Bladder-bowel interactions: Do we understand Pelvic organ cross-sensitization?

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Running title: Pelvic organ cross-sensitization

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Abstract

Aims: Mounting evidence from experimental animal and human studies suggests that cross-sensitization exists between different organs. Lower urinary tract (LUT) and bowel dysfunction commonly overlap, and the role of cross-sensitization between pelvic visceral organs is uncertain.

Methods: At the International Consultation on Incontinence Research Society (ICI-RS) meeting in 2018, a panel of clinicians participated in a discussion on bladder and bowel interactions in the context of pelvic organ cross-sensitization.

Results: Bladder and bowel problems commonly co-occur in adults and children across different disorders, and the mechanism responsible for overlapping dysfunction is uncertain in most instances. At a neuronal level, cross-sensitization occurs as a result of afferent signalling from the LUT and lower bowel through different central and peripheral mechanisms. Studies in animals and humans have demonstrated evidence for cross-organ sensitization following experimental inflammation or distension of the lower bowel, affecting the LUT. Nerve stimulation is an effective treatment for different functional LUT and bowel disorders, and whether this treatment may influence cross-organ sensitization remains uncertain. The

role of physiologically dormant C-Fibres, the bladder-gut-brain axis and gut microbiome in cross-sensitization are speculative.

Conclusion: Recommendations for research were made to explore the role of cross-organ sensitization in the pathogenesis of co-occurring LUT and bowel dysfunction in humans.

Introduction

The lower urinary tract (LUT) and bowel share a common embryological origin and perform similar functions of storage and evacuation. Micturition and defaecation are highly synchronised responses which are mediated by sensory and motor signalling (1), and the functional interaction between these pelvic organs was first reported by Denny-Brown and Robertson (2). Reciprocal modulation of pelvic organ functions was demonstrated in humans by Kock and Pompeius in studies demonstrating inhibition of detrusor activity following anal distension (3). Neural “cross-talk” through convergent sensory pathways at a peripheral, spinal and supraspinal level is likely to play a critical role in the regulation of LUT and bowel functions in health.

It is also apparent that disease of one of the visceral organs can subsequently result in the development of pathological changes in otherwise unaffected adjacent organs (4) (5). Called “cross-organ sensitization “, this is particularly relevant in the understanding of the pathogenesis of chronic pain syndromes affecting the abdominal and pelvic regions. There is considerable overlap between pelvic pain disorders, irritable bowel syndrome (IBS) and bladder pain syndrome (BPS) and

mounting evidence suggests that cross-organ sensitization is likely to be contributing to LUT and lower bowel dysfunction in different disease states. Similarities in function and innervation, and proximity between the LUT and lower bowel, make this a plausible notion, and experimental studies in animal and human models are expanding our understanding of the nature of the relationship between these two visceral systems (5) (6). We review bladder and bowel interactions observed in clinical practice, and explore whether currently used models can be used to study possible cross-organ sensitization in overlapping functional pelvic disorders.

Methods

At the International Consultation on Incontinence Research Society (ICI-RS) held in Bristol, United Kingdom in 2018, a panel of clinicians participated in a discussion on bladder and bowel interactions in the context of pelvic organ cross-sensitization. The panellists reviewed the literature around bladder-bowel interactions in clinical practice in the context of non-neurological and neurological disease in adult and paediatric populations, experimental and clinical models of pelvic organ cross-sensitization in inflammatory and functional disorders and explored the role of sacral nerve stimulation (SNS). From the discussions at the meeting

and subsequent e-mail iterations, the panel proposed priority areas of further research.

Co-occurrence of bladder and bowel dysfunction

Bladder and bowel dysfunction commonly co-occur in clinical practice (figure 1). Women with urinary incontinence more often report bowel symptoms compared to control groups without incontinence (7). Conversely, women with gastrointestinal problems report more LUT symptoms compared to those without bowel complaints (8, 9). Furthermore, problems with defaecation and constipation are known risk factors for developing LUT symptoms (10). Likewise, chronic constipation and faecal incontinence are more prevalent in men reporting overactive bladder (OAB) symptoms compared to those without LUT symptoms (11). In a large cross-sectional population cohort study, LUT symptoms in a cohort of male patients was associated with low stool frequency (12). Indeed, urodynamic testing has demonstrated that rectal distension significantly alters the perception of sensations of bladder filling (13).

The neural control of the LUT and lower bowel is shared at different levels across the central and peripheral nervous system and it is not surprising,

therefore, that dysfunction of both organs often co-exist following neurological disease. In a large cohort of patients with Multiple sclerosis, bladder and bowel symptoms were reported in 87% and 74%, respectively (14). Following neurological disease, the pattern of LUT dysfunction is influenced by the level and extent of neurological injury (15). However, the pattern of bowel dysfunction is influenced by the additional modulating effect of the peripheral enteric nervous system (ENS) (16).

Functional disorders of the LUT and lower bowel commonly co-exist in children and approximately one-third of children with functional constipation, and one-fifth of those with non-retentive faecal incontinence report urinary incontinence (17). Different mechanisms for co-existent LUT and bowel dysfunction have been proposed including mechanical compression of the bladder by local stool masses leading to residual urine (18), involuntary contractions of the detrusor (19), and concomitant contractions of the anal and urethral striated sphincters representing a common physiological unit (20). Additionally, close relationships form between pelvic organs starting from foetal development and continuing throughout childhood maturation, which underpins the physiological foundation for cross-sensitization in adulthood (21).

Cross-sensitization

Cross- sensitization is best explained in the setting of referred viscero-somatic and viscero-visceral sensitization. There are different mechanisms postulated for cross-sensitization and the *central theory* proposes that afferent input from different somatic and visceral structures converge onto the same second-order spinal neurons in the dorsal horn(6). Disease and inflammation in one organ results in increased excitability of the spinal neurons, and application of stimuli in other organs or tissues whose neural input converge onto the same spinal neurons in the dorsal horn results in an exaggerated response in that organ (6). In additional to the spinal cord, convergence has been documented in other regions of the CNS, namely the Barrington's nucleus in the pons and in the thalamus (22) (23). The *peripheral theory* proposes that different tissues are innervated by dichotomizing sensory endings arising from a single first-order neuron in the dorsal root ganglia (DRG). Electrophysiological and morphological studies in rats have demonstrated the presence of dichotomising fibres, however the number of such fibres varies between studies and is limited to between 0.1% to 21% of traced neurons (24) (25). Dichotomizing fibres have been demonstrated for colon and bladder DRG neurons in male rats

(26), however the extent to which peripheral mechanisms contribute to cross-sensitization needs further evaluation(6).

Other peripheral mechanisms of sensitization include alterations in afferent processing of DRG neurons and their projections through electrical and chemical coupling (27) and local inflammatory changes (28). Our understanding of the mechanisms responsible for (pelvic) cross-organ sensitization in humans are derived from findings in experimental animal models and therefore several questions still remain unanswered:

- Are the proposed central and peripheral postulates for cross-sensitization applicable to humans?
- How can central convergence and sensitization be studied *in vivo* in humans?
- Is there a role for functional brain imaging to investigate sensitization at brain stem and cortical levels?
- To what extent does cross-sensitization occur at a supraspinal level in humans?
- How does pelvic cross-talk develop in early life?

- What are the risk factors for developing cross-sensitization in childhood?
- Which children with co-existent lower urinary and gastrointestinal disorders are susceptible for disorders in adulthood?
- Does cross-organ sensitization feed into a neurally mediated reflex that regulates visceral functions?
- What are the neural pathways that mediate cross-sensitization between different pelvic organs? Do these involve the pelvic sympathetic and parasympathetic innervation?
- To what extent does the endogenous enkephalinergic system contribute to the development of cross-organ sensitization?
- To what extent does cross-sensitization between different pelvic organs contribute to co-occurring LUT and bowel dysfunction in neurological patients?
- In animal models, sensitization often persists after the removal of the original trigger, and what are the factors responsible for perpetuation of cross- sensitization between organs?
- What is the role of spinal interneurons in cross-organ sensitization, and can “cross-organ inhibition” exist between viscera?

Experimental studies investigating cross-organ sensitization

Functional disorders and cross-sensitization- human studies

Few clinical models exist that explore the interactions between pelvic visceral organs. Rectal distension during standard filling cystometry is the most commonly used model to demonstrate functional cross-organ sensitization in healthy individuals and patients (Table 1). Despite being an acute model, the results correlate to the clinical observation of frequent co-occurrence of storage LUT symptoms and chronic constipation (8, 9). It has been shown that rectal filling increases bladder sensations both in healthy individuals and in patients with OAB. The mechanisms by which colorectal afferent activity from rectal distension leads to an increased perception of LUT afferent activity, and at which level (peripheral, spinal or supraspinal), needs to be further studied.

LUT symptoms frequently occur with irritable bowel syndrome (IBS), a functional disorder of the bowel characterized by abdominal pain and changes in the pattern of bowel movements without apparent inflammation. Performing filling cystometry following (colo-)rectal distension in patients with IBS may provide useful insights into the functional consequences on the LUT. Furthermore, the concomitance of urinary and faecal

incontinence occurs mainly between the “urgency”-subtypes (8, 9), and therefore combined urodynamics and anal manometry in patients with double incontinence may be useful. Lastly, OAB can be regarded as a manifestation of bladder hypersensitivity, caused either by an increase in bladder afferent activity in response to certain stimuli, or an increased perception of afferent activity in the brain. Convergence of bladder and bowel activity in the brain could be studied through functional MRI studies comparing controls with patients with coexisting OAB or urgency incontinence, and constipation, IBS or faecal incontinence.

Constipation and voiding difficulties often overlap (8, 9) and to-date, no clinical studies have been performed evaluating the effects of acute rectal distension during the pressure-flow studies in healthy volunteers or patients. On the other hand, the effects of bladder distension on recto-anal motility, have been studied(29).

Functional disorders and cross-sensitization- animal studies

Clinical observations in healthy volunteers and in patients with coexistent LUT and anorectal dysfunction initiated translational and basic science studies aimed at revealing underlying mechanisms responsible for

physiological and pathological interactions. The existing models permit evaluation of the effects of bladder stimulation (by distension or vesical nerve stimulation) on internal and external anal sphincter activity and colonic motility, as well as evaluation of the effect of colorectal stimulation (by distension or nerve stimulation) on external urethral sphincter and bladder (afferent) activity (Table 2).

Although systemic administration of pharmacological agents may directly influence the functioning of both the LUT and bowel, medications (e.g. naloxone, hexamethonium, atropine, nicergoline, phentolamine, guanethidine, intrathecal strychnine or bicuculline) have been used to identify different peripheral pathways through which the LUT and bowel interact. Alternatively, topical application or instillation of the bladder or lower bowel with irritants (e.g.allyl isothyocyanate) or local anesthetics (e.g. lidocaine) can be used to create and study pathological models of cystitis, overactive bladder, IBS and colitis. Transection of the dorsal root at different spinal levels, or even complete nerve or spinal cord transection, has also helped in identifying pathways responsible for bladder-bowel interaction. However, some findings appear contradictory, e.g. colorectal distension inhibits bladder contractions during filling and during micturition,

yet on the other hand causes an increase in bladder afferent activity (table 2). The mechanism behind these seemingly opposing interactions remains unclear. Ganglia may play a role therein, and further studies with mecamylamine or substance P therefore may provide further insight in the role of the pelvic and dorsal root ganglia in pelvic cross-organ sensitization.

Inflammatory disorders and cross-sensitization

Bowel inflammation

Inflammatory bowel disease (IBD), manifesting as ulcerative colitis or Crohn's disease, is characterized by chronic inflammation of the small or large intestine due to an exaggerated immune response to luminal antigens. There is a clear correlation between IBD and IBS, the incidence of IBS being 2-3x greater in IBD patients compared to the general population (30). Several studies suggest that patients with IBD in remission retain altered rectal hypersensitivity and remain intolerant to rectal distension(31, 32). Increased neuroplasticity might arise after acute episodes of intestinal inflammation have resolved, or might be the result of low grade inflammation that remains undetected during routine clinical screening (33).

The effect of colonic inflammation on LUT functions has been studied in rodent models (26, 34). During the acute phase of chemically induced colitis, changes in voiding functions have been consistently demonstrated, including decreased voided volume and bladder capacity and increased voiding frequency. Experimental studies in animals have shown that there is significant hypersensitivity of mechanosensitive bladder afferents, and alterations in the excitation of bladder-innervating neurons occur both during and following colitis(35, 36). However no inflammatory changes have been shown in the bladder wall.

Interstitial cystitis/Bladder pain syndrome

Bladder pain syndrome is strongly associated with other functional disorders such as IBS, fibromyalgia, migraine and vulvodynia. In a questionnaire-based survey assessing the association between Interstitial cystitis/Bladder pain syndrome (IC/BPS) and other chronic diseases, a significantly higher prevalence of IBS was observed, with a reported rate of 34% that was more than 10 times higher than the general population. A significant proportion of patients reported IBD (8%) and this was almost 100 times higher than the general population (37). It is unclear whether the overlap in co-morbidities reflects cause or effect, or shared pathogenesis,

however it does raise the question whether IC/BPS could be a consequence of cross-organ sensitization in patients with chronic bowel inflammation. The study also evaluated the relative onset of these associated conditions, and it was established that patients with IBD, allergies, migraine, endometriosis or asthma have a greater risk for developing IC/BPS, whereas individuals who already have IC/BPS show a greater likelihood for developing fibromyalgia, incontinence or chronic fatigue syndrome. According to the bladder–gut–brain axis model, psychological and physical stress pathways contribute to alarm falsification, and neuroticism could be a risk factor for the co-occurrence of functional disorders and affective conditions (38). Moreover, physical threat from external or internal sources such as infection might influence body–brain “cross-talk”, thereby affecting mood, cognition, and behaviour. Patients with organ-specific functional syndromes such as IBS or IC/BPS might therefore undergo phenotypic progression to regional or systemic syndromes, affecting other organs (figure 2) (39).

There is a need to further understanding the nature of the association between LUT and lower bowel dysfunction in functional and inflammatory disorders:

- Can functional MRI be used to study bladder-bowel interactions or cross-organ sensitization at a supraspinal level in rat models of colorectal distension during bladder filling?
- What is the role of colonic inflammation in the pathophysiology of BPS?
- What is the prevalence of lower urinary tract symptoms in patients with IBD? Is there a correlation between exacerbations of Crohn's disease/colitis and voiding (or urodynamic) parameters?
- How does the brain influence the development of functional bladder or bowel disorders?

Nerve stimulation and cross-organ sensitization

Sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS) are effective for the treatment of different functional disorders of the pelvic viscera such as OAB, urinary retention and faecal incontinence (40) (41). Irrespective whether the indication is for bladder or bowel dysfunction, the nerve root that is stimulated is identical however the clinical observations of sensations and physiological measures of continence are different and different efficacy measures are used, which

often are performed mutually exclusively (42). Mechanisms for cross-sensitization between the LUT and lower bowel have yet to be identified (43), however intuitively treatments that modulate sensory nerve activity should influence both organs if dysfunction is due to cross-organ sensitization.

Sacral nerve stimulation has been shown to improve both LUT and lower bowel functions (44). Between 30 and 100% of patients with double incontinence experience improvement in LUT and bowel functions after treatment with SNS (45). Furthermore, early SNS in spinal cord injured patients not only prevents UI, but also improves bowel movements, thereby reducing the need for oral laxatives (46) (47). Intravesical electrical stimulation for treating detrusor overactivity has been shown to improve bowel dysfunction in children with spina bifida (48). The mechanisms by which SNS helps with both LUT and bowel functions is uncertain, and research exploring whether nerve stimulation can influence cross-organ sensitization in patients reporting bladder and bowel disease needs to be further explored:

- Which combination of diagnostic parameters (history, investigations) should be used when evaluating bladder and bowel outcomes following SNS and PTNS?
- How would a successful outcome be defined following nerve stimulation (PTNS or SNS) in patients reporting coexistent LUT and bowel dysfunction?
- Which would be the optimal stimulation settings for PTNS or SNS in patients reporting coexistent LUT and bowel dysfunction? Do these settings differ between storage and evacuation disorders?
- How would a successful outcome be defined following nerve stimulation (PTNS or SNS) in patients reporting concomitant sensory, storage and evacuation disorders?

Experimental studies in animals are required to explore:

- What changes does nerve stimulation induce in animal models of cross-sensitization?
- Does modulating the endogenous enkephalinergic system influence the effects of nerve stimulation on cross-sensitization?

- What effects does nerve stimulation have on combined storage and/or evacuation disorders of the LUT and bowel at a peripheral, spinal or supraspinal level?
- Are the effects of nerve stimulation achieved through combined / facilitating / competitive mechanisms of action?

Other factors

Interactions between the LUT and the bowel are complex and occur at different levels. Evidence from animal and human studies support the notion that “cross-talk” exists between the pelvic visceral organs. However, for reasons that are unclear, the LUT appears to be more vulnerable to cross-modulation than the bowels. In humans, sensitization is likely to be occurring through postulated central and peripheral mechanisms, however the pathogenesis is likely to be more diverse. For example, physiologically dormant C-nerve fibres become active following exposure to several of the noxious stimuli that induce cross-organ sensitization, and therefore the role of active C-fibres in disease states such as BPS and neurological disease in inducing a state of spinal hypersensitivity needs to be further evaluated (49).

The role that the bladder-gut-brain axis plays in the coexistence of bladder (50) and bowel (51) dysfunction in patients with mood and anxiety disorders requires further evaluation. According to this framework, physical and psychological stress results in functional bladder and bowel complaints which represent a sensitized defence reaction to normal physical stimuli to expel urine and/or faeces and thereby alarm falsification. For instance, unresolved stress experience, such as childhood adversity or traumas are important in the reaction to physical and psychological stress and could lead to an exaggerated response to normal physical stimuli (38). The importance of perception of bodily signals is underlined by mindfulness-based stress reduction studies, in which individuals learn to be non-judgemental towards perceived body sensations instead of interpreting them, which is beneficial in OAB and IBS(52, 53).

Considerable overlap exists between central sensitivity syndromes and psychological factors (54), and an underlying shared mechanism of sensitization could be altered serotonin functions. In humans, duloxetine, a serotonin-noradrenaline reuptake inhibitor (SNRI) that increases synaptic levels of serotonin, is licensed for use as an antidepressant. In addition, duloxetine has been shown to be effective for bowel complaints in IBS

patients reporting depression and anxiety disorder (55). Duloxetine has also been shown to help with OAB (56) and therefore the link between behavioural and functional bowel and bladder disturbances needs further evaluation. Children with functional gastrointestinal disorders are more susceptible to developing emotional and behavioural symptoms, and electrophysiological studies have shown that children with faecal incontinence have increased responses in the processing of emotions; this suggests neurobiological vulnerability and could possibly be due to “cross talk” between the ENS and CNS. The responses are even more pronounced than in children with enuresis (57).

The role for the gut microbiome in sensitization is speculative as it has been postulated that bidirectional communication between the microbiome and brain plays a role in depression and bowel symptoms(58). Bacteriuria is associated with a range of LUT symptoms, and the role of a putative bladder microbiome in the sensitization of spinal neurons needs to be further explored. To further understand the role that pelvic organ cross-sensitization plays in the pathogenesis of coexistent bladder and bowel dysfunction in humans, research is needed to establish standard protocols and validated outcome measures evaluating the pathophysiological

consequences of sensitization to help identify novel therapeutic targets to reverse or prevent cross-organ sensitization.

Conclusions

Recommendations for research were made to study the role of cross-organ sensitization in the pathogenesis of co-occurring LUT and bowel dysfunction in humans.

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Table 1. Experimental studies in humans exploring alterations in bowel and lower urinary tract functions following different pelvic organ interventions

Intervention	Recording	Outcome measure	Subjects	Effect	Author
Anal stimulation (distension or skin touch)		Vesical motor activity	Healthy volunteers	↓	Kock (3)
Rectal distension (balloon / Barostat)	Filling cystometry	Sensation of bladder filling	Young healthy women	↑	De Wachter (13)
			Women with OAB	↑	Panayi (28), Akl (29)
			Children with LUTS	↑	Burgers (30)
		Electrical perception threshold (bladder)	Young healthy women	↑	De Wachter (13)
		Maximum bladder capacity	Young healthy women	↓	De Wachter (13)
			Women with OAB	↓	Panayi (28)
			Children with LUTS	↓	Burgers (30)
		Number of detrusor contractions	Women with OAB	↑ / =	Panayi (28), Akl (29)
		Detrusor overactivity	Children with LUTS	↑	Burgers (30)
		Bladder compliance	Spinal Cord Injury	↓	Carone (31)
		First involuntary DO	Spinal Cord Injury	↑	Carone (31)

		DSD	Spinal Cord Injury	↑	Carone (31)
Bladder distension	Rectal distension (balloon)	Sensation of rectal filling	Young healthy women	↓	De Wachter (32)
	See reference (illustration)	Anal tone	Patients undergoing intestinal resection	↑	Buntzen (33)
	See reference (illustration)	Recto-anal motility	Patients undergoing intestinal resection	=	Buntzen (33)
	Pudendal nerve stimulation - EMG	EAS activity	Healthy volunteers	↓	Vitton (34)
			Spinal Cord Injury	=	Vitton (34)
Nicergoline	Pudendal nerve stimulation - EMG	EAS activity	Healthy volunteers	↓	Vitton (34)
			Spinal Cord Injury	=	Vitton (34)

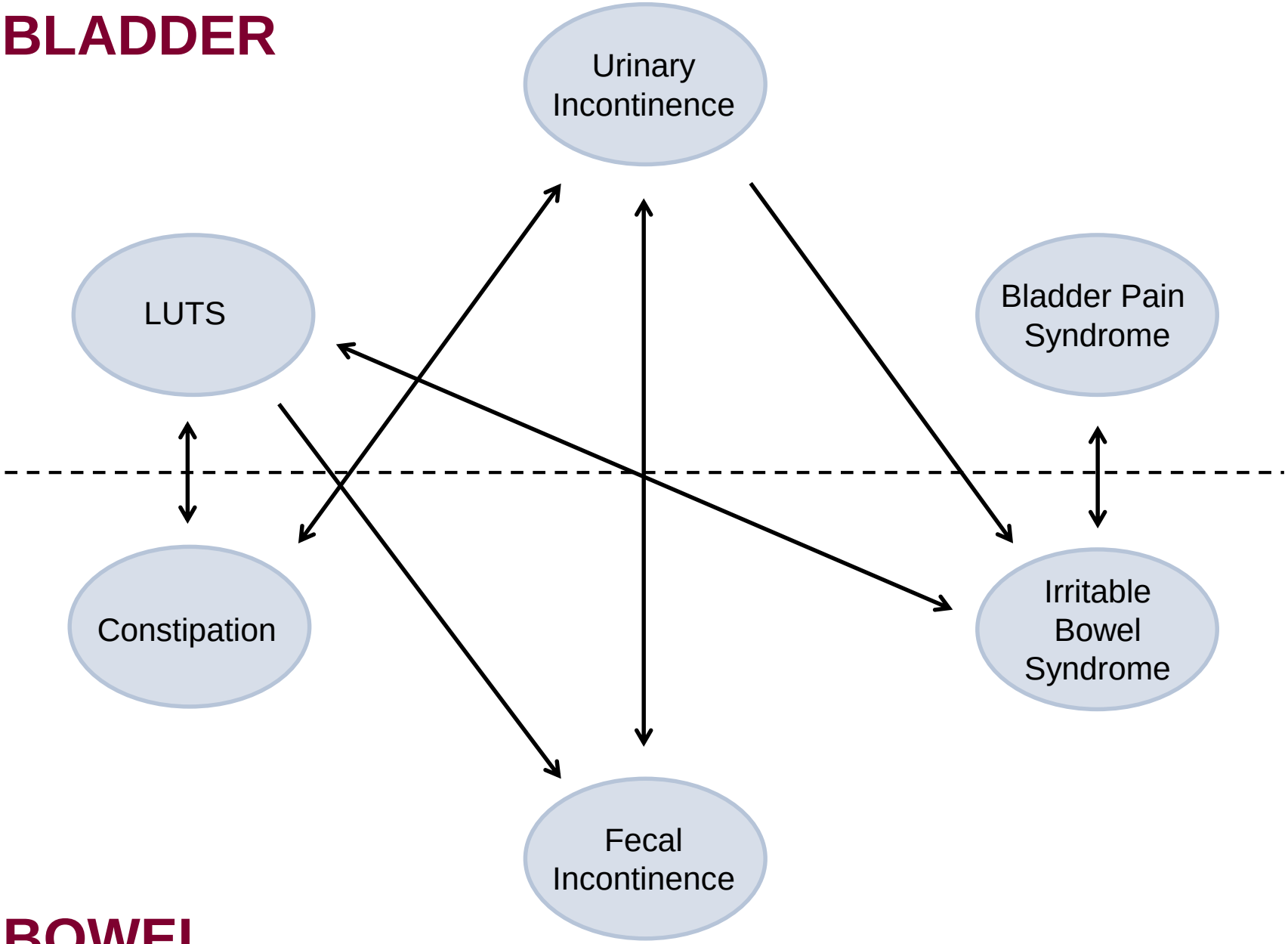
DO: Detrusor overactivity
DSD: Detrusor sphincter dyssynergia
EAS: External anal sphincter
EMG: electromyography
LUTS: lower urinary tract symptoms
OAB: overactive bladder

Table 2. Experimental studies in animals exploring alterations in bowel and lower urinary tract functions following different pelvic organ interventions

INTERVENTION	METHOD	PARAMETER	ANIMAL MODEL	EFFECT	AUTHOR
Rapid rise intravesical pressure	Balloon tambour	EAS contractions	Dogs - SCI	↓	Date (35)
Bladder stimulation: - Distension - Nerve stimulation	Pudendal nerve stimulation - EMG	EAS activity	Cats (SCI)	↓ (=)	Vitton (34)
	EMG	IAS activity	Cats	↑	Bouvier (36), Buntzen (33)
		Colon activity	Cats	↓	Bouvier (36)
	Balloon tambour	Colon motility	Dogs - SCI	↓ then ↑	Hiraoka (37)
Bladder emptying / Micturition	EMG	Colon activity	Cats (SCI)	↑ (↑)	Bouvier (36)
		EAS	Rats	↑	Pezzone (38)
(Colo)rectal stimulation: - Distension - Nerve stimulation	Cystometry	Spontaneous Detrusor contractions	Cats	↓	Buntzen (39), Floyd (40) Hellstrom

					(41)
		Isovolumetric bladder contractions	Rats (SCI)	↓ (↓)	Miyazato (42) (43) Wyndaele (44)
		Micturition	Rats	↓	Pezzone (38)
		Pelvic nerve activity (vesical branches)	Cats	↓	Floyd (40)
		EUS activity	Rats	↓	Pezzone (38)
	Cystometry + electrical stimulation of PMC	Bladder contractions	Cats	↓	Kruse (45)
	Afferent bladder measurements	Bladder afferent activity	Rats	↑ (Aδ only)	Minagawa (46)
Peri-anal stimulation	Cystometry	Isovolumetