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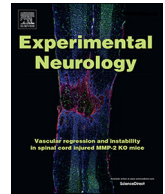
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Review Article

Translating promising strategies for bowel and bladder management in spinal cord injury



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ABSTRACT

Loss of control over voiding following spinal cord injury (SCI) impacts autonomy, participation and dignity, and can cause life-threatening complications. The importance of SCI bowel and bladder dysfunction warrants significantly more attention from researchers in the field. To address this gap, key SCI clinicians, researchers, government and private funding organizations met to share knowledge and examine emerging approaches. This report reviews recommendations from this effort to identify and prioritize near-term treatment, investigational and translational approaches to addressing the pressing needs of people with SCI.

1. Introduction

Restoring bowel and bladder function following spinal cord injury (SCI) is a top consumer and research priority (Anderson, 2004; Ditunno et al., 2008; Liu et al., 2009; Braaf et al., 2017). Unfortunately, current levels of research activity and emerging translational approaches do not reflect this importance. The inability to control voiding is a persistent problem for persons with SCI that reduces participation in activities and deprives them of privacy and dignity. Because of the clear impact bowel and bladder dysfunction has on the quality of life of these individuals, the Craig H. Neilsen Foundation conducted a workshop to identify, target and accelerate research areas ready for translation. This report provides an overview of recommendations developed during the workshop, reviews current efforts that arose from the workshop, and provides descriptions of activities needed from the larger community to advance promising strategies for bowel and bladder management after

SCI.

Experts in SCI urogenital research, physiology, autonomic function, biomedical engineering, clinical care, and patient advocacy formed an advisory committee to assist in developing the workshop agenda, participant list and plans to disseminate workshop outcomes (Appendix 1). The event was held March 3–4, 2017 in Washington, D.C. with three main goals: identify the most promising approaches for which a 10-year translational timeline would be considered both reasonable and achievable; bring together researchers and clinicians to exchange information and increase communication and cooperation between them; and build collaborations between leaders in medical, industrial, patient advocacy, research, regulatory and funding organizations to accelerate future approaches that provide more effective treatment options.

Participants worked in small groups on structured roadmap building activities to develop a list of focus areas. First, clinicians, consumer representatives and industry representatives shared their research and

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¹ See Appendix.

experience to present the issues. Next, breakout groups shared additional insight, deliberated and prioritized issues into a list of problems to solve. Throughout the workshop, focus was directed to the most pressing constituent needs and identification of opportunities to address these needs. Small group recommendations were presented and discussed at the end of the two-day event. Interestingly, 5 out of the 6 small groups identified the same first step for improving bowel and bladder management. This recommendation, to identify and disseminate treatment guidelines, was described as readily achievable.

As the main outcome of the workshop, these working groups developed collective recommendations that were organized into five thematic areas. They range from steps described as immediately achievable to areas that require further investigation and longer development timelines. Recommendations also span broad but distinct skill areas such as communication and biomedical engineering.

2. Summary of recommendations

Theme/focus Area	Description
Education & clinical care standards	Update, disseminate, and provide guidance to consumers and clinicians on current therapeutic approaches. Create a consumer profile to characterize needs, including lifestyle and poly-pharmacy.
Bowel physiology	Prioritize efforts to understand gastrointestinal physiology to elucidate the effects of SCI and therapeutic interventions on bowel function, including its relationship to the urinary system.
Sensory awareness	Identify technology and approaches that can measure key indicators of the need to void or system dysfunction and thereby enable patient awareness in daily activities and potential for improved diagnosis.
Neuromodulation	Use existing systems or create novel technologies that can replace or restore control of gastrointestinal and urinary system functions.
Rehabilitation activity & exercise	Quantify evidence and build an understanding of how seemingly unrelated approaches (e.g., exoskeletons, treadmills, overground walking, and other therapies) have a positive effect on bowel and bladder function.

2.1. The problem and how it is managed

Neurogenic bladder is a broad term for bladder and sphincter dysfunction due to a neurological disease or condition. In SCI, urologic clinical manifestations depend on the level and extent of the injury (Wein and Dmochowski, 2011). A complete lesion above the sacral spinal cord results in detrusor overactivity, smooth muscle sphincter dyssynergia and striated muscle sphincter dyssynergia. Striated sphincter dyssynergia will result in an obstruction with high detrusor pressure and poor bladder emptying. Sacral SCI will usually demonstrate bladder atony or areflexia with normal or high bladder compliance (elasticity). Decreased compliance may develop, which can lead to hydronephrosis and irreversible kidney damage.

