MSBEST

MULTIPLE SCLEROSIS BEST EVIDENCE-BASED STRATEGIES AND TREATMENT/THERAPIES FOR REHABILITATION

Neurogenic Bowel

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Key Points

- Intrathecal baclofen may improve ease of care with neurogenic bowel management in select MS patients with severe lower limb spasticity who meet the criteria for baclofen pump implantation for spasticity indications.
- Sacral neuromodulation may improve constipation symptoms in select persons living with MS.
- Functional electrical stimulation applied to the abdominal muscles may improve gut motility in persons with MS.
- Percutaneous posterior tibial nerve stimulation may improve bowel incontinence symptoms in a select group of people with MS.
- Biofeedback may improve bowel symptoms in some people with MS. It remains unclear who may best respond to biofeedback treatment for improving bowel symptoms.
- Transanal irrigation may improve constipation and fecal incontinence in persons with MS, with possibly a greater effect on fecal incontinence.
- It is unclear if abdominal massage combined with advice on bowel management improves constipation more than advice alone in persons with MS.
- Abdominal massage combined with advice on bowel management may improve the frequency of stool evacuations compared to advice alone.
- Standing frames may not be beneficial for improving bowel frequency in persons with progressive MS, but may result in fewer new bowel related symptoms.
- Orem's self care model may help to improve constipation in persons with MS.
- Apitherapy may not improve bowel and bladder symptom severity ratings in persons with MS.

Amiraslany A, Turnbull G, Mirkowski M, Short C, Knox K, on behalf of the MSBEST Team. (2020). Neurogenic Bowel. *Multiple Sclerosis Best Evidence-Based Strategies and Treatment/Therapies for Rehabilitation*. Version 1.0: p 1-35.

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- Reflexology may improve short-term constipation symptoms in persons with MS with lower levels of physical disability.

- Hyperbaric oxygen treatment may not improve bowel and/or bladder symptoms in persons with MS.

- Extracranial venous therapy may not improve bowel control in persons with MS.

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Abbreviations

CAS	Constipation Assessment Scale
CCSVI	Chronic Cerebrospinal Venous Insufficiency
CSS	Constipation Scoring System
CTT	Colonic Transit Time
EDSS	Expanded Disability Status Scale
EVT	Extracranial Venous Therapy
FES	Functional Electrical Stimulation
GABA	Gamma Aminobutyric Acid
HADS	Hospital Anxiety and Depression Scale
KFSS	Kurtzke Functional Systems Scores
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NBD	Neurogenic Bowel Dysfunction
NBDS	Neurogenic Bowel Dysfunction Score
PAC-QOL	Patient Assessment of Constipation Quality of Life
PCT	Prospective Controlled Trial
PECS	Patient Evaluation Conference System
PEDro	Physiotherapy Evidence Database
PPMS	Primary Progressive Multiple Sclerosis
PwMS	Persons with Multiple Sclerosis
RCT	Randomized Controlled Trial
RRMS	Relapsing-Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
TAI	Transanal Irrigation
WC	Wexner Constipation
WGTT	Whole Gut Transit Time
WI	Wexner Incontinence

Neurogenic Bowel

1.0 Introduction

Bowel symptoms are a common concern among persons with multiple sclerosis (PwMS) and negatively affect quality of life. The prevalence of bowel symptoms in PwMS ranges between 27-73% in published studies (Chia et al., 1995; Hennessey, Robertson, Swingler, & Compston, 1999; Hinds, Eidelman, & Wald, 1990; Kraft, Freal, & Coryell, 1986; Preziosi, Gordon-Dixon, & Emmanuel, 2018; Wang et al., 2018). In one of the earliest and largest studies by Hinds et al. in 1990, constipation symptoms were reported by 43% of the 280 unselected patients with MS. Constipation symptoms were associated with longer MS disease duration and a history of genitourinary symptoms. They were similarly prevalent in males and females and not strongly associated with level of physical disability. Fecal incontinence occurred at least once a week or more in 25% of the sample, and 51% experienced one or more fecal incontinence episodes in the prior three months.

Despite a high prevalence of bowel symptoms, there are no standardized evidence-based bowel management guidelines for PwMS. Management of bowel symptoms in PwMS relies largely on clinical experience and evidence learned from other patient populations. This introduction will briefly discuss some of these borrowed approaches, resources, and expert opinions for the management of bowel symptoms in PwMS.

The pathophysiology of bowel dysfunction in MS has some similarities with spinal cord injury. An early paper found slower colonic transit times in PwMS (Weber et al., 1987); however, delayed emptying of the rectum due to abnormal rectal evacuation may also slow colonic transit times. Subsequent research in PwMS has shown that most people with constipation have abnormal rectal evacuation as the primary cause for their constipation (Jameson et al., 1994; Karasick & Ehrlich, 1996). Appreciating that bowel symptoms in PwMS may be complex and multi-factorial is important to their management (Preziosi et al., 2018). For example, a patient may report they have “diarrhea” in the case of severe constipation with overflow liquid incontinence around impacted stool. A complete history and a rectal exam help to arrive at an appropriate management plan with the least amount of trial and error. The *Spinal Cord Injury Research Evidence (SCIRE)* Project and *Neurogenic bowel: What you should know – a guide for people with spinal cord injury* are online resources which may be applicable to PwMS who have spinal cord involvement. Other sources detailing the pathophysiology of neurogenic bowel or management include Rao (2004), DasGupta and Fowler (2003), and Preziosi et al. (2018).

Comorbid bowel conditions, medications, mobility, physical activity levels, bowel routines, and diet may all contribute to symptoms of constipation. Adequate fluid intake is critical (Markland et al., 2013), especially since PwMS may self restrict fluids to manage bladder symptoms. The type and amount of fibre intake are also relevant. The usual North American diet only contains 10g of fibre, however up to 20 to 30g may be helpful for managing constipation, with dosing individualized and adjusted gradually. Psyllium fibre is generally better tolerated than wheat bran fibre since the latter may be more likely to cause increased bloating, cramping, or diarrhea (Bharucha, Pemberton, & Locke, 2013). Dietary intake also affects the gut microbiome, which may also play a role in immune regulation (Mirza et al., 2020). Methanogenic bacteria are important for digesting complex sugars, however, may also be associated with constipation and bloating symptoms. At least two studies have reported a higher abundance of Methanobrevibacter in PwMS (Mirza et al., 2020). Fruits and vegetables contain complex, poorly digested

sugars associated with increased symptoms of bloating (Gibson & Shepherd, 2012). However, generous portions of a variety of fruits and vegetables are associated with multiple established health benefits. SCIRE includes a patient-friendly resource discussing dietary considerations in neurogenic bowel, which may be applicable to PwMS.

Bowel routines for constipation may include planning a sufficient amount of time to regularly empty the bowels, finding the optimal position (ideally a seated position with the knees higher than the hips), having assistive aids or care in place, and medication regimes. Timing a bowel routine half an hour after a meal and using digital rectal stimulation has the advantage of using the gastro-colic and anal-rectal reflexes, respectively, to aid in emptying the bowels.

Pharmacotherapies for treating constipation in PwMS are not rigorously established, although frequently used. Options may include suppositories and oral stool softeners (i.e., polyethylene glycol products), and less frequently stimulants (i.e., sennosides) and prokinetic agents. Water soluble based suppositories (i.e., Magic Bullet) are more effective than oil-based suppositories in spinal cord injury (Frisbie, 1997; Stiens, Luttrel, & Binard, 1998). Prokinetic agents are prescribed in chronic constipation of unknown cause and may warrant further investigation in PwMS. Prucalopride is a 5-hydroxytryptamine-4 receptor agonist prokinetic agent indicated for chronic constipation (Camilleri, Kerstens, Rykx, & Vandeplassche, 2008) and improved constipation in a small study with spinal cord injury patients (Krogh et al., 2002). Side effects of abdominal pain and diarrhea are not well tolerated, but may improve after subsequent doses. Linaclotide, another prokinetic agent indicated for irritable bowel syndrome or constipation of unknown cause (Lembo et al., 2011) has the advantage of three doses (72mcg, 150mcg, and 290mcg), allowing gradual dose escalation as needed to help reduce side effects. Linaclotide activates guanylate cyclase-C to increase intestinal fluid secretion and is administered once daily on an empty stomach with water in the morning. Linaclotide has not been studied in neurogenic bowel or PwMS, and it is contraindicated in children because of risk of severe dehydration.

Diarrhea is less common in PwMS and is important to differentiate from fecal incontinence episodes. Despite formed stools, a person may report diarrhea if mobility restrictions do not allow timely access to a toilet. If fecal incontinence episodes occur but the episode is not recognized until after the incident, a reduced awareness of rectal distension with fecal impaction and overflow incontinence may have occurred. An empty rectum on physical exam does not rule out severe constipation. An abdominal x-ray film may identify if there is excess fecal loading in the colon in the case of overflow diarrhea.

Episodes of incontinence may also be described with pelvic floor dyssynergia where the anal sphincter contracts (rather than relaxes with defecation) and thus the rectum fails to completely empty. This may lead to residual stool leaking out after a partial bowel movement. Placing a step in front of the toilet to allow a more physiologic pelvic position that straightens the anal opening and can facilitate rectal emptying, as well as a lubricating suppository (i.e., glycerin). Medication (i.e., loperamide) may be effective for managing incontinence episodes if there is no fecal loading, when bowel movements are regular, and if other causes for diarrhea have been excluded. One approach is loperamide 2mg taken after the first bowel movement of the day. The dose is increased only after four to five days and as needed to reduce incontinence episodes (Ford et al., 2014). Incontinence or diarrhea may occur when eating out or being physically active and away from a toilet. Dosing loperamide 2mg approximately an hour before eating out or being physically active may help reduce these episodes and improve quality of life. However, pharmacotherapy for diarrhea or incontinence episodes in PwMS has not been systematically evaluated, and may increase the risk of constipation.

In the absence of standard protocols, and due to limited research and individual differences in bowel habits, it is often the case of trial and error to identify what works best for each individual patient. Being able to control bowel elimination predictably may help to avoid episodes of fecal incontinence and other bowel symptoms interfering with quality of life.

This module provides an overview of the available evidence for pharmacological and non-pharmacological interventions for neurogenic bowel rehabilitation in PwMS.

2.0 Neurogenic Bowel Outcome Measures

Outcome measures used to assess the severity of neurogenic bowel dysfunction (NBD) or NBD-related symptoms include the following:

- **The Modified Patient Evaluation Conference System (PECS) scale** (Harvey & Jellinek, 1981) is a functional performance scale in which items are evaluated in terms of progress. Part of this scale includes bowel and bladder programs. This 8-point scale ranges from 0 to 7, with 0 representing unmeasured or unmeasurable function and 7 representing fully independent or normal function. A score ≥ 5 represents varying degrees of independent function.
- **The Kurtzke Functional Systems Scores (KFSS)** (Kurtzke, 1965) involves 7 functional systems. These systems include visual, pyramidal, cerebellar, brainstem, sensory, mental, and bowel and bladder. Bowel and bladder functions are scored from 0 to 6, with 0 being normal and 6 being loss of bowel and bladder function.
- **The Wexner Constipation (WC) score** or **Constipation Scoring System (CSS)** (Agachan, Chen, Pfeifer, Reissman, & Wexner, 1996) determines the severity of constipation with eight constipation-related items. Scores range from 0 to 30, with 0 indicating normal and 30 indicating severe constipation. These items include frequency of bowel movements, painful evacuation, feeling of incomplete evacuation, abdominal pain, minutes in lavatory per attempt, type of assistance, unsuccessful attempts for evacuation per 24 hours, and duration of constipation in years.
- **The Wexner Incontinence (WI) score** (Jorge & Wexner, 1993) assesses the severity of fecal incontinence with five incontinence related items: incontinence to solid stool, incontinence to liquid stool, incontinence to gas, wears pad, and lifestyle alteration (the extent to which it alters the patient's life). Scores range from 0 to 20, with 0 indicating perfect continence and 20 indicating complete incontinence.
- **Whole Gut Transit Time (WGTT)** and **Colonic Transit Time (CTT)** (Lee, Erdogan, & Rao, 2014) involve the assessment of transit time of fecal material through the human gastrointestinal tract. The normal range for WGTT is 10 to 73 hours, and 10 to 59 hours for CTT.
- **The Patient Assessment of Constipation Quality of Life (PAC-QOL)** (Marquis, De La Loge, Dubois, McDermott, & Chassany, 2005) is a comprehensive assessment of the burden of constipation on everyday functioning and well-being. It includes 28 questions related to constipation and other associated symptoms that have burdened the patient within the past two weeks. Each question is scored from either 1 to 4 or 1 to 5. The higher the overall score, the more constipation has impacted the patient's life.
- **The Neurogenic Bowel Dysfunction Score (NBDS)** (Krogh, Christensen, Sabroe, & Laurberg, 2006) is a validated questionnaire that generates scores based on clinical assessment of colorectal and anal dysfunction in neurological patients. Scores range from 0 to 47. The severity

of dysfunction is divided into four categories: very minor (0-6), minor (7-9), moderate (10-13), and severe (12-47).

- **The Constipation Assessment Scale (CAS)** (McMillan & Williams, 1989) is a scale where constipation severity is rated from 0 to 4 in eight different categories. Total scores range from 0 to 32 where scores between 0 to 8 indicate the least degree of constipation-related problems, 9 to 16 indicate some problems related to constipation, 17 to 24 indicate severe constipation, and 25 to 32 indicate very severe constipation.
- **The Rockwood score** (Rockwood et al., 2000) is a validated quality of life measuring tool specific for fecal incontinence which assigns a score in four categories: lifestyle, coping, depression, and embarrassment. Each category is rated from 1 to 5, with 5 indicating a better quality of life.
- **The Bristol Stool Form Scale** (Blake, Raker, & Whelan, 2016) is a 7-point scale used in clinical settings to measure how formed or loose the stools are. A score of 3 or 4 indicates normally formed stools, a score of 1 indicates hard and dry stools, and a score of 7 indicates watery diarrhea-type stools.

3.0 Pharmacological Interventions

3.1 Intrathecal Baclofen

Baclofen is a gamma aminobutyric acid (GABA)-B receptor agonist used in the treatment of spasticity. Spasticity and incoordination of pelvic floor muscles could be a cause of pelvic floor dyssynergia leading to functional constipation in MS (Preziosi et al., 2018). Oral baclofen may be poorly tolerated in PwMS and intrathecal baclofen has a role in the treatment of severe spasticity (Erwin et al., 2011). For intrathecal administration, a catheter is placed into the lumbar intrathecal space and is connected to a subcutaneous pump and medication reservoir inserted into the abdominal wall (Parke, Penn, Savoy, & Corcos, 1989). As the spinal cord expresses a high density of GABA-B receptors, low dose intrathecal baclofen may significantly reduce spasticity, especially below the level of catheter placement (Sammaraiee et al., 2019).

Table 1. Studies Examining Intrathecal Baclofen for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Parke et al. 1989 *Functional outcome after delivery of intrathecal baclofen* US Pre-Post $N_{Initial}$=8, N_{Final}=8	**Population:** *MS Participants (n=4)*: Mean age=41yr; Sex: males=0, females=4; Disease course: unspecified; Severity: unspecified; Disease duration: unspecified. **Intervention:** The treatment offered to patients was an intrathecal delivery of baclofen at an initial dose of 50-100mcg via an implanted programmable drug pump. Dose adjustments were made with a radiofrequency link. Patients were followed for 6mo. **Outcomes/Outcome Measures:** Modified Patient Evaluation Conference System (PECS).	1. All patients except for one improved in the bowel and bladder programs. No further information was provided.

Discussion

One pre-post study by Parke et al. (1989) examined the effects of intrathecal baclofen on bowel management and spasticity in PwMS. Bowel management was a secondary outcome measured only as a component of the PECS. Every patient in this small study reported improved bowel management (alongside bladder management) with the exception of one patient who had an effective urinary program before the study.

Intrathecal baclofen is considered for select PwMS who may have failed other treatments for predominant lower limb spasticity interfering with function or personal care. Intrathecal baclofen is currently not standard care in the management of neurogenic bowel. Patients must be appropriately selected and willing to undergo the required surgery for intrathecal pump placement and attend regular pump refill appointments, which may be limiting factors (Chang et al., 2013). Rare adverse events of intrathecal baclofen include overdose leading to weakness, serious baclofen withdrawal symptoms in the case of a pump failure, and infections, none of which are reported in this study. Since intrathecal baclofen can have a profound effect on reducing lower limb spasticity, as expected, spasticity symptoms improved on the Ashworth Scale in this study. The decrease in spasticity coincided with improved functioning in the areas of self-care and activities of daily living. It is possible the main improvements in bowel management were the result of increased mobility and improved ease of transferring and toileting. Importantly, incontinence also improved in this study, yet not mentioned is how the incontinence data was collected. Incontinence data would be important to detail since sphincter tone could affect incontinence.

The limitations of this study include the lack of a validated neurogenic bowel outcome measure, the pre-post design, and a small MS sample. There is limited evidence for the efficacy of intrathecal baclofen for directly improving NBD in PwMS. At this time intrathecal baclofen is not indicated for the management of neurogenic bowel alone. However, the indirect effects of improving the ease of care associated with a neurogenic bowel routine in PwMS with severe spasticity may be clinically relevant and warrants further study.

Conclusion

There is level 4 evidence (from one pre-post study; Parke et al. 1989) that intrathecal baclofen may improve neurogenic bowel management in persons with MS who received intrathecal baclofen therapy for severe lower limb spasticity.

Intrathecal baclofen may improve ease of care with neurogenic bowel management in select MS patients with severe lower limb spasticity who meet the criteria for baclofen pump implantation for spasticity indications.

4.0 Non-pharmacological Interventions

4.1 Electrical Stimulation

Electrical stimulation approaches involve the delivery of an electrical current to tissues that may result in stimulated action potentials of neurons, muscle contraction, sensory feedback, and/or neuromodulation. A recent review and meta-analysis of neuromodulation approaches involving electrical stimulation for the treatment of bowel disorders in general concluded that there is low-level evidence for most approaches, although future advancements in the field are anticipated (Southwell, 2020).

4.1.1 Sacral Nerve Stimulation

Muscular control is a key element in the act of defecation and complete voiding. Sacral neuromodulation involves an implanted pulse generator, and electrodes typically placed on the anterior sacral nerve roots. Sacral neuromodulation for bladder dysfunction was first approved by the Food and Drug Administration in 1997 and the treatment continues to be increasingly accessed as a third line treatment for bladder symptoms (Kirby & Kellogg, 2018). This approach is not well established in clinical care settings for bowel symptoms but many patients with neurogenic bladder complaints also have bowel complaints and there are many reports by patients of improvement in their bowel complaints with sacral neuromodulation. Sacral neuromodulation may modify the neural control of the anal sphincter and thereby improve incontinence and coordinated defecation (Ganio et al., 2001). At this time, it is not clear how this treatment works to improve neurogenic bowel symptoms.

Table 2. Studies Examining Sacral Nerve Stimulation for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Minardi & Muzzonigro 2005 *Lower urinary tract and bowel disorders and multiple sclerosis: role of sacral neuromodulation: a preliminary report* Italy Pre-Post $N_{Initial}$=5, N_{Final}=5	**Population:** Mean age=48.6yr; Sex: males=2, females=3; Disease course: unspecified; Severity: unspecified; Mean disease duration=25.4yr. **Intervention:** Participants received treatment of sacral neuromodulation via InterStim pulse generator implantation. Outcomes were assessed at baseline and a mean follow-up of 30.4mo. **Outcomes/Outcome Measures** Wexner Constipation (WC) score.	1. Participants showed a decrease in mean WC scores (10.8 to 5.6) after sacral neuromodulation.

Discussion

One small pre-post study reported mild improvements in constipation in PwMS according to WC scores after sacral neuromodulation (Minardi & Muzzonigro, 2005). All five study participants had the InterStim (Medtronic™) system implanted with the stimulating electrode placed within the third sacral (S3) level foramen. Only a small, nonsignificant improvement in constipation symptoms occurred in this sample where the primary outcome of interest was related to bladder symptoms. The mechanism and rationale for electrode placement at the S3 foramen is not well established in terms of the effects on sphincter coordination. Even though urinary urgency and frequency decreased by 81%, quality of life index scores improved, and the incidence of urinary tract infections decreased, this small study had many limitations.

The selection of study participants was very specific; they all had external bladder sphincter dyssynergia on urodynamic studies at baseline. Participants were included only after confirmation that bladder or bowel symptoms improved with a temporary initial stimulation trial. It is unknown how many patients failed the temporary percutaneous electrode stimulation trials prior to proceeding with the implanted electrode, or how the selection for a temporary trial occurred. Mean baseline WC scores for the five patients were not in the severe constipation range, yet they all required either digital assistance or squeezing to empty the rectum at baseline, or had incomplete evacuation in more than half of all bowel movements in the past year. They also had failed other dietary and pharmacotherapy treatments for constipation.

Other considerations for sacral nerve stimulation include that magnetic resonance imaging (MRI) is contraindicated because the neurostimulators are not MRI compatible. Complications include infections, lead breakage, or equipment failure requiring surgical revision or removal. Sacral nerve stimulation must be carried out in a center with the required access and expertise for regular review. The treatment is costly, and even with careful patient selection, it does not eliminate all bowel or bladder incontinence episodes. Sacral neuromodulation may improve bladder symptoms refractory to other treatments; however, its effectiveness for managing bowel symptoms in MS requires further study.

Conclusion

There is level 4 evidence (from one pre-post study; Minardi & Muzzonigro, 2005) that sacral neuromodulation may improve constipation symptoms in persons with MS as measured by the Wexner Constipation score.

Sacral neuromodulation may improve constipation symptoms in select persons living with MS.

4.1.2 Functional Electrical Stimulation

Functional electrical stimulation (FES) is a type of therapy that can be applied transcutaneously whereby electrical currents are applied over the skin, or alternatively can be delivered through implanted subcutaneous electrodes. FES aims to create a muscle contraction traditionally for improving a motor functional outcome (Peckham & Knutson, 2005). Relatively low-cost FES units with transcutaneous

electrodes designed to safely deliver electric pulses are available, and FES may be self-administered at home by patients or caregivers. Contraindications for FES include patients with implanted electrical devices, pacemakers, and epilepsy (Singleton, Bakheit, & Peace, 2016). In patients with tetraplegia from spinal cord injury, there is strong evidence from one randomized controlled trial (RCT) that FES of the abdominal muscles can improve bowel symptoms (Korsten et al., 2004).

Table 3. Studies Examining Functional Electrical Stimulation for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Singleton et al. 2016 *The efficacy of functional electrical stimulation of the abdominal muscles in the treatment of chronic constipation in patients with multiple sclerosis: A pilot study* UK Pre-Post $N_{Initial}$=5, N_{Final}=4	**Population:** Mean age=53.2yr; Sex: males=0, females=4; Disease course: unspecified; Severity: unspecified; Mean disease duration=22.7yr. **Intervention:** Individuals with chronic constipation received 30min of functional electrical stimulation (FES) 2x/d for 6wks, with the exception of the first 2d which were 15min 2x/d. FES was applied to the external oblique and transverse abdominis muscles, at 40Hz, 330μ pulse and 40-50mA. Individuals or caregivers administered the treatment. SmartPill motility capsules were used to measure transit time. Assessments were completed at baseline and at 6wks. Statistical analyses were not conducted due to small sample size. **Outcomes/Outcome Measures:** Whole gut transit time (WGTT); Colonic transit time (CTT); Patient Assessment of Constipation Quality of Life (PAC-QOL); Bowel diary.	1. Gut motility trended toward improvement according to WGTT and CTT following FES treatment compared to baseline, suggesting that FES strengthened abdominal muscles and increased intra-abdominal pressure to allow easier propulsion of bowel contents. Scores post treatment were close to those of healthy subjects. 2. PAC-QOL improved following FES treatment compared to baseline; however, none of the patients met the critical threshold for meaningful clinical improvement. 3. Improvement in bowel habits were also evident in all participants from the bowel diaries following FES treatment compared to baseline. 4. There were no adverse effects of FES treatment.

Discussion

One small study involving four participants used multiple bowel related outcomes to investigate the effects of transcutaneous FES via surface electrodes placed on the abdomen in PwMS (Singleton et al., 2016). All four participants showed improvement in all outcomes (reduced transit time, improved bowel habits, and quality of life), and no adverse events were reported. Functional constipation was a requirement for participation, as was the failure of treatment with laxatives. Exclusion criteria included other bowel diseases such as irritable bowel syndrome and organic bowel obstruction. While transit times improved objectively as measured by motility capsules, the small sample size, no control group, and a short run time of six weeks are significant limitations. The authors propose that FES may strengthen the abdominal muscles over time, allow the generation of increased intra-abdominal pressure, and relieve constipation symptoms. However, in the absence of larger and longer-term studies, clinicians may be less likely to recommend electrical stimulation for the treatment of neurogenic bowel (Worsoe, Rasmussen, Christensen, & Krogh, 2013). Larger studies and a better understanding of the possible mechanisms by which FES may improve constipation are warranted.

Conclusion

There is level 4 evidence (from one pre-post study; Singleton et al. 2016) that functional electrical stimulation of abdominal muscles may improve gut motility in persons with MS.

Functional electrical stimulation applied to the abdominal muscles may improve gut motility in persons with MS.

4.1.3 Percutaneous Posterior Tibial Nerve Stimulation

Percutaneous posterior tibial nerve stimulation is a minimally invasive procedure associated with subjective improvements in overactive bladder syndrome (de Wall & Heesakkers, 2017). Objective urodynamic testing yields conflicting results for overactive bladder syndrome. In PwMS, the treatment may improve maximum detrusor capacity before first contraction on objective urodynamic assessment (Kabay, Yucel, & Kabay, 2008). The concept that peripheral neurostimulation provides a therapeutic effect likely originates from acupuncture, a traditional Chinese medicine practised in some form as early as approximately 500 BC (de Wall & Heesakkers, 2017). A proposed mechanism of action for a therapeutic effect on bowel symptoms may be the modulation of efferent and afferent pathways involving colorectal motility (Duelund-Jakobsen, Worsoe, Lundby, Christensen, & Krogh, 2016). Posterior tibial nerve stimulation involves outpatient treatments at least once a week where a needle electrode inserted above the ankle is positioned in close proximity to the tibial nerve. A neurostimulator delivers the stimulation for about half hour sessions while the patient is in the supine or sitting position. Treatment protocols differ and are time consuming, and implantable tibial nerve neurostimulation is an area of ongoing research (de Wall & Heesakkers, 2017).

Table 4. Studies Examining Percutaneous Posterior Tibial Nerve Stimulation for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Sanagapalli et al. 2018 *Efficacy of percutaneous posterior tibial nerve stimulation for the management of fecal incontinence in multiple sclerosis: A pilot study* UK Pre-Post $N_{Initial}$=33, N_{Final}=33	**Population:** Mean age=48yr; Sex: males=25, females=8; Disease course: RRMS=22, PPMS=3, SPMS=8; Severity: unspecified; Median disease duration=14yr. **Intervention:** Participants received neuromodulation therapy for 30min each wk for a minimum of 8wks. Responders continued therapy for 12wks total. **Outcomes/Outcome Measures:** Wexner Incontinence (WI) score; percent of responders according to a 50% improvement or a 10 point improvement on the WI; Rockwood score; visual analogue scale for bowel symptoms; Bristol Stool Form Scale.	1. 79% of participants met criteria for responding to treatment on the WI. 2. Responders (n=26) trended towards improvement on the WI scores (13.5±3.8 pre treatment vs. 7.0±2.8 post treatment). 3. Non-responders (n=7) trended towards worsening on the WI scores (13.4±3.9 pre treatment to 13.9±3.1 post treatment). 4. Mean scores on the depression and self-perception sub score of the Rockwood quality of life outcome improved only in

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
		responders (2.7±0.8 pre treatment to 3.1±0.9 post treatment; p=0.01). 5. Mean Bristol Stool Form Scale scores changed to more formed stools only in responders (5 (5-6) pre treatment to 4 (3-4) post treatment; p=0.02).

Discussion

One small study reported a trend towards improvement in bowel symptoms on the WI score in a subgroup of the study patients (Sanagapalli et al., 2018). In this study, 33 consecutively treated patients referred to a tertiary referral centre (University College, London Hospital) received percutaneous tibial nerve stimulation for at least eight weeks. Among the 26 patients defined as "responders", the only significant improvements post treatment occurred for the Bristol Stool Form Scale (to more formed stools) and on the depression and self-perception subscale of the Rockwood quality of life outcome measure. However, at baseline, responders also had significantly lower depression and self-perception scores.

Since non-responders trended towards worsening on the majority of the outcomes, predictors for a response to treatment would seem critical. The analysis of predictors for response to treatment is limited by the small sample size. However, 20 out of the 26 responders had relapsing-remitting MS compared to only two out of the seven non-responders ($p<0.5$). Other baseline demographics, including age and baseline comprehensive anal-rectal physiology test results, were not predictive of responders.

To deliver the protocol, a stimulation device (Urgent PC, Congentix) was utilized and a 34 gauge needle was inserted posterior to the tibia and proximal to the medial malleolus to achieve "flexion of big toe, fanning of all toes or tingling sensation of foot extending to all toes" (Sanagapalli et al., 2018, p. 683). The stimulation settings were individually adjusted according to patient comfort. The protocol for posterior tibial nerve stimulation requires access to specialized expertise and longer-term effects are not known. While this pilot study suggests that a sub-group of patients may benefit from treatment, further research is needed to determine its efficacy, patient selection, and feasibility in PwMS.

Conclusion

There is level 4 evidence (from one pre-post study; Sanagapalli et al. 2018) that percutaneous posterior tibial nerve stimulation may improve incontinence symptoms as measured by the Wexner Incontinence score in a sub-group of people with MS.

Percutaneous posterior tibial nerve stimulation may improve bowel incontinence symptoms in a select group of people with MS.

