskeletons to support the musculoskeletal system in adults and children with complex neurological impairments or spinal cord injuries
Summary of findings:	A powered lower limb exoskeleton (PoLLE) is a wearable robotic-driven orthoses system which provides musculoskeletal support to the lower limbs in a pattern which matches natural gait. It is intended to be used as part of the management of complex neurological disabilities (including stroke, brain injury, multiple sclerosis, muscular dystrophy and cerebral palsy) and spinal cord injuries. A number of secondary studies were identified for this topic. The majority of the evidence we identified focuses on PoLLEs in adults with stroke or spinal cord injuries. We also identified secondary evidence for the use of PoLLEs in adults with acquired brain injury and multiple sclerosis, and adults and children with cerebral palsy. Some of the evidence suggests that PoLLEs may improve walking and energy expenditure, but there were other studies which did not report any benefit. However, the studies included in the systematic reviews were not based in the UK, focused on short-term outcomes, and were reported by the review authors as generally being of low methodological and reporting certainty. The majority of evidence comes from small case studies and non-randomised studies, but there were some randomised controlled trials identified for stroke and spinal cord injuries. In addition, current research suggests the use of PoLLEs is limited to clinical, controlled environments: there are gaps in the evidence regarding the transition from clinical rehabilitation to home-based therapy. We did not identify any economic evaluations, but two National Institute for Health and Care Excellence (NICE) medtech innovation briefings reported the cost of two PoLLEs used in SCI and stroke, and also stated that

	the resource impact was unclear (for the PoLLE used in SCI) and greater than standard care (for the PoLLE used in stroke). There is a high level of uncertainty on the effectiveness of PoLLEs. This may be due to the differences in the types of PoLLEs, the different stages of development of the PoLLEs included in the studies, and the variety of conditions they are used in and outcomes they measure. It is also unclear what the comparator(s) would be in Wales due to the number of conditions.

Introduction and aims

Health Technology Wales researchers searched for evidence on powered lower limb exoskeletons (PoLLEs) to support the musculoskeletal system in adults and children with complex neurological impairments or spinal cord injuries. We identified a systematic review of systematic reviews (Dijkers et al. 2021) that investigated this topic, and reported studies until January 2018. Our literature search therefore looked for additional studies published after this date.

A PoLLE is defined as a wearable robotic-driven orthoses system which provides musculoskeletal support to the lower limbs in a pattern which matches natural gait (Mehrholz et al. 2020). They should not be confused with grounded systems, which can be identified commonly as having a treadmill as part of the set up or, end-effector systems which rely on fixed footplates that move through the phases of gait (Mehrholz et al. 2020; Rodríguez-Fernández et al. 2021).

The purpose of PoLLEs is to increase the mobility level of its users thereby aiding recovery or delaying disease progression. PoLLEs are intended to be used as part of the management of complex neurological disabilities (including stroke, brain injury, multiple sclerosis, muscular dystrophy and cerebral palsy) and spinal cord injuries (SCIs). Motor impairments of people with these disabilities can include muscle weakness and fatigue, atypical muscle tone and joint contractures: all which result in affected gait and a sedentary lifestyle.

Current treatment options for people with these conditions include physiotherapy, occupational therapy, medicine, orthoses, standing frames and wheelchairs.

Evidence overview

HTW researchers identified two National Institute for Health and Care Excellence (NICE) medtech innovation briefings (MIBs), which focused on SCI and stroke, and also described the cost associated with the PoLLEs. We described a systematic review of systematic reviews (Dijkers et al. 2021), which investigated PoLLEs in patients with SCI and stroke, and reported studies until January 2018. Since January 2018, we found a number of systematic reviews investigating PoLLE-use in SCI and stroke. As none of the studies in the systematic reviews for SCIs were reported as being randomised controlled trials (RCTs), we also reported on RCTs on PoLLE-use in SCI. Some of the studies in the systematic reviews of patients with stroke are RCTs and so we did not search for primary evidence for this indication. HTW researchers also found systematic reviews for cerebral palsy, multiple sclerosis, acquired brain injury, and adverse events in different conditions.

Spinal cord injuries

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NICE published MIB93 in 2017, reporting on the Ekso GT robotic exoskeleton: a PoLLE for use in rehabilitation activities for people who have weak or paralysed legs and sufficient arm strength to use crutches. Based on one systematic review and five case series, involving a total of 41 patients with an SCI who used Ekso, patients were able to walk without assistance and their walking speed and distance increased. No serious adverse events were reported.

Secondary evidence

The systematic review of systematic reviews by Dijkers et al. (2021) reported studies published before January 2018. Out of the 17 systematic reviews they included, 15 of them (consisting of 56 primary studies) included adults who used PoLLEs for SCI. Nine of these systematic reviews reported some benefits to outcomes related to walking or energy expenditure.

We identified another three systematic reviews (total of 528 patients) published since January 2018. Duddy et al. (2020) found that patients using PoLLEs were able to walk faster and for longer between PoLLE sessions. Oxygen intake and heart rate data collected also indicated that the PoLLE increased metabolic rate and cardiac health. Rodríguez-Fernández et al. (2021) found that use of PoLLEs increased speed and reduced exertion, compared to passive knee-ankle-foot orthoses. Most of the studies in Shackleton et al (2021) showed decreases in exertion ratings, pain and spasticity and reported positive well-being post-intervention. Shackleton et al. (2021) also conducted a meta-analyses on walking performance, showing significant improvements post-PoLLE ($p < 0.05$), with pooled effects for the 6-minute walking test and 10-metre walking test of -0.94 (95% confidence interval [CI]: -1.53 to -0.36) and -1.22 (95% CI: -1.87 to -0.57), respectively. However, no significant cardiovascular changes were found over time.

Primary evidence

An RCT of 88 patients with SCI compared robotic therapy training to conventional therapy. A significant improvement was observed in both groups according to Walking Index for Spinal Cord Injury II and Functional Independence Measure scores ($P < 0.001$). However, a significantly higher improvement according to the Walking Index for Spinal Cord Injury II ($P = 0.011$) and Functional Independence Measure scores ($p = 0.022$) was seen in the robotic group than in the control group (Yildirim et al. 2019).

Xiang et al. (2021) conducted an RCT pilot study in which nine SCI patients were randomised into the exoskeleton-assisted walking group and nine SCI patients into the conventional group. They found that the exoskeleton-assisted walking group had potential benefits to facilitate pulmonary function parameters among individuals with lower thoracic neurological level of SCI compared with conventional trainings. Additionally, robotic exoskeleton helped walking.

Another pilot study by Faulkner et al. (2019) compared six patients with SCI who used a PoLLE plus physiotherapy with six patients who only used physiotherapy, and found that there was a significant reduction in arterial wave reflection and mean arterial pressure following completion of the PoLLE programme compared to the control group.

Stroke

HTA bodies

NICE MIB239 (2020) reported on the ReStore Soft Exo-Suit for people having gait rehabilitation to relearn to walk after a stroke or brain injury. Based on three non-comparative studies, including a total of 53 adults recovering from stroke in the USA, patients showed reduced circumduction and hip hiking when using the PoLLE. Patients also reported an increase in confidence during walking and improved balance leading to less falls.

Secondary evidence
The systematic review of systematic reviews by Dijkers et al. (2021) reported studies published before January 2018. Out of the 17 systematic reviews they included, six of them (consisting of 16 primary studies) included adults who used PoLLEs for stroke. Three of these systematic reviews reported some benefits to outcomes related to walking or energy expenditure.

We identified another five systematic reviews published since January 2018: Rodríguez-Fernández et al. (2021) found that use of PoLLEs improved gait characteristics compared to physiotherapy. Duddy et al. (2020) found that 18 post-stroke patients using PoLLEs were able to walk faster and for longer between PoLLE sessions. Oxygen intake and heart rate data collected also indicated that the PoLLE increased metabolic rate and cardiac health. Mehrholz et al (2020) reported that PoLLE treatment had benefits if adopted within three months of stroke. Additionally, they reported more benefits for non-ambulatory patients.

Two systematic reviews included RCTs in the systematic reviews. In Calafiore et al (2021), 306 sub-acute stroke survivors received robot-assisted gait training, and 270 underwent conventional rehabilitation. The meta-analysis demonstrated a non-significant difference of −0.09 in functional ambulation category (95% CI: -0.22 to 0.03) between the Lokomat PoLLE and conventional therapy. RCTs were also included in the systematic review by Nedergård et al. (2021), studying PoLLEs or end effectors (only one of the 13 included studies looked at end-effectors). The meta-analyses by Nedergård et al. (2021) for gait speed, cadence, step length and spatial asymmetry revealed no significant differences between the robot-assisted gait training device and comparator groups, while stride length, step length and temporal asymmetry improved slightly more in the robot-assisted gait training groups.

Cerebral palsy

Secondary evidence
A systematic review by Bunge et al. (2021) investigating the effectiveness of PoLLE-use on gait in 82 adults and children indicates there is some consistent positive evidence on the effectiveness of PoLLE in improving gait, with minimal adverse effects. Cumplido et al (2021) studied PoLLEs in 108 children with cerebral palsy and reported that they appeared to be safe but were not able to report on efficacy.

Acquired brain injury

Secondary evidence
In the systematic review by Postol et al. (2019), 13 studies were included (322 adults). Five studies were included in the meta-analysis, which found no difference between PoLLEs and control for the six-Minute Walk Test, Timed Up and Go test or 10-Metre Walk Test. Berg Balance Scale outcomes were significantly better in controls. There were no severe adverse events but 11.5% (37 participants) dropped out of the study.

Multiple sclerosis

Secondary evidence
Bowman et al. (2021) included 12 studies in their systematic review (exoskeleton in ten studies and end-effector in 2 studies). They found that robot-assisted gait training, mostly provided with exoskeleton devices, improves balance and gait outcomes.

Adverse events

Secondary evidence

A systematic review by Bessler et al. (2020) described robot-assisted gait training (end-effector devices and exoskeletons) in 14 healthy individuals, 341 SCI patients, 326 stroke patients, 42 traumatic brain injury patients, 67 cerebral palsy patients, 74 Parkinson's disease patients, 76 multiple sclerosis patients, 15 cardiac patients, and 30 patients with other diagnoses. Two of the included studies focused on children. Many of the adverse events reports were incomplete or did not include sufficient detail on different aspects, such as severity or patient characteristics. Musculoskeletal adverse events had the second highest prevalence and occurred mainly in exoskeleton-type devices. The authors further identified physiological adverse events including blood pressure changes that occurred in both exoskeleton-type and end-effector-type devices. Training in stationary gait robots can cause injuries or discomfort to the skin, underlying tissue, and musculoskeletal system, as well as unwanted blood pressure changes.

Economic evidence

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NICE MIB93 states that The cost of the Ekso GT exoskeleton is £98,000 per unit (excluding VAT), which includes staff training, software and all supporting equipment but not ongoing maintenance and support costs. They noted that the resource impact is currently unclear because of a lack of evidence. NICE MIB 239 states that the cost of ReStore is £22,995 per unit (excluding VAT) with around £4,000 in consumables (when used by 10 patients per month and both cartridges are replaced yearly). As an add-on intervention, the resource impact was reported as being greater than standard care.

We did not identify any other economic evidence for PoLLEs.

Areas of uncertainty

Whilst we identified numerous systematic reviews, the majority of which focuses on adults with stroke or SCIs, assessment of the literature is difficult due to the differences in the types of PoLLEs and the variety of conditions PoLLEs are used in and outcomes they measure. It is also unclear what the comparator(s) would be in Wales due to the number of conditions and types of treatment.

In addition, many of the devices were referred to as robotic-assisted gait training, and it was unclear whether the type of device would be considered a PoLLE. Some of the systematic reviews highlighted that the PoLLEs used were in the early stages of development. NICE MIBs highlighted that the data only focuses on short-term clinical and cost outcomes, and that the studies were done outside the UK and so the results may not be generalisable to the NHS.

HTW researchers identified a systematic review analysing the key characteristics of published systematic reviews on PoLLEs until January 2018. The systematic review highlighted that the included systematic reviews generally were of poor methodological and reporting certainty, including mainly small case studies and non-randomised studies. They failed to report some information on patients (e.g. height, weight, baseline ambulatory status) and interventions (e.g. treatment hours or sessions planned and delivered), and often failed to notice that the primary studies duplicated subjects.

Regarding the setting, current research suggests the use of PoLLEs is limited to clinical, controlled environments: there are gaps in the evidence regarding the transition from clinical rehabilitation to home-based therapy. There is currently one RCT comparing an exoskeletal-assisted walking device for in-home use for four months with wheelchair-use in 161 patients with SCI. This study was completed in September 2021, but has not yet been published (NCT02658656).

The economic evidence we identified for PoLLEs came from NICE MIBs, which reported device cost only for use in SCI and stroke. We did not identify any other economic evidence for PoLLEs.

Literature search results

Health technology assessments and guidance
MIB93: Ekso exoskeleton for rehabilitation in people with neurological weakness or paralysis. January 2017: https://www.nice.org.uk/advice/mib93 MIB239: ReStore Soft Exo-Suit for gait rehabilitation. December 2020: https://www.nice.org.uk/advice/mib239
Evidence reviews and economic evaluations
Bessler J, Gerdienke B. Prange-Lasonder 1,3, Robert V. Schulte1,2 , Leendert Schaake1 , Erik C. Prinsen1,3 and Jaap H. Buurke. 2020. Occurrence and Type of Adverse Events During the Use of Stationary Gait Robots-A systematic literature review. Frontiers in Robotics and AI: https://doi.org/10.3389/frobt.2020.557606 Bowman T, Gervasoni E, Amico AP, Antenucci R, Benanti P, Boldrini P, et al.; "Cicerone" Italian Consensus Group for Robotic Rehabilitation. What is the impact of robotic rehabilitation on balance and gait outcomes in people with multiple sclerosis? A systematic review of randomized control trials. Eur J Phys Rehabil Med 2021;57:246-53. DOI: 10.23736/S1973-9087.21.06692-2 Bunge LR, Davidson AJ, Helmore BR, Mavrandonis AD, Page TD, Schuster-Bayly TR, Kumar S. 2021. Effectiveness of powered exoskeleton use on gait in individuals with cerebral palsy: A systematic review. 2o21. PLOSONE. https://doi.org/10.1371/journal.pone.0252193 Calafiore D, Negrini F, Tottoli N, Ferraro F, Ozyemisci Taskiran O, de Sire A (2021). Efficacy of robotic exoskeleton for gait rehabilitation in patients with subacute stroke: a systematic review with meta-analysis. European journal of physical and rehabilitation medicine. DOI: 10.23736/S1973-9087.21.06846-5 Cumplido, Carlos et al. Gait-assisted Exoskeletons for Children with Cerebral Palsy or Spinal Muscular Atrophy: A Systematic Review. 1 Jan. 2021 : 333 – 348. https://content.iospress.com/articles/neurorehabilitation/nre210135 Dijkers MP, Akers KG, Dieffenbach S, Galen SS. 2021. Archives of Physical Medicine and Rehabilitation, 2021-02-01, Volume 102, Issue 2, Pages 300-313, DOI: 10.1016/j.apmr.2019.01.025 Nedergård, H., Arumugam, A., Sandlund, M. et al. (2021) Effect of robotic-assisted gait training on objective biomechanical measures of gait in persons post-stroke: a systematic review and meta-analysis. J NeuroEngineering Rehabil 18, 64. https://doi.org/10.1186/s12984-021-00857-9 Postol N, Marquez J, Spartalis S, Bivard A, Spratt NJ. 2018. Do powered over-ground lower limb robotic exoskeletons affect outcomes in the rehabilitation of people with acquired brain injury? Disability and Rehabilitation: Assistive Technology. 14(8). https://www.tandfonline.com/doi/full/10.1080/17483107.2018.1499137 Shackleton C, Evans R, Shamley D, West S, Albertus Y (2019). Effectiveness of over-ground robotic locomotor training in improving walking performance, cardiovascular demands, secondary complications and user-satisfaction in individuals with spinal cord injuries: a systematic review. J. Rehabil Med, 51: 723-733. DOI: 10.2340/16501977-2601
Individual studies

Faulkner J, Martinelli L, Cook K, Stoner L, Ryan-Stewart H, Paine E, Hobbs H, Lambrick D (2019). Effects of robotic-assisted gait training on the central vascular health of individuals with spinal cord injury: A pilot study. The Journal of Spinal Cord Medicine. 44(2). https://doi.org/10.1080/10790268.2019.1656849

Xiang, XN., Zong, HY., Ou, Y. *et al.* Exoskeleton-assisted walking improves pulmonary function and walking parameters among individuals with spinal cord injury: a randomized controlled pilot study. *J NeuroEngineering Rehabil* **18,** 86 (2021). https://doi.org/10.1186/s12984-021-00880-w

YILDIRIM MA, ÖNEŞ K, GÖKŞENOĞLU G. 2019. Turk J Med Sci; 49(3): 838–843. doi: 10.3906/sag-1809-7

Ongoing research

NCT02658656: https://www.clinicaltrials.gov/ct2/show/NCT02658656

Evidence supplied by topic proposer

Duddy, D., Doherty, R., Connolly, J., McNally, S., Loughrey, J. and Faulkner, M., 2021. The Effects of Powered Exoskeleton Gait Training on Cardiovascular Function and Gait Performance: A Systematic Review. Sensors, 21(9), p.3207. doi: 10.3390/s21093207

Mehrholz, J., Thomas, S., Kugler, J., Pohl, M. and Elsner, B., 2020. Electromechanical-assisted training for walking after stroke. Cochrane database of systematic reviews, (10). https://doi.org/10.1002/14651858.CD006185.pub5

Rodríguez-Fernández, A., Lobo-Prat, J. and Font-Llagunes, J.M., 2021. Systematic review on wearable lower-limb exoskeletons for gait training in neuromuscular impairments. Journal of neuroengineering and rehabilitation, 18(1), pp.1-21. https://jneuroengrehab.biomedcentral.com/articles/10.1186/s12984-021-00815-5

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Concepts used:	Powered lower limb exoskeletons (PoLLE), Ekso, robotic exoskeleton