In practice, SCI neurogenic bladder dysfunction's presentation is as varied as the individuals affected with SCI, almost all of whom face a struggle to manage this condition on a day-to-day basis. A key issue was described as the inability, for those with SCI, to detect rising bladder pressure or bladder fullness in a "closed loop system." Additionally, the

level of injury was also discussed in its relationship to symptomatic presentation and intervention targets. "The Functional System" describes the bladder dysfunction in terms of occurring in the filling/storage or emptying/voiding phase of micturition (Wein and Barrett, 1988). This classification, generally divided into "Failure to Store" and "Failure to Empty," has been expanded to include specific urodynamic findings based upon the activity of the detrusor and sphincter outlet noted as either hyperreflexic, normoreflexic, or areflexic (Krane and Siroky, 1984). These three classifications define the main therapeutic targets: failure of storage (incontinence), failure to empty or a combination of the two. Each condition could be due to dysfunction of the bladder, the sphincter, or both.

Urological systems are fairly well described in the scientific literature (de Groat et al., 2015), which enabled robust discussions regarding the appropriateness and effectiveness of long-term treatment options. Clinicians described their standard practices for developing a bladder management strategy for consumers with SCI, which they admitted rely heavily on where they conducted their residency and what options they had experience with. Non-electrical devices comprise the majority of supportive technology used in standard practice. These devices are either catheters (intermittent and indwelling (e.g., Foley)) or stents (prostatic and urethral). Surgical approaches were described as an option recommended only when patients expressed deep dissatisfaction with their current management approach. Surgical options include sphincterotomy, bladder enlargement (i.e., augmentation cystoplasty), urinary diversion or cystectomy to by-pass the bladder and lumbar sacral rerouting. Botulinum toxin injections are often used to relax the bladder and this option is growing in popularity due to the reversible nature of this approach. Workshop participants also received an overview of emerging, and hence, less commonly utilized electrical approaches to restore bladder function. The biological targets include stimulation at the level of the spinal cord, spinal nerve roots, peripheral nerves or muscles of the bladder wall and sphincter. These targets are reached via a multitude of stimulation modalities, including pharmacological, ultrasonic, magnetic, or electrical delivered through devices (i.e., surface and implanted) (Gaunt and Prochazka, 2006) or pharmacological routes of administration (e.g., oral, rectal). Hence, a wide range of options need to be considered, in relation to both clinical effectiveness and patient preference.

Neurogenic bowel is a colonic dysfunction resulting from a lack of central nervous control of the gastrointestinal tract (Krassioukov et al., 2010a, 2010b). This condition is commonly observed in individuals with SCI and clinically presents as two distinct patterns of bowel dysfunction; injury above the conus medullaris results in upper motor neuron bowel syndrome and injury at the conus medullaris and cauda equina results in lower motor neuron bowel syndrome (Krassioukov et al., 2010a, 2010b). Upper motor neuron bowel syndrome is characterized by high pressure and lost coordination of rectal contractions that result in a failure to relax the anal sphincter. Lower motor neuron bowel syndrome is characterized by areflexic rectum and low anal sphincter pressure. Both of these conditions have been shown to reduce transit through the colon. Similar to bladder, failure to store (fecal incontinence) and empty could be due to either/both bowel or sphincter dysfunction. Neurogenic bowel dysfunction is a major physical and psychosocial problem for individuals with SCI, as changes in bowel motility and sphincter control are coupled with impaired mobility and loss of hand dexterity. The clinical management approach to bowel dysfunction after SCI is overwhelmingly the use of digital stimulation (Stiens et al., 1997; Correa and Rotter, 2000; Yim et al., 2001; Krassioukov et al., 2010a, 2010b). This was described as the routine practice in therapy and, in many centers, demonstrated success is required prior to hospital release. *trans*-Anal irrigation is utilized more commonly in Europe than in the US, and is mainly used when other approaches fail (Emmanuel, et al., 2013). The primary goals of therapy are to reduce the amount of time spent on defecation, minimize fecal incontinence and reduce the impact of bowel management on quality of

life (Christensen and Krogh, 2010). Pulse irrigation is effective, but impractical due to the bulky machinery that is needed. Initially, unmanageable fecal incontinence is treated by use of absorbent undergarments, anal plugs, or rectal catheters such as ProCon2® devices (Duelund-Jakobsen et al., 2016). Surgery, such as bowel diversion (i.e., latissimus dorsi myorrhaphy) or sphincter augmentation, is used as a last resort due to poor long-term outcomes (Lehto et al., 2013; Bravo Gutierrez et al., 2004). Emerging electrical approaches include sacral nerve stimulation, however, participants expressed doubt regarding the value and effectiveness of this approach as reported in previous studies (Binnie et al., 1991). Overall, it was noted that much more scientific study of bowel physiology is needed to target next-generation therapy development (Duelund-Jakobsen et al., 2016 for review). There was a discussion specifically about need to develop better measures of physiology (in spinally injured as well as other individuals) in addition to a need for better understanding of the relationship between abnormal gut physiology and symptoms.

3. Expanded recommendations

3.1. Education and clinical care standards

Clinicians described the paucity of current guideline documents and the challenges they face when their patients are either uninformed or misinformed. Consumer representatives echoed this concern and confirmed that the majority of individuals with SCI turn to online resources as a first step (Matter et al., 2009), which can yield inconsistent and questionable information. Although clinicians and consumers harbor the same concerns, they also described the tendency to talk past each other. Clinicians prioritize health and resolution of physical dysfunction whereas consumers prioritize convenience, reliability, ease of use, cost and practicality. Physician resources for SCI bowel and bladder dysfunction are provided through multiple sources. The Paralyzed Veterans of America (PVA) and associated Consortium for Spinal Cord Medicine develop some of the most well-known clinical practice guidelines (CPG) for consumers and health-care providers in the U.S. [<http://www.pva.org/publications/clinical-practice-guidelines>]. Downloadable and freely available, they contain evidence-based recommendations and guidance to address common concerns in SCI practice. However, the PVA bladder and bowel guidelines were originally published in 2006 and 1998, respectively, and clearly need to be updated (Consortium for Spinal Cord Medicine, 2006; Consortium for Spinal Cord Medicine, 1998). In Canada, the Rick Hansen Institute (RHI) has developed a broad resource for clinicians worldwide, Spinal Cord Injury Research Evidence (SCIRE), that includes treatment approaches, instructional videos and toolkits on many topics. The bladder and bowel guidelines were published in 2014 (Coggrave et al., 2014; Hsieh et al., 2014), and an updated version is being released in sections, starting in January 2017 [<https://scireproject.com>]. The existence of these and other resources and guidelines, developed independently, led participants to prioritize the need for coordinated communication, awareness, updates, consumer access and clinician usability. They recommended the following next steps.

Recommended community actions

1. Conduct a systematic review of available resources and best practices.
2. Collaborate domestically and internationally to centralize materials.
3. Update resources and incorporate diet, nutrition, and sexual function.
4. Develop versions for patient (description) and clinician (technique).
5. Standardize measures for future studies where possible and utilize common data elements.
6. Develop a consumer profile and incorporate patient priorities and preferences in treatment pyramid and decision tree.
7. Ensure care standards are easy to use, downloadable and freely-

available through traditional and modern sources such as social media and peer support sites.

8. Utilize advocacy/organizational groups for wide dissemination.

Further discussion topics included the potential benefits of expanding telemedicine and development of a support organization to bring groups together for research/information standardization every few years.

As an initial step toward centralization and dissemination of current materials within the U.S., a few participants recommended working with the large longitudinal database of the SCI Model Systems Centers. These Centers, funded through 5-year awards from the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR), are recognized for their leadership in medical research and patient care. Other large data resources include the Rick Hansen SCI Registry (RHSCIR) (Fehlings et al., 2017), and a new effort to coordinate data sharing in SCI research in a “FAIR” Findable, Accessible, Interoperable and Reusable manner (Callahan, et al., 2017). Utilization of common data elements for clinical documentation as well as research (Biering-Sørensen et al., 2015) would also support efforts in another important thematic area, bowel physiology.

3.2. Bowel physiology

The workshop agenda was designed such that a review of bowel and bladder systems would inform breakout groups in identifying pathophysiological intervention targets. Compared to urological systems, bowel physiology and the mechanisms of dysfunction after SCI are not well understood. Although bowel and bladder are related systems, the imbalance of knowledge between them became clearly apparent. The ability of able-bodied individuals to selectively evacuate material based on its structure (e.g., solid, liquid, gas) underscores the complexity of the healthy enteric nervous system. Many argued that what is known about colonic transit, rectal compliance and anal reflexes provide only the most basic information. The lack of information on mechanisms of gastrointestinal dysfunction after SCI hampers the ability to identify surgical, pharmacological, and neuromodulatory targets to manage or reverse people's symptoms. Although there is much to be learned about bowel pathophysiology following SCI, clinicians and consumers were fairly well aligned in describing available treatment approaches: Diet, exercise and managing poly-pharmacy are the most common front-line approaches. Clothing and schedule adjustments are often considered along with practicality and lifestyle. Devices such as trans-anal irrigation systems, neuromodulation and surgical interventions are reserved for treatment-resistant cases when risk of the intervention is outweighed by lifestyle impact due to the declining functional status. Although doctor/patient communication on bowel dysfunction was described as well-aligned, data presented from a recent sociological research study on challenges and life with bowel dysfunction highlighted the urgency of addressing several issues. These topics regarding bowel dysfunction in general, and relating to SCI specifically, were documented in an ethnographic study with a quantitative part, involving 74 people with SCI, of a total of 361 respondents with bowel dysfunction of diverse origin (Coloplast Market Study [dataset], 2017):

Bowel dysfunction in SCI and other medical conditions

- Bowel problems are usually treated through symptom management over years (and often decades) as the systemic dysfunction continues unresolved.
- About half (54%) of people with bowel problems in this sample sought medical attention within a month of symptom onset, but 11% waited 6 months or more and some may not have sought attention until hospitalized. The proportions were similar in those individuals in the sample with SCI as the underlying cause of their bowel problems.
- Social media, websites and peer support groups are the main source

of information for those with bowel dysfunction (66% collectively), about which, physicians express concern regarding misinformation in online sources. A healthcare professional is the main source of information about bowel problems for 26% of the respondents across patient groups, including SCI.

- Bowel and bladder dysfunction comorbidity is high; urinary incontinence and urinary tract infections are the most common comorbidities. For 78% of the responding SCI participants, bowel problems were considered equally or more important than urinary incontinence.
- Bowel dysfunction seems to coexist with mental health problems such as depression and anxiety. Although 71% of responding physicians and nurses treating bowel dysfunction are acutely aware of these relationships, treatment referrals are seldom provided for this cause.
- Bowel incontinence is an important and persistent problem that can lead to hospitalizations. Fifty-six percent of the responding SCI patients affirmed having been hospitalized at least once due to a bowel problem in the previous 12 months; 68% of those were emergency admissions.
- Fifty-five percent of individuals with SCI who responded said their bowel problems have caused them to avoid activities or cancel social engagements in the past year.
- A significant number of SCI respondents said they had tried over the counter medication and/or natural remedies for their bowel problems without consulting with a healthcare professional (45% and 37%, respectively).
- Among the many individuals with SCI who experienced a change in their bowel health in the previous year, most (63%) described it as ‘getting worse.’
- Most clinicians are unaware or avoid use of tools such as the neurogenic bowel disorder score (Krogh et al., 2006) or the 2013 pyramid of bowel dysfunction (Emmanuel, et al., 2013) and therefore are unsure how to escalate interventional strategies. Even if these tools were used more commonly, many argue that more metrics to accurately assess bowel problems are needed.

Although these data indicate significant challenges related to bowel dysfunction care, participants discussed several effective treatments that do exist and worked to identify additional opportunities. Evacuation, constipation and gut motility can be addressed through pharmacological approaches, including laxatives and serotonin agonists (Krassioukov et al., 2010a, 2010b; Singal et al., 2006). Neostigmine effectively treats acute colonic pseudo-obstruction, Cisapride increases motility in the upper intestinal tract, however, cardio-vascular complication risk must be considered and Prucalopride has shown good results in handling chronic constipation (Geders et al., 1995). Physical therapy, neuromodulation or surgical approaches for fecal incontinence have shown some success, but participant opinions varied widely and the prevalence of use of these approaches differed across countries and the institutions therein. It was agreed that no approach has demonstrated reliability in addressing fecal incontinence. Workshop participants could identify few researchers actively addressing these issues or specific approaches under development that show particular promise. There was strong consensus that the field needs more basic information to generate priority targets. It also was noted that growing research regarding the microbiome warrants further development in this area (Gungor et al., 2016). In summary, the following recommendations were put forward to improve bowel care after SCI:

Recommended community actions

- Provide gastroenterologists, colorectal surgeons, general practitioners, and neurologists who treat bowel dysfunction, tools and referral resources to identify and address psychological conditions such as anxiety and depression.
- Develop diagnostic tools and a clear medical referral pathway for

treatment that accounts for level of injury, completeness, time postinjury, age and gender. Physiological phenotypes are needed for bowel dysfunction based on level and severity of injury, for example, to enable clinicians to determine high/low compliance and with/without anal dyssynergia.

- Develop and make available resources for patients to address potential misinformation as well as encourage individuals to seek proper treatment from the medical professionals best equipped to help them.
- Conduct research to understand bowel function, identify potential intervention targets and clarify the close relationship with bladder system dysfunctions.

Many of the breakout groups suggested that inroads in bowel management would likely have a positive impact on bladder systems due to potential interrelationships between the two systems. The three remaining thematic areas support this assertion; sensory awareness, neuromodulation, and secondary effects of other rehabilitation, activity and exercise interventions, all of which apply equally to both bowel and bladder.

3.3. Sensory awareness

Participants in all working groups were asked to identify emerging approaches that have translation potential within the decade. There was agreement early in the discussion that many serious health issues and potential incontinence “accidents” could be avoided if sensory information, such as bladder fullness, pain due to impaction or urinary tract infection (UTI) was available. For example, it is well documented that autonomic dysreflexia can be triggered by activation of the sensory afferents due to an over-filled bladder or colon, routine bladder emptying, digital stimulation or the process of manual evacuation (Faaborg et al., 2014; Lee et al., 2017; Vaidyanathan et al., 2017, 2018). Dysfunction in sensory feedback varies based on each injury; while some individuals with SCI retain some sensation, others have little or no sensory warning before a bowel or bladder movement. First line management approaches described previously, such as digital stimulation and catheter use, are most effective when sensory awareness is present. Individuals with reduced or absent sensory awareness must rely on scheduled bowel and bladder care and are more prone to accidents or serious complications.

Workshop participants argue that sensory awareness as a substitute to normal sensation would significantly reduce and potentially prevent accidents and medical consequences. Even without improved bladder and/or bowel evacuation approaches, an alert that bowel/bladder emptying needs are approaching a critical point would be an important advancement. Participant recommendations focused on developing diagnostic and monitoring systems that provide notification of the need to evacuate (Craggs et al., 2006). Short and long-term approaches for the development of surrogate signals to monitor key parameters (e.g., distention, solid vs. gaseous pressure) were identified. Monitors could be developed for biological targets such as the bladder wall and sphincters as well as non-biological targets such as indwelling and intermittent catheters. Devices will require specialized sensor development because as one participant noted, catheter-based pressure systems used in bladder have been proven unreliable for bowel. The need to focus on devices that treat both failure to empty and failure to store were also described by several breakout groups.

Recommended community actions.

Short term

- Develop a pressure monitor for indwelling bladder catheters and consider application of valved catheters, where this would increase convenience.

Long term

- Develop wireless volume and pressure monitoring for bladder to

inform a person in a discrete manner when catheterization is needed. This type of novel device would enable more independence to travel, work, and participate in social activities without worry.

- Similarly, development of a continual monitoring device to give patients continuous health information on state of their bowel: distension, motility, volume, strain.
- Promising implant locations for bowel sensor(s) were identified as being submucosal in the rectum and/or sigmoid colon (Trivedi et al., 2016).

Monitoring devices could be either permanent or built to function for a month or so to give consumers a better sense of what their surrogate sensations “mean.” Workshop participants argue that in the future data from these devices would inform clinicians for diagnostic and therapeutic purposes and provide consumers with more independence. Technology development should be geared toward dynamic monitoring of combined measures, such as pressure and volume in distal bowel, as current approaches such as anal manometry provide only static measurements. Further benefits of chronic monitoring are tracking of change over time, allowing clinicians to monitor or fine tune treatments or developing new therapies. Participants discussed common clinical observations where management programs remain effective for decades then unexpectedly fail. The ability to track changes in pressure, distention and fullness over time would provide insight into the source of these failures, which are currently hypothesized to be due to age or scarring. In the absence of better clinical data, maintenance of effective bowel and bladder management strategies will remain difficult. Some of these recommended long-term approaches were known to currently be in development, such as indwelling pressure measurement devices, but others, including molecular sensing for UTI and ultrasonic detection of fullness, were in the early stages of idea generation. A critical first step is to exploit an animal model to help develop such technology and initiate testing of its safety and utility.

In summary, restoring sensory awareness was recognized as a highly important, yet underdeveloped emerging approach that holds great potential. Since the workshop was held, one company, Spinal Singularity, began clinical safety trials on a bladder device called the Connected Catheter, which has an imbedded sensor and wireless alert system (<https://clinicaltrials.gov/ct2/show/NCT03405285>). Although this company was not part of our workshop, their effort to develop technology in line with this consensus recommendation seems to confirm the importance. Once reliable sensory awareness is established and determined safe for people with SCI, use as a clinical diagnostic tool or to provide feedback control of other emerging approaches will also be enabled. Participants formed a sensation working group, with the goal of identifying available and/or emerging technology that could be leveraged within 10 years. Detailing the steps the field could take next on priority areas will involve identifying the opportunities and barriers that exist in accomplishing these goals and dissemination to the larger community. As this group evolves and progresses, they will add needed expertise and foster a relationship with other working groups. Indeed, in addition to providing the user with important feedback, sensors would enable closed-loop neuromodulation systems.

3.4. Neuromodulation

Control of nervous system function through electrical, chemical or other stimulus delivery methods has experienced significant advancement in scientific research and clinical practice (McGee et al., 2015). Although the neuromodulation sector for incontinence is projected to grow 13% annually (Cavuoto and French, 2018), additional randomized control trials are necessary to determine the efficacy of these approaches in SCI (Kessler et al., 2010). Electrical stimulation targets to restore bladder function include the nerves of the sacrum such as the pudendal and tibial nerves or the sacral roots. Targeting these nerves with electrical, optogenetic, ultrasonic, or pharmacological approaches

can range from precise (e.g., microscale, cellular specific) to systemic delivery (i.e., drugs). There are many types of devices that provide targeted stimulation, such as highly investigational micro- and nanoscale technologies created in laboratories across the globe (e.g., Seo et al., 2016) and clinically-used milli-scale devices from Medtronic, Boston Scientific, St. Jude and others (Kumsa et al., 2018). Although devices designed specifically for those with SCI are urgently needed, while focusing on a 10-year timeframe, participants recommended avoiding an exclusive focus on developing new technology for several reasons. First, they agreed there were many devices already on the market or in advanced stages of development that might be applied to treat bladder and bowel dysfunction. Many advances in technology are being made through recent initiatives such as NIH's SPARC and DARPA's ElectRx programs, and leveraging technology should be possible. Several groups also expressed concern over translation of wholly new approaches within a reasonable timeframe due to the long-development timeline for regulatory approval of new devices. Instead, a focus on developing neuromodulation approaches that leverage existing and emerging technology was recommended.

Several decades have passed since the emergence of sacral anterior root stimulation using the Finetech-Brindley bladder system (Vocare). This device provides on-demand urination and reduces residual urine volume in persons with SCI who have clinically complete spinal cord lesions with intact parasympathetic innervation of the bladder. This device showed positive results in over 2000 users worldwide (Gaunt and Prochazka, 2006), many of whom reported experiencing benefits to defecation, as well. Workshop participants' views and experience regarding consumer acceptance of this approach varied. Many argued that those who have received the surgically implanted device are the strongest advocates; they also described potential bias against this approach as accounting for decreased use. Others noted that many potential users are intolerant to the thought of elective posterior rhizotomy (severing intact sensory nerves) and cited individual cases with disappointing results. The rhizotomy procedure is required to treat neurogenic detrusor overactivity (incontinence) and bladder sphincter dyssynergia (Kirkham et al., 2002), as the stimulator only addresses bladder emptying. It was clear that there is little consensus in recommending this approach, and further systematic analysis of user outcomes would be beneficial.

Examples of other electrical stimulation approaches that avoid the need for a posterior rhizotomy were discussed including sacral neuromodulation (Wöllner et al., 2015; Lombardi et al., 2014), epidural spinal cord stimulation (Pettigrew et al., 2017), pudendal nerve stimulation (Horvath et al., 2010; Yoo et al., 2011), and tibial nerve stimulation (Chen et al., 2015). However, well-designed, randomized and controlled studies are required to evaluate these emerging approaches (Ren et al., 2016). The Wöllner and Lombardi studies specifically describe recommendations to avoid use in incomplete SCI with neurogenic detrusor overactivity (NDO) or chronic retention. It was also noted that sacral neuromodulation cannot reliably suppress NDO and should only be considered as a treatment option for symptomatic neurogenic lower urinary tract dysfunction in carefully selected scenarios where there is low risk for upper urinary tract damage. kHz-frequency biphasic stimulation can block conduction in the pudendal nerve and may be chronically reversible and repeatable (Kilgore and Bhadra, 2014 for review). The benefits of neuromodulation to keep bladder pressures low through relaxation of the detrusor muscle was acknowledged, however, opinions varied regarding what approach and level of invasiveness would be required to achieve this, as well as other, similar goals. Participants identified numerous opportunities in neuromodulation for bowel and bladder control, related to identification and focus on specific biological targets, and as well as enhancing emerging stimulation modalities. Clinical use of kHz peripheral nerve block has been approved by the FDA and studied in obesity (Ikramuddin et al., 2014) which may support its translation in other therapeutic conditions. There was broad agreement that pursuing neuromodulation

strategies has strong potential; there was less agreement about which specific approach holds the most promise. There was consensus, however, that leveraging existing technologies would increase the likelihood of translating approaches within the decade.

Recommended community actions

- Enhance existing sacral anterior root electrical stimulation systems to maintain efficacy while eliminating the need for a rhizotomy.
- Focus efforts on repurposing existing neuromodulatory drugs and devices for use in SCI bowel and bladder management, with consumer preference guiding development.
- Develop staged translational approaches beginning with surface stimulation such as targeting the genital branches of the pudendal nerve for bladder control and possibly bowel continence.
- Perform mechanistic studies of sacral neuromodulation to support the development of safe and effective stimulation approaches for bowel and bladder management.
- Develop reliable selection criteria and incorporate quantifiable measurement criteria to assess efficacy.
- Identify early intervention strategies to prevent the development of detrusor sphincter dyssynergia (Sievert et al., 2010) and other unfavorable symptoms.
- Incorporate biofeedback to enhance control in those with incomplete lesions.
- Explore a combination of therapies (e.g., electrical stimulation and drugs).
- Leverage known recto-colonic reflex functions to replace current approaches such digital stimulation.

It became apparent during discussions that awareness of existing and emerging technologies varied greatly. Researcher scientists shared knowledge of novel electrical, optogenetic and ultrasonic approaches whereas clinicians provided insight into surgical, pharmacology and transanal irrigation benefits and drawbacks. Potential options to combine known approaches (e.g., targeted drug delivery via transanal irrigation) or build upon emerging technology (e.g., optogenetic stimulation or inhibition) were evaluated in terms of their likely translational timeline. One participant described the potential to accelerate this timeline through the development of public/private partnerships [<http://mdic.org/>]. Similarly, industry representatives described opportunities and experience with collaborative research and development efforts.

In an effort to consider both emerging and existing technology, a Neuromodulation working group was created to identify technology, either available or emerging, which could be leveraged within 10 years, and the steps needed to make meaningful progress. This will again involve identifying key opportunities and barriers and informing the field on these recommendations through a publication. In addition to high-tech research and development in neurotechnology, participants identified several clinical trials in SCI that reported improvements in bowel and bladder function as a secondary or unexpected outcome. Understanding and capturing such data emerged as a high priority during the workshop discussion.

3.5. Rehabilitation, activity and exercise

Current clinical trials in SCI that listed bowel and/or bladder as a primary or secondary outcome measure were reviewed during the workshop. In most, bladder or bowel outcomes were secondary to the trial focus on areas such as locomotor function, pain and respiration. Interventions included rehabilitation, cell transplants, scaffolds, electrical or magnetic stimulation, activity-based training, or various combinations thereof. Many workshop participants described anecdotal findings from trials and case studies that underscore the broad impact physical movement has on individuals with SCI. There was consensus that such observations are intriguing, but not rigorous enough to affect

implementation. These data are beginning to be collected and assessed (Hubscher et al., 2018), but a more comprehensive approach is needed to learn from and leverage any potential benefits. Participants noted that data collection approaches varied in the studies reviewed, with no single bowel or bladder measurement technique or regimen common to all. Outcomes tools have been developed to address concerns of comparability between studies, including the SCIRE project [<https://scireproject.com/>], NIH's common data elements [<https://www.nlm.nih.gov/cde/>] International SCI data sets [<http://www.iscos.org.uk/international-sci-data-sets>], and The SCI-Quality of Life measurement system (Tulsky and Kisala, 2015), but most published studies have yet to incorporate or report on standardized outcomes. The need to better capture and quantify improvements in bowel and bladder function was apparent throughout the workshop discussion. A summary of areas that should be addressed is provided below.

Recommended community actions

- Identify core QOL measures for SCI in bladder and bowel based on consumer preference for meaningful improvement.
- Encourage use of bowel and bladder outcome measures that can become standards in studies where the intervention target is not specific to bowel and bladder management.
- Define types of data to collect and specific methods or biomarkers (e.g., UTI incidence with specific definition of what constitutes a UTI in individuals with SCI.) for all ongoing SCI trials.
- Use health economics to define important outcomes related to bowel and bladder management to inform regulators and payers.
- Systematically encourage/expect capture and sharing of common data elements consistently to enable meta-analyses.

These recommendations appear straightforward, yet require extensive collaboration to be successful. Participants emphasized that variations in measurement approaches are necessary for both dysfunction-specific and trial-specific reasons, and the desire for consistent measurement should not outweigh strong experimental design. Instead, participants argued that if a key set of supplemental bowel and bladder measures could be developed with a low data collection administrative burden, researchers would likely embrace collection and reporting of such outcomes. Participants concluded that this topic required additional consideration, so a third working group was convened to begin developing this core list of bowel and bladder measurement tools. The objective of this working group is to act as a collective voice to develop and disseminate bowel and bladder measurement recommendations to the larger community.

4. Discussion/summary

The inability to control voiding, particularly incontinence, is a deeply personal topic. It reduces participation in public activities, decreases sexual confidence, and is considered by many to be one of the most debilitating aspects of life after SCI (Rubin et al., 2016). One participant summarized the workshop with this simple message: "It's about dignity." Until quite recently, SCI researchers devoted little focus to studies in bowel and bladder management, even though dysfunction in these systems has serious medical complications and psychological impact for those living with SCI. The Craig H. Neilsen Foundation bowel and bladder workshop was designed as a first step in addressing this research gap. Discussions weighed strategies and options, set priorities and outlined actions to advance promising approaches. It was apparent that significant actions remain to be undertaken in order to achieve real change in the lives of those living with SCI. Three working groups were formed to begin addressing the identified gaps, however, real changes in foreseeable future require a larger community effort. Funders, industry, regulatory, and community groups must act within their disciplines and build or join collaborative efforts. Researchers and clinicians need to continue to build momentum in these areas. The

recommendations and subsequent activities described here, are presented to help the community move forward. In 2004 a seminal paper was published describing research priorities according to those living with SCI, and few changes in treatment have been made since then (Anderson, 2004).

Consensus and momentum were developed during this workshop that should result in tangible improvements in bowel and bladder management after SCI. Participants noted that although addressing key issues of reliable continence, voiding and access to current information may require a decade for achievement, recommendations provided herein can reasonably be accomplished within that time. Opportunities identified span a spectrum of technical challenges from those considered low-hanging fruit (e.g., updated guidance) to more difficult engineering and basic science research. Similarly, they range in development time from long-term solutions, which require additional scientific exploration and identification, to numerous readily achievable goals such as updating CPGs, maximizing FAIR data usage, and expanding telemedicine. Strategies also included prevention of known progressive health-related issues such as DSD, bowel impaction and UTIs and also highlighted the need to consider and incorporate user lifestyle for optimal care. Workshop participants' contributions before, during and after the meeting in the post-workshop working groups described, have already moved us closer to achieving these goals. The Neilsen Foundation has also committed to support, and thereby accelerate, the PVA's updating of the Bowel Management CPGs. Although the accomplishments described are important, they are just a beginning. It is hoped that others in the community will now join these efforts.

Appendix 1. Appendix

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