4.2 Biofeedback

Anorectal biofeedback for the treatment of bowel incontinence is based on the theory of operant conditioning (Engel, Nikoomanesh, & Schuster, 1974). Conditioning leads to a learned behaviour by the conscious modification of an organic function through an external stimulus. For example, to improve incontinence symptoms, a balloon inflated in the rectum may provide the external stimulus and a conscious effort is made to encourage contraction of the external sphincter (Preziosi et al., 2011). There is a lack of standardization concerning what constitutes a biofeedback protocol. In the protocol described by Preziosi et al. (2011), education about normal gut function and images of proper toileting techniques as well as balloon-assisted sensory training tailored to the patient's symptoms comprised part of the "package of care" for a biofeedback intervention in PwMS (Preziosi et al., 2011).

A review by Enck, Van der Voort, and Klosterhalfen (2009) describes biofeedback training and its use in treating fecal incontinence and pelvic floor dyssynergia with constipation, and outlines the shortcomings in published research. The techniques described for pelvic floor dyssynergia overall may be effective at improving related bowel symptoms. The patient and the therapist spend a great deal of time together with biofeedback interventions. The extensive patient-therapist interaction may increase the chance of a placebo response, an important consideration in biofeedback research and clinical care. Additionally, therapists with relevant expertise in this field may not be easily accessible.

Table 5. Studies Examining Biofeedback for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Preziosi et al. 2011 *Bowel biofeedback treatment in patients with multiple sclerosis and bowel symptoms* UK Pre-Post $N_{Initial}$=39, N_{Final}=30	**Population:** Median age=38yr; Sex: males=9, females=30; Disease course: unspecified; Median EDSS=5; Median disease duration=9yr. **Intervention:** Subjects received a median of 3 individualized biofeedback sessions spaced 4wks apart. The biofeedback protocol included recto-anal coordination, sensory training, improving evacuation, as well as balloon-assisted defecatory coordination tailored to baseline symptoms. Outcomes were assessed at baseline and after a median of 11wks. **Outcomes/Outcome Measures:** Wexner Constipation (WC) score; Wexner incontinence (WI) score; Anorectal physiology parameters including: anal resting, squeeze, and 5-second endurance pressures; threshold, urge, and maximum tolerated volumes; rectal sensitivity to balloon pressure; anal electrosensitivity; rectal electrosensitivity; % responders on WC and WI; regression analysis for predicting responders.	1. Median WC scores improved from 12 (range 5-19) pre treatment to 8 (range 4-14) post treatment (p=0.001). 2. Median WI scores improved from 12 (range 3-15) pre treatment to 4 (range 6-10) post treatment (p<0.001). 3. Median 5-second endurance anal squeeze pressure increased from 21 mmHg (interquartile range 11-24) pre treatment to 43 mmHg (interquartile range 46-59) post treatment (p=0.001). 4. No significant changes were found for all other anorectal physiology parameters. 5. 18 patients (46%) met responder criteria of improvement for the 25% percentile change in WC and/or WI scores. 6. Worse baseline WC and WI was associated with improvement on WC and WI scores. 7. No baseline characteristics were predictive of responders.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Wiesel et al. 2000 *Gut focused behavioural treatment (biofeedback) for constipation and faecal incontinence in multiple sclerosis* England Pre-Post N_{Inital}=13, N_{Final}=13	**Population:** Median age=38yr; Sex: males=5, females=8; Disease course: RRMS=7, SPMS=2; Median EDSS=4; Median disease duration=10yr. **Intervention:** Subjects received 2-5 individualized biofeedback sessions over a period of 4-6mo. Outcomes were assessed at a median follow-up of 14mo (range 5-23) after treatment. **Outcomes/Outcome Measures:** Self-reported change in bowel measures.	1. 5 subjects reported a marked or moderate benefit from biofeedback at follow-up. 2. In these subjects, constipation-related straining was reduced at follow-up. Laxative usage was decreased in 2 subjects and was stopped in 1 subject. 3. In these subjects, urgency and incontinence persisted or returned at follow-up, but incontinence was reported as less severe. 4. 8 subjects reported a slight or no benefit from biofeedback at follow-up. Of these, 2 had reported a benefit after treatment that was not sustained at follow-up. 5. Those patients who did respond had only mild or moderate disability and their disease had been stable in the yr before treatment started.

Discussion

Two pre-post studies reported improvement in bowel symptoms in a portion of the study sample using biofeedback protocols (Preziosi et al., 2011; Wiesel et al., 2000). The treatment protocols are complex, resource intensive, and individualized, making it challenging to discern which aspects of the protocol are most critical for success.

The first larger study reported significant improvements in WI and WC scores post treatment; however, less than half of the sample were categorized as responders (Preziosi et al., 2011). For those with predominant constipation symptoms, pelvic floor dyssynergia was targeted with progressively lower balloon distensions while side lying, followed by seated diaphragmatic and abdominal muscle training without the balloon in the rectum. For those with predominant incontinence symptoms, the patient was "encouraged to recognize urgency" with balloon rectal inflation and they received voluntary squeeze sphincter exercises. Some patients had overlapping symptoms of both constipation and incontinence, yet how their protocols were individualized is less clear. Depression scores according to the Hospital Anxiety and Depression Scale (HADS) significantly improved post treatment for the entire group while the HADS anxiety scores did not. Neither HADS depression nor anxiety scores at baseline were predictive of responders. Regression analysis did not identify any baseline predictors of responders, except those with worse WC and WI scores at baseline were more likely to improve on the WC and WI outcomes, respectively. Responders were also more likely to improve on the 5-second endurance anal squeeze pressure test, supporting a physiologic change associated with the bowel symptom score improvements.

The second study included fewer patients and provided mixed results for the efficacy of biofeedback treatment (Wiesel et al., 2000). The results were based on self-reports via a questionnaire and the biofeedback therapy was again individualized and non-homogenous. The five of 13 participants who

responded to biofeedback had mild to moderate disability compared to none of the eight participants with severe disability ($p<0.05$). Non-responders to biofeedback were also more likely to have had a progressive MS course in the last year (7 of 8 patients) compared to none of the responders. A limitation of this study is that the authors did not report post-treatment bowel symptom severity using a standard questionnaire. None of the anorectal physiological tests performed at baseline were predictive of a response to biofeedback in this small study. However, there may be less success for biofeedback techniques in patients with more advanced disability. Biofeedback is intended to allow the patient to improve their sphincter function, and an awareness of rectal distension and motor sensory training requires good neuromuscular function. This function may not be present with advanced MS, or when MS is actively progressing at the time of starting biofeedback training. In this study, 66% of the sample had reduced voluntary squeeze pressures and 85% had impaired pelvic floor coordination at baseline, and two patients with the most advanced levels of disability had impaired rectal sensation. Larger studies selecting those with similar bowel symptoms and sphincter function at baseline, and studies with simpler, more directed protocols may be warranted.

Conclusion

There is level 4 evidence (from two pre-post studies; Preziosi et al. 2011; Weisel et al. 2000) that biofeedback may improve neurogenic bowel symptoms in some people with MS.

Biofeedback may improve bowel symptoms in some people with MS. It remains unclear who may best respond to biofeedback treatment for improving bowel symptoms.

4.3 Transanal Irrigation

Transanal irrigation (TAI) is used as a treatment to achieve mechanical bowel emptying. The Peristeen® TAI system is indicated for the treatment of constipation and incontinence refractory to conservative management. This system involves a rubber catheter and inflatable cuff connected to a water bag. This bag is filled with lukewarm water and is attached to a handheld pump. Water is then flushed into the bowel using the pump and when the catheter is removed, both the irrigation water and bowel contents empty (Preziosi et al., 2012). The Peristeen® TAI system may be self-administered in people with adequate hand function in order to increase independence with bowel care, or may be administered by a care provider. Studies involving TAI for NBD symptoms have included people with spinal cord injury and have reported decreased time spent on the toilet and a reduced incidence of urinary tract infections (Christensen et al., 2006; Del Popolo et al., 2008).

Table 6. Studies Examining Transanal Irrigation for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Passananti et al. 2016 *Long-term efficacy and safety of transanal irrigation in multiple sclerosis* UK Pre-Post $N_{Initial}$=49, N_{Final}=27	**Population:** Mean age=51yr; Sex: males=12, females=37; Disease course: RRMS=18, PPMS=6, SPMS=25; Severity: unspecified; Mean disease duration=12yr. **Intervention:** Individuals with neurogenic bowel dysfunction who were unresponsive to standard therapy underwent transanal irrigation (TAI). TAI was performed daily at the outset, and then adjusted according to the individual. Assessments were completed at baseline and at a mean follow-up of 40mo. **Outcomes/Outcome Measures:** Neurogenic Bowel Dysfunction Score (NBDS); Self-reported episodes of incontinence.	1. Mean weekly episodes of incontinence decreased significantly after TAI compared to baseline (p<0.005). 2. There was a non-significant improvement on NBDS after TAI.
Preziosi et al. 2012 *Transanal irrigation for bowel symptoms in patients with multiple sclerosis* UK Pre-Post N_{Inital}=37, N_{Final}=30	**Population:** *Responders (n=16):* Mean age=48yr; Sex: unspecified; Disease course: unspecified; EDSS=5; Mean disease duration: unspecified. *Non-responders (n=14):* Mean age=53yr; Sex: unspecified; Disease course: unspecified; EDSS=6; Mean disease duration: unspecified. **Intervention:** All study participants received Peristeen transanal irrigation (TAI) training to use independently for a period of 6wks. **Outcomes/Outcome Measures:** Wexner Constipation (WC) score; Wexner Incontinence (WI) score.	1. At 6wks, WC scores significantly improved (p=0.001; Student's t-test) and WI scores significantly improved (p<0.001; Student's t-test). 2. Over half (16/30) of the patients responded to TAI. Responders were characterized by a 50% improvement in bowel symptoms or higher, as measured by Wexner scores. 3. Responders had higher WI scores (p=0.038), maximum tolerated volume to balloon distention (p=0.017), and rectal compliance (p=0.019) at baseline compared to non-responders.

Discussion

Two pre-post studies examined the effects of TAI on NBD symptoms in PwMS. Both studies used the same TAI device, Peristeen® TAI, which was the only TAI device reimbursed by the National Health Service at the time.

Passananti et al. (2016) recruited 49 sequential participants with a mean of 40 months follow-up. At last follow-up, 27 were successfully continuing with treatment (13 irrigating daily, 13 every other day, and one participant every third day). This 55% success rate with continued TAI is similar to that observed in spinal cord injury studies (Christensen & Krogh, 2010; Emmanuel, 2010). Reasons for discontinuing treatment were mainly a result of a dislike of the treatment or insufficient effect. Reported adverse events leading to treatment discontinuation included anal bleeding (n=1), abdominal cramps (n=1), uterine cancer (n=1), and colonic adenoma (n=1). One participant discontinued treatment due to a technical issue with the balloon bursting. The Peristeen® TAI device employed in this case was a device from before alteration of the catheter design in 2011. The main bowel symptoms reported before TAI included constipation (67%) and fecal incontinence (33%). Self-reported episodes of incontinence significantly improved from 4.8 per week (range 1-21) to 0.9 per week (range 0-7) with TAI. At the last follow-up there was also a shift in the

severity of the patients' NBDS from mostly very severe scores to mostly very minor scores. On regression analysis, the only significant predictor of continued TAI utilization was impaired anal electrosensitivity at baseline. In a comparison of annual health care utilization before and after TAI at one year follow-up, the reported number of treated UTIs decreased from 69 to 32, the number of hospitalizations decreased from 32 to 19, and the proportion of participants visiting a general practitioner decreased by 27%. The level of carer dependency and assistance from family members was also reduced by 44%. Despite these findings, this study did not find significant differences on the EuroQol-5D generic health utility index between TAI users and discontinuers. Scores on the EuroQol-5D worsened over time in both TAI users and discontinuers, and on further regression analysis, a nonsignificant utility gain was observed only among continued TAI users. It is possible that generic quality of life outcomes or utility indexes such as the EuroQol-5D may not be sufficiently sensitive to smaller but clinically meaningful changes in the MS population.

In the Preziosi et al. (2012) study, participants were categorized as responders if they had a 50% improvement on their Wexner score. Despite this rigid definition, 16/30 participants met the responder criteria. Similar to Passananti et al. (2016), a generic measure of quality of life (Short Form (36) Health Survey) was not sensitive to change over the study period. Participants experienced a greater improvement in incontinence than constipation symptoms, but both improved in tandem. Those with the largest improvement in symptoms had higher baseline incontinence scores, greater tolerance to rectal balloon distinction, greater rectal compliance, and a better perception of their health.

A key question remains in terms of how to identify the best candidates for TAI at the bedside. In the Passananti et al. (2016) study, among the 211 patients with neurogenic bowel symptoms seen over the enrollment period, only 49 enrolled in the study. It was felt that the remaining patients were sufficiently managing their symptoms without TAI. Barriers for trialing the TAI also require consideration, including psychological and funding barriers and access to health care professionals familiar with TAI. In routine clinical care, extensive physiological testing of anal rectal function is not a practical means of identifying those who may be more likely to respond (i.e., greater tolerance to rectal balloon distinction, greater rectal compliance, and reduced anal rectal sensation). Loss of anal rectal sensation may lead to more incontinence and those with higher incontinence scores at baseline may be more likely to continue with TAI. An incontinence history and examination may be a feasible way to select appropriate patients for TAI at the bedside. As theorized by Preziosi et al. (2012), the TAI water irrigation system may not reach far enough to mobilize the stools in patients with constipation from reduced colonic motility, making this system less effective for more predominant constipation symptoms. In the Passananti et al. (2016) study, the visual analogue sub-scale of the EuroQol-5D improved by 42% among continued TAI users and declined by six percent in discontinuers. Similar to the spinal cord injury literature, TAI may improve neurogenic bowel symptoms, decrease health care utilization, and improve patient reported quality of life.

Conclusion

There is level 4 evidence (from two pre-post studies; Passananti et al. 2016; Preziosi et al. 2012) that transanal irrigation may improve fecal incontinence in persons with MS.

There is level 4 evidence (from one pre-post study; Preziosi et al. 2012) that transanal irrigation may improve constipation symptoms in persons with MS.

Transanal irrigation may improve constipation and fecal incontinence in persons with MS, with possibly a greater effect on fecal incontinence.

4.4 Abdominal Massage

Abdominal massage is a technique that involves stroking, effleurage, palmar kneading, and vibration over the abdomen and large intestine (McClurg, Hagen, Hawkins, & Lowe-Strong, 2011; McClurg et al., 2018). Although the mechanisms through which abdominal massage exert an effect on bowel function are not fully understood, it has been suggested that this therapy can facilitate defecation by stimulating the bowel, decreasing colonic transit time, and promoting stronger colon propulsion (McClurg et al., 2018).

Table 7. Studies Examining Abdominal Massage for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
McClurg et al. 2018 *Abdominal massage plus advice, compared with advice only for neurogenic bowel dysfunction in MS: a RCT* UK RCT PEDro=8 N_{Inital}=191, N_{Final}=189	**Population:** *Massage Group (n=90)*: Mean age=53.5yr; Sex: males=14, females=76; Disease course: RRMS=45, PPMS=9, SPMS=36; Severity: unspecified; Disease duration=14.8yr. *Control Group (n=99):* Mean age=51.3yr; Sex: males=21, females=78; Disease course: RRMS=61, PPMS=13, SPMS=23, Benign=1; Severity: unspecified; Disease duration=13.9yr. **Intervention:** Participants were randomized to either the massage group, who received advice on bowel management and instruction on delivering a daily abdominal massage, or the control group, who received only advice on bowel management. All participants received weekly telephone calls from a research nurse. Abdominal massage was undertaken daily for 6wks. Outcomes were assessed at baseline, 6wks, and 24wks. **Outcomes/Outcome Measures:** Neurogenic Bowel Dysfunction Score (NBDS; primary analysis adjusted for sex, mobility and baseline score); 7-day bowel diary (including frequency of stools and number of times felt bowels emptied); Constipation Scoring System (CSS); Neurogenic Bowel Impact Score (NBIS); colonic transit tests.	1. There was no significant change in adjusted NBDS between groups from baseline to wk 6 or wk 24 (mean between-group change score difference at wk 24: -1.64, 95% CI -3.32 to 0.04; p=0.055). The median NBDS in the massage group at baseline was 6 (range 0-21) vs. 9 (range 0-22) in the control group. At the 24wk follow-up, the median NBDS for the massage group was 7.0 (range 0 -24) vs. 7.5 (range 0-24) in the control group. 2. There was no significant change in adjusted CSS scores between groups from baseline to wk 6 or wk 24 (mean between-group change score difference at wk 24: –0.88, 95% CI –2.03 to 0.27; p=0.1308) 3. There was a significant increase in the frequency of stool evacuations from baseline to wk 24 in the massage group compared to the control group (mean difference 0.62, 95% CI 0.03 to 1.21; p=0.039), and an increase in the number of times per wk participants felt they emptied their bowels completely (mean difference 1.08, 95% CI 0.41 to 1.76; p=0.002). 4. There was no significant difference in the mean change between groups in time spent on the toilet (mean difference -3.35min 95% CI -23.1 to 16.4min;

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
		p=0.7377) or the number of attempts to pass stool (mean difference 1.14 95% CI 0.92 to 3.19; p=0.2770) at wk 24. 5. For the subgroup that had colonic transit tests performed (11 in massage group and 12 in control group), 54.5% and 75% demonstrated slow colonic transit at baseline in the massage and control groups, respectively. 6. There were no significant changes on the NBIS.
McClurg et al. 2011 *Abdominal massage for the alleviation of constipation symptoms in people with multiple sclerosis: a randomized controlled feasibility study* UK RCT PEDro=6 N_{Inital}=30, N_{Final}=29	**Population:** *Massage Group (n=15)*: Mean age=52.4yr; Sex: males=5, females=10; Disease course: RRMS=6, PPMS=1, SPMS=8; Mean EDSS=2; Disease duration: unspecified. *Control Group (n=15):* Mean age=59.3yr; Sex: males=7, females=8; Disease course: RRMS=1, PPMS=3, SPMS=10, Benign=1; Mean EDSS=3; Disease duration: unspecified. **Intervention:** Participants were randomized to either the massage group, who received advice on bowel management and instruction on delivering a daily abdominal massage, or the control group, who received only advice on bowel management. Both groups received treatments over a 4wk period. Outcomes were assessed at baseline and wks 4 and 8. The 7-day bowel diary was assessed during the 7d prior to baseline, during the 4wk intervention, and for 7d prior to wk 8. **Outcomes/Outcome Measures:** Constipation Scoring System (CSS); Neurogenic Bowel Dysfunction Score (NBDS); 7-day bowel diary (frequency of defecation, time spent defecating, Bristol Stool Chart, number of fecal incontinence episodes, use of laxatives, feeling of incomplete evacuation).	1. CSS scores improved in both groups at wk 4 compared to baseline, but scores improved significantly more in the massage group than in the control group (between-group change score difference -5.0, 95% CI -8.1 to -1.8; p=0.003). At wk 8, there was no significant difference in CSS change scores between groups compared to baseline (p=0.112). 2. NBDS improved significantly more in the massage group compared to the control group at wk 8 compared to baseline (between-group change score difference -7.35, 95% CI -12.45 to -2.25; p=0.006). At wk 4, there was no significant between-group difference in NBDS change scores from baseline (p=0.086). 3. The frequency of defecation improved in both groups from baseline to wk 4, but improved significantly more in the massage group than in the control group (p=0.001). 4. The mean time spent defecating per day decreased in both groups from baseline to wk 4, from 10min to 6min in the massage group and from 12min to 10min in the control group. 5. One person in the massage group reduced their laxative intake at wk 4 compared with baseline, while there was no change in laxative use in the control group. 6. Most participants in both groups had Bristol Stool Chart Scale scores that increased from 1 or 2 (indicating constipation) at baseline to 3 or 4 (softer stools) at wk 4.

Discussion

One pilot study RCT and one larger multi-centre trial led by the same author investigated the effects of abdominal massage on bowel dysfunction in PwMS. McClurg et al. (2011) first investigated a four-week abdominal massage protocol combined with advice on bowel management and compared this to bowel advice alone. Participants who received the combination of abdominal massage and advice improved significantly more on the Constipation Scoring System (CSS) at the four-week follow-up and on the NBDS at the eight-week follow-up. An increase in bowel frequency and less time spent toileting was also observed in the massage group according to the bowel diaries. Based on these preliminary positive results, McClurg et al. (2018) conducted a larger study and extended the massage intervention period to six weeks of in-person consultation with the study therapist.

The larger McClurg et al. (2018) study did not find a significant between-group difference in change scores on the primary NBDS outcome when comparing again abdominal massage plus bowel management advice to advice alone. However, participants in the abdominal massage group did improve significantly more than the control group on frequency of stool evacuations and feelings of complete emptying according to the bowel diaries. A limitation of this 12-site multi-centre trial was the recruitment of participants with NBDS within the minor impact range in terms of bowel symptoms at baseline in both groups (i.e., mean scores <11 out of a worse possible score of 47). In addition, by random allocation, the massage group started with better scores at baseline, although the analysis adjusted for these baseline differences in scores. Interestingly, despite low mean scores on the NBDS in this study, approximately 30% of the participants in both groups utilized digital stimulation techniques to evacuate their bowels at baseline. This suggests that some participants recruited already had neurogenic bowel management strategies in place. Other secondary outcomes including the CSS, time spent on the toilet, or number of attempts to pass stool also did not reach statistical significance for between-group differences at 24 weeks.

The McClurg et al. 2018 study also included a process evaluation, a quality of life and an economic analysis, and a small subgroup of 23 participants had transit time evaluations. All participants in both groups received bowel management advice by a member of the research team, including advice on diet and toileting techniques. The massage group watched an instructional video and a trained health care provider then taught the massage techniques directly to the person doing the massage, either the PwMS or their care provider. Massage was intended to be done 10 minutes daily, however, it is unclear how compliant participants were with the massage out to 24 weeks. Qualitative data supported participants' perceived benefit from the intervention and fewer bowel medications were started in the intervention group. Change in quality of life did not differ significantly between groups according to the generic EuroQol-5D-5L questionnaire and a novel patient-reported NBD questionnaire (Neurogenic Bowel Impact Score). However, the Neurogenic Bowel Impact Score strongly correlated with the NBDS. The authors suggest a need for outcome measures more sensitive to meaningful changes in bowel symptoms for PwMS. The analysis of quality of life adjusted life years reported the massage intervention to be more costly than standard care. No conclusions could be made concerning the effect on transit times because of the small sample limitations. Future research exploring lower cost abdominal massage protocols for select patients may be warranted.

Conclusion

There is conflicting evidence (from two randomized controlled trials; McClurg et al. 2011; 2018) regarding whether or not abdominal massage combined with bowel management advice improves constipation outcomes as per the Neurogenic Bowel Dysfunction Score or the Constipation Scoring System compared to advice alone in persons with MS.

There is level 1a evidence (from two randomized controlled trials; McClurg et al. 2011; 2018) that abdominal massage combined with bowel management advice may improve the frequency of stool evacuations compared to advice alone in persons with MS.

It is unclear if abdominal massage combined with advice on bowel management improves constipation more than advice alone in persons with MS.

Abdominal massage combined with advice on bowel management may improve the frequency of stool evacuations compared to advice alone.

4.5 Standing Frames

Standing frames allow for regular supported standing in persons with impaired mobility. This may improve complications secondary to immobility such as muscle weakness, pressure sores, and constipation (Freeman et al., 2019). Standing frames are used for rehabilitation in neurological clinical populations such as spinal cord injury, stroke, and MS (Theo Davies & Sons Ltd, 2020).

Table 8. Studies Examining Standing Frames for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Freeman et al. 2019 *Assessment of a home-based standing frame programme in people with progressive multiple sclerosis (SUMS): a pragmatic, multi-centre, randomised, controlled trial and cost-effectiveness analysis* UK	**Population:** *Standing frame group (n=71):* Mean age=58.5yr; Sex: males=31, females=40; Disease course: PPMS=28, SPMS=43; Mean EDSS=7.3; Mean disease duration: unspecified. *Usual care group (n=69)*: Mean age=60.1yr; Sex: males=19, females=50; Disease course: PPMS=16, SPMS=53; Mean EDSS=7.2; Mean disease duration: unspecified. **Intervention:** Participants were randomly assigned to a standing frame programme plus usual care or to usual care alone. The standing frame programme consisted of two 60min home-based physiotherapy sessions and two 15min telephone calls. Participants	1. Results of the bladder and bowel control scales were not reported. 2. Constipation or diarrhea were reported as adverse events lasting <7d in 7 participants in the standing frame group and 17 participants in the usual care group. 3. Bowel difficulties were reported as adverse events lasting ≥7d in 0 participants in the standing frame group and 3 participants in the usual care group.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
RCT PEDro=7 $N_{Initial}$=140, N_{Final}=122	were asked to stand in the Oswestry frame for 30min 3x/wk for 20wks. Outcomes were assessed at baseline, and 20 and 36wks after randomisation. **Outcomes/Outcome Measures:** Bladder and bowel control scales.	
Hendrie et al. 2015 *A pilot mixed methods investigation of the use of Oswestry standing frames in the homes of nine people with severe multiple sclerosis* UK Pre-Post $N_{Initial}$=9, N_{Final}=9	**Population:** Mean age=54yr; Sex: males=3, females=6; Disease course: PPMS=2, SPMS=7; Mean EDSS=7.5; Mean disease duration=11.6yr. **Intervention:** Participants used an Oswestry standing frame at home for 30min/d, 3d/wk for either 24, 20, or 16wks. In the next phase of the study, participants chose if they wanted to continue standing and for how long for another 12wks. Assessments of primary outcomes occurred every 2wks in the first phase, and then at the end of the second phase. Secondary outcomes were recorded daily in a diary by the participants. **Outcomes/Outcome Measures:** Bowel frequency.	1. There were no improvements in frequency of bowel movements in the 4 individuals who reported having constipation.

Discussion

Hendrie et al. (2015) conducted a mixed-methods study to investigate the effect of regular standing using Oswestry frames on complications due to immobility in nine persons with progressive forms of MS, including bowel function. Of the four participants who reported having constipation at the outset of the study, no improvements were recorded in bowel frequency. In this study, PwMS used an Oswestry standing frame at home for 16, 20, or 24 weeks, for 30 minutes per day, three times per week. After this first phase of the study, participants chose whether they wanted to continue standing and for how long for another 12 weeks. Change in bowel function was measured quantitatively using bowel frequency, which was recorded daily in participant diaries.

One other study by Freeman et al. (2019) planned to examine the effect of a standing frame program in addition to usual care compared to usual care alone on bowel control scales as one of the secondary outcomes. However, these bowel control scale data were not presented. Instead, the frequency of new bowel symptoms from patient diaries were reported in an adverse events table, and these were encouragingly lower in the standing frame group. Diarrhea symptoms were not separated from constipation symptoms, and all other new bowel symptoms fell under an adverse event category titled “bowel difficulties”. This study did find a greater improvement in general motor function in favour of the standing frame group for their primary outcome, the Amended Motor Club Assessment Score. It is plausible that regular standing improves gut motility, leading to an initial increase in incontinence episodes in an individual with chronic constipation. Persistent standing may actually lead to improved overall bowel function by improving constipation. Further research may help better understand the role of standing in bowel motility and control in MS.

Conclusion

There is level 4 evidence (from one pre-post study; Hendrie et al. 2015) that standing frames may not improve bowel frequency in persons with progressive MS.

There is level 1b evidence (from one randomized controlled trial; Freeman et al. 2019) that standing frames combined with usual care may be associated with fewer new bowel symptoms compared to usual care alone in persons with advanced levels of MS disability.

Standing frames may not be beneficial for improving bowel frequency in persons with progressive MS, but may result in fewer new bowel related symptoms.

4.6 Self-Management Programs

4.6.1 Orem's Model

Comprehensive or symptom specific self-management approaches are a growing area of research in MS (Arafah, Bouchard, & Mayo, 2017). Orem's original self-care nursing theory was proposed in 1995 (Denyes, Orem, Bekel, & SozWiss, 2001). Orem's self-care model has been studied in other chronic diseases and may be an effective model for caring for PwMS (Afrasiabifar, Mehri, & Ghaffarian Shirazi, 2020). In Orem's self-care model the role of the health care professional is to provide patients with support and education so that they may be empowered to perform self-care outside of clinical settings (Denyes et al., 2001).

Table 9. Studies Examining Orem's Model for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	**Methods**	**Results**
Dahmardeh et al. 2017 *Effect of self-care program based on Orem's model on complications of disease in patients with multiple sclerosis* Iran PCT $N_{Initial}$=88, N_{Final}=unspecified	**Population:** *Intervention group (n=44)*: Mean age=34.1yr; Sex: males=8, females=31; Disease course: unspecified; Severity: unspecified; Mean disease duration: 5.72yr. *Control group (n=44)*: Mean age=35.6yr; Sex: males=13, females=26; Disease course: unspecified; Severity: unspecified; Mean disease duration: 4.81yr. **Intervention:** Participants were assigned to the intervention or control group. Participants in the intervention group received nine self-care training and educational 45min program sessions based on Orem's Model, which were designed and conducted based on the patients' needs. Participants' needs	1. Within the intervention group, the self-care program resulted in a significant decrease in constipation from 38% to 12% (p=0.0001) post intervention compared to pre intervention. 2. No between-group analyses were reported. 3. No results from the control group were reported.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	assessment forms were evaluated before and 3mo after the intervention. **Outcomes/Outcome Measures:** Percent of participants with self-reported MS symptoms on a self-report symptom checklist including constipation and fecal incontinence.	

Discussion

One study reported an improvement in constipation symptoms following intervention with Orem's self-care program in PwMS (Dahmardeh et al., 2017). The authors described their research as quasi-experimental, conducted using a before and after design. It included assignment of participants into a control and interventional group; however, only the pre-post results for the intervention group were reported. In this study, other symptoms such as cramps, fatigue, and self-esteem were also reported to improve in the intervention group. These symptoms, in addition to bowel symptoms, are important factors affecting patients' quality of life. Limitations of this study include that no data were reported for the control group and only symptoms that improved in the intervention group were discussed. Two other studies (Madani, Navipoor, & Roozbayani, 2009; Masoudi, Mohammadi, Ahmadi, & Hasanpour-Dehkordi, 2009) obtained similar results for constipation symptoms in PwMS; however, they did not meet inclusion criteria for this module as they were not written in the English language. Further research is warranted in order to better understand the value of Orem's self-care model for managing bowel symptoms in MS.

Conclusion

There is level 4 evidence (from the pre-post analysis of one prospective controlled trial; Dahmardeh et al. 2017) that Orem's Model of self-care may reduce constipation in persons with MS.

Orem's self care model may help to improve constipation in persons with MS.

4.7 Apitherapy

Apitherapy is a complementary treatment that dates back to ancient times for the treatment of pain and autoimmune diseases (Hegazi, 2012). Honeybee products such as honey, pollen, venom, propolis, royal jelly, and apilarnil have been utilized for medicinal purposes. Reports on the use of apitherapy are mostly anecdotal, although at least four clinical trials have been published involving PwMS with negative or inconclusive results (Castro et al., 2005; Hauser et al., 2004; Helal, Hegazi, & Al-Menabbawy, 2014; Wesselius et al., 2005). Apitherapy is currently not standard clinical care, nor is it routinely accessed as a complementary treatment. Bee venom is composed of peptides proposed to act therapeutically through

immunogenic or neuroprotective effects (Castro et al., 2005; de Souza, Goncalves, Gomez, Vieira, & Ribeiro, 2018).

Table 10. Studies Examining Apitherapy for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Helal et al. 2014 *Apitherapy have a role in treatment of multiple sclerosis* Egypt PCT $N_{Initial}$=50, N_{Final}=50	**Population:** Mean age=38.7yr; Sex: males=12, females=38. No further information provided. **Intervention:** Participants assigned to Group I (n=25) were treated with bee stings 3x/wk for 12mo, beginning with one sting and working up to 25 per session. Participants also received honey, pollen, royal jelly, and propolis. Group II (n=25) remained on standard medical care. All participants maintained regular corticosteroid or interferon treatment and received additional nutritional supplementation. Full neurological and general assessments were completed at baseline (not reported) and then every 2mo after. **Outcomes/Outcome Measures:** Patient reported bowel and bladder severity on a scale of 1-7 (1 being no symptoms).	1. At 12mo scores for bowel and bladder control trended towards improvement overtime in both groups; intervention group scores decreased from 4.12±0.580 at 2mo to 2.12±0.226 at 12mo; control group scores decreased from 3.09±0.35 at 2mo to 2.63±0.16 at 12mo. 2. Four of nine (44%) participants with paraparesis in the intervention group improved in constipation and bowel control from baseline to 12mo (no statistical analysis reported).

Discussion

Only one trial reported on bowel symptoms combined with bladder symptoms in PwMS comparing various types of apitherapy (including bee stings, honey, pollen, royal jelly, and propolis) delivered alongside standard medical care (Helal et al., 2014). The apitherapy protocol was well tolerated, and no adverse events were reported. The bowel and bladder symptoms combined were evaluated on a scale of 1 to 7, with higher scores indicating more severe symptoms. Bowel and bladder were included among 20 different symptom categories assessed. While the mean scores were lower in both groups in the bowel and bladder and other symptom categories over time, this study had many limitations. Symptom severity scores were reported to an assessor who was not blinded to treatment group allocation, there was no separate or validated outcome measure for bowel symptoms, and group allocation was not randomized. At baseline, there were between-group differences in symptom severity scores for many symptoms including bowel and bladder, and there was no between-group statistical analysis of symptom change scores completed. The authors did report the anecdotal observation that a minority of patients within a subgroup of their population (patients with paraparesis) had improvement in bowel symptoms. The low-quality evidence and results from this study do not support that apitherapy improves bowel or other MS symptoms.

Conclusion

There is level 2 evidence (from one prospective controlled trial; Helal et al. 2014) that apitherapy does not improve bowel and bladder symptoms as measured by an ordinal scale compared to standard care in persons with MS.

Apitherapy may not improve bowel and bladder symptom severity ratings in persons with MS.

4.8 Foot Reflexology

Reflexology is a non-invasive complementary medicine that dates back to ancient China and Egypt. Foot reflexology applies pressure on specific reflex points of the foot. The Rwo Shur method involves thumb sliding in a slow speed at a depth of one to three millimetres. Reflexology is proposed to increase blood flow to the area, reduce stress, and create a sense of well-being (Sajadi, Davodabady, Naseri-Salahshour, Harorani, & Ebrahimi-Monfared, 2020). Reflexology has been explored for improving constipation symptoms in children with cerebral palsy (Ozkan & Zincir, 2018) and chronic constipation (Bishop, McKinnon, Weir, & Brown, 2003), as well as females with idiopathic constipation (Woodward, Norton, & Barriball, 2010).

Table 11. Studies Examining Foot Reflexology for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Sajadi et al. 2020 *The effect of foot reflexology on constipation and quality of life in patients with multiple sclerosis. A randomized trial* Iran RCT PEDro=6 $N_{Initial}$=63, N_{Final}=63	**Population:** *Intervention group (n=33)*: Mean age=34.52yr; Sex: males=2, females=31; Disease course: unspecified; EDSS≤4; Disease duration: unspecified. *Control group (n=30)*: Mean age=32.1yr; Sex: males=2, females=28; Disease course: unspecified; EDSS≤4; Disease duration: unspecified. **Intervention:** Participants were randomly assigned to the intervention or control group. Participants in the intervention group received the Rwo Shur method of reflexology 2x/wk for 6wks, with 30-40min spent on each foot. The control group received a regular foot massage for the same period of time. Both groups were told not to take anti-constipation medications for the duration of the study. **Outcomes/Outcome Measures:** Constipation Assessment scale (CAS); Stool frequency.	1. Following intervention, the total CAS scores significantly improved compared to control group scores (intervention: 6.39±3.51, control: 14.97±4.92; p=0.001). 2. Following intervention, stool frequency increased significantly in the intervention group compared to the control group (intervention: 2.48±0.91d, control: 4.17±1.17d; p=0.001).

Discussion

A single RCT by Sajadi et al. (2020) studied the efficacy of foot reflexology compared to foot massage alone on constipation and quality of life in PwMS. Exclusion criteria included vascular disease, a common comorbidity in PwMS (Marrie et al., 2015; Marrie et al., 2010). At baseline, both groups had moderate to severe constipation on the CAS, and these scores improved only in the reflexology group into the mild constipation range. Stool frequency accordingly also increased in the reflexology group, yet it is unclear by the methods how stool frequency data were collected. Participants were instructed not to change their diet or mobility routines and not to take bowel medications over the six weeks; however, these potential confounders were not tracked over the intervention period. Although constipation CAS scores improved and stool frequency almost doubled in the reflexology group, quality of life scores on the Short Form (36) Health Survey and the Short Form (36) Health Survey social function and emotional wellbeing sub-scores did not reach a statistically significant between-group difference at last follow-up. Reflexology may offer a non-invasive approach for the management of constipation in PwMS. It is unclear if PwMS with disability that is more advanced or with impaired sensory or proprioceptive loss of the lower extremities would affect the response to reflexology. Other limitations to consider include the short follow-up, the small single-centre RCT design, and that reflexology may be dependent on the expertise of the provider and challenging to access.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Sajadi et al. 2020) that foot reflexology may improve constipation in persons with MS with EDSS<4.

Reflexology may improve short-term constipation symptoms in persons with MS with lower levels of physical disability.

4.9 Hyperbaric Oxygen

Hyperbaric oxygen therapy has been well established for decompression sickness (Mayo Clinic, 2018; Moon, 2014). A compression chamber delivers up to 100% oxygen leading to increased measured arterial partial pressures of oxygen. Contraindications to this therapy include respiratory diseases, glaucoma, ostitis, sinusitis, and abnormal electroencephalography results or seizure disorders (Oriani et al., 1990). In the 1970s, studies were performed on animal models of MS which later led to RCTs on human patients in the 1980s and early 1990s. A Cochrane review last updated in 2011 reported nine small trials (504 participants total) evaluating hyperbaric oxygen on MS disability or relapse outcomes. Only two trials reported positive outcomes in terms of improvement on the Expanded Disability Status Scale. The authors concluded that there is no evidence for hyperbaric oxygen treatment to improve disability or prevent disability progression in MS. With respect to bowel function, only three studies have reported on combined bowel and bladder functional system outcomes.

Table 12. Studies Examining Hyperbaric Oxygen for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Oriani et al. 1990 *Long-term hyperbaric oxygen in multiple sclerosis: A placebo-controlled, double-blind trial with evoked potentials studies* Italy RCT PEDro=6 $N_{initial}$=44, N_{final}=44	**Population:** *Hyperbaric oxygen group (n=22):* Mean age=37.8yr; Sex: males=4, females=18; Disease course: unspecified; Mean EDSS=3.39; Mean disease duration=14.5yr. *Placebo group (n=22):* Mean age=41.7yr; Sex: males=2, females=20; Disease course: unspecified; Mean EDSS=2.97; Mean disease duration=11.9yr. **Intervention:** Participants were randomly allocated to the hyperbaric oxygen (HBO) or placebo group. The HBO group received 100% oxygen at 2.5 atm abs, and the placebo group received air (a mixture of oxygen (20%) and nitrogen (80%)) at the same pressure. Both treatments were administered for 90min 5d/wk for 1mo, followed by "booster" treatments of 90min 5d/wk for 1yr. Outcomes were reported immediately before treatment, and at 1, 6, and 12mo time points from start of treatment. **Outcomes/Outcome Measures:** Functional Systems Scale (FSS): bowel and bladder subscale.	1. There was no between-group statistical analysis reported for between-group mean bowel and bladder FSS scores. 2. For the HBO group, there were no significant within-group differences in mean bowel bladder scores comparing all time points: mean FSS scores were 0.64 at baseline, 0.56 at 1mo, 0.45 at 6mo, and 0.44 at 1yr. Number of participants with stable or changed scores were: At 1mo, 20 participants unchanged and 2 improved. At 6mo, 18 unchanged and 4 improved. At1yr, 17 unchanged and 5 improved. 3. For the placebo group, there were no significant within-group differences in mean bowel bladder scores comparing all time points: mean FSS scores were 0 at baseline and stayed at 0 at 1mo, 0.13 at 6mo, and 0.13 at 1yr. After 6mo and 1yr, 20 participants had unchanged FSS bowel scores and 2 worsened.
Barnes et al. 1987 *Hyperbaric oxygen and multiple sclerosis: final results of a placebo-controlled, double-blind trial* England RCT PEDro=7 $N_{initial}$=120, N_{final}=117	**Population:** *Oxygen Group (n=60)*: Mean age=41.8yr; Sex: males=23, females=37; Disease course: static=32, progressive=28; Mean EDSS=5.1; Mean disease duration=12.3yr. *Placebo Group (n=57)*: Mean age=42.1yr; Sex: males=26, females=31; Disease course: static=35, progressive=22; Mean EDSS=5.5; Mean disease duration=12.8yr. **Intervention:** Subjects were randomized to either the oxygen group, who received treatment with 100% oxygen at 2 atmospheres for 90min daily for 20 exposures, or to the placebo group, who received treatment with normal air at normal pressure for the same length of time within the same compression chamber. **Outcomes/Outcome Measures:** Kurtzke Functional Systems Scores (KFSS), including bowel and bladder function.	1. The short-term subjective improvement that was found in mean bladder/bowel function on the KFSS (Barnes et al. 1985) was sustained at 6mo but not at 1yr.
Barnes et al. 1985 *Hyperbaric oxygen and multiple sclerosis: short-term results of a placebo-*	**Population:** *Oxygen Group (n=60)*: Mean age=41.8yr; Sex: males=23, females=37; Disease course: static=32, progressive=28; Mean EDSS=5.1; Mean disease duration=12.3yr. *Control Group (n=57)*: Mean age=42.1yr; Sex: males=26, females=31; Disease course: static=35, progressive=22;	1. Mean KFSS significantly improved in 12 hyperbaric oxygen group patients compared to 3 control group patients after treatment (p=0.0338) on the KFSS subjective functional systems bladder/bowel parameter only.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
controlled, double-blind trial England RCT PEDro=7 N_{Inital}=120, N_{Final}=117	Mean EDSS=5.5; Mean disease duration=12.8yr. **Intervention:** Subjects were randomized to either the oxygen group, who received treatment of 100% oxygen at 2 atmospheres for 90min daily for 20 exposures (20d), or to the control group, who received treatment of normal air at normal pressure for the same length of time within the same compression chamber. Outcomes were assessed before and after treatment. **Outcomes/Outcome Measures:** Kurtzke Functional Systems Scores (KFSS), including bowel and bladder function.	

Discussion

Three studies reported hyperbaric oxygen therapy as a non-efficacious treatment for neurogenic bowel in PwMS (Barnes et al., 1987; Barnes et al., 1985; Oriani et al., 1990). Two of these studies were by the same authors reporting on different follow-up periods. Although the first study reported short-term improvements in KFSS bladder and bowel scores after 20 treatments (Barnes et al., 1985), this improvement was not sustained at the one-year follow-up (Barnes et al., 1987). Complications included one patient with a tympanic membrane perforation. Patients also reported increased subjective fatigue and several patients reported nausea, headaches, or blurred vision. The study by Oriani et al. (1990) provided hyperbaric treatments for one year to explore the long-term effects of continued treatment. Again, no significant improvements on the KFSS bowel/bladder outcome were found. A limitation with the hyperbaric oxygen studies is that both bladder and bowel outcomes are reported as a single system KFSS score. Furthermore, the participants in these studies had lower (less impaired) scores on the bowel and bladder KFSS, indicating that the majority only had mild bladder symptoms. However, bladder and bowel symptoms do frequently correlate and therefore, to be inclusive, research studies reporting on the bowel and bladder KFSS are included in this module.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Barnes et al. 1985; 1987) that hyperbaric oxygen treatment does not improve neurogenic bowel and/or bladder symptoms in persons with MS as measured by the Kurtzke Functional Systems Scores for bowel and bladder.

Hyperbaric oxygen treatment may not improve bowel and/or bladder symptoms in persons with MS.

4.10 Extracranial Venous Therapy

Extracranial venous therapy (EVT) was proposed as an alternative treatment for MS based on a theory that MS was strongly associated with a condition described as chronic cerebrospinal venous insufficiency (CCSVI) (Zamboni et al., 2009). EVT involves venoplasty of one or both internal jugular veins thought to have a stenosis or occlusion. A catheter with a balloon is advanced into the jugular vein, the balloon is then inflated to dilate the vein, and a stent may be placed. A review of EVT did not support that venous stenosis or occlusions as proposed by the CCSVI theory were associated with MS, or that EVT was efficacious in treating MS (Tsivgoulis et al., 2015). The Tsivgoulis et al. (2015) review included diagnostic studies, open label studies, and RCTs from independent investigators. The authors concluded that EVT may exacerbate MS disease and the procedures were associated with other serious adverse events. EVT is not an approved treatment for MS, however some PwMS sought out EVT procedures outside of their home countries (Vera et al., 2012).

Table 13. Studies Examining Venous Therapies for Neurogenic Bowel in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Sadovnick et al. 2017 *Patient-reported benefits of extracranial venous therapy: British Columbia CCSVI Registry* Canada Post-Test $N_{Initial}$=102, N_{Final}=81	**Population:** Mean age=55.5yr; Sex: males=28, females=74; Disease course: RRMS=65, PPMS & SPMS=23, Other=6, Don't know=8; Severity: unspecified; Disease duration: unspecified. **Intervention:** MS patients who self-reported prior venoplasty procedures completed telephone questionnaires at the time of registry enrollment (initial interview) and at 6, 12, and 24mo. **Outcomes/Outcome Measures:** Patient-reported bowel control relative to recalled pre-venoplasty treatment status.	1. Compared to pre-treatment with venoplasty, better bowel control was reported by 25.9% of participants at the initial interview, 6.2% at the 6mo follow-up, and 9.9% at the 1yr follow-up. 2. Compared to pre-treatment with venoplasty, the same bowel control was reported by 71.6% of participants at the initial interview, 86.4% at the 6mo follow-up, and 81.5% at the 1yr follow-up. 3. Compared to pre-treatment with venoplasty, worse bowel control was reported by 2.5% of participants at the initial interview, 7.4% at the 6mo follow-up, and 8.6% at the 1yr follow-up.

Discussion

One British Columbia registry reported on bowel control in PwMS after they had undergone EVT (Sadovnick et al., 2017). The EVT procedures were done through medical tourism and the exact dates of the procedures were not reported. Recall bias is a limitation since data on symptom severity was not collected prior to the procedure. However, 71.6% of participants reported the same level of bowel control at their first post-EVT interview assessment with the registry, indicating that the majority of patients did not recall a change in bowel control after their procedures. Of concern, the registry also reported 12 participants with an adverse event during the procedure and 18 participants reported serious complications within a month. The adverse events included a tear in the azygos vein, bursting of the catheter balloon, haematoma in groin, thrombosis, bleeding, stroke, chest pain, depression, stroke, and arrythmia. In this registry, self-reported general health condition, fatigue, and other MS symptoms initially

improved at the first post-EVT assessment for many participants; however, these self-reported improvements were not sustained in the majority of participants at the six-month or one-year follow-up. In the case of bowel control specifically, some patients reported worsening of bowel control over time. EVT interventions or further EVT research in MS are not recommended.

Conclusion

There is level 4 evidence (from one post-test study; Sadovnick et al. 2017) that extracranial venous therapy may not improve patient reported bowel control in persons with MS.

Extracranial venous therapy may not improve bowel control in persons with MS.

5.0 Summary

There is level 4 evidence (from one pre-post study; Parke et al. 1989) that intrathecal baclofen may improve neurogenic bowel management in persons with MS who received intrathecal baclofen therapy for severe lower limb spasticity.

There is level 4 evidence (from one pre-post study; Minardi & Muzzonigro, 2005) that sacral neuromodulation may improve constipation symptoms in persons with MS as measured by the Wexner Constipation score.

There is level 4 evidence (from one pre-post study; Singleton et al. 2016) that functional electrical stimulation of abdominal muscles may improve gut motility in persons with MS.

There is level 4 evidence (from one pre-post study; Sanagapalli et al. 2018) that percutaneous posterior tibial nerve stimulation may improve incontinence symptoms as measured by the Wexner Incontinence score in a sub-group of people with MS.

There is level 4 evidence (from two pre-post studies; Preziosi et al. 2011; Weisel et al. 2000) that biofeedback may improve neurogenic bowel symptoms in some people with MS.

There is level 4 evidence (from two pre-post studies; Passananti et al. 2016; Preziosi et al. 2012) that transanal irrigation may improve fecal incontinence in persons with MS.

There is level 4 evidence (from one pre-post study; Preziosi et al. 2012) that transanal irrigation may improve constipation symptoms in persons with MS.

There is conflicting evidence (from two randomized controlled trials; McClurg et al. 2011; 2018) regarding whether or not abdominal massage combined with bowel management advice improves constipation outcomes as per the Neurogenic Bowel Dysfunction Score or the Constipation Scoring System compared to advice alone in persons with MS.

There is level 1a evidence (from two randomized controlled trials; McClurg et al. 2011; 2018) that abdominal massage combined with bowel management advice may improve the frequency of stool evacuations compared to advice alone in persons with MS.

There is level 4 evidence (from one pre-post study; Hendrie et al. 2015) that standing frames may not improve bowel frequency in persons with progressive MS.

There is level 1b evidence (from one randomized controlled trial; Freeman et al. 2019) that standing frames combined with usual care may be associated with fewer new bowel symptoms compared to usual care alone in persons with advanced levels of MS disability.

There is level 4 evidence (from the pre-post analysis of one prospective controlled trial; Dahmardeh et al. 2017) that Orem's Model of self-care may reduce constipation in persons with MS.

There is level 2 evidence (from one prospective controlled trial; Helal et al. 2014) that apitherapy does not improve bowel and bladder symptoms as measured by an ordinal scale compared to standard care in persons with MS.

There is level 1b evidence (from one randomized controlled trial; Sajadi et al. 2020) that foot reflexology may improve constipation in persons with MS with EDSS<4.

There is level 1b evidence (from one randomized controlled trial; Barnes et al. 1985; 1987) that hyperbaric oxygen treatment does not improve neurogenic bowel and/or bladder symptoms in persons with MS as measured by the Kurtzke Functional Systems Scores for bowel and bladder.

There is level 4 evidence (from one post-test study; Sadovnick et al. 2017) that extracranial venous therapy may not improve patient reported bowel control in persons with MS.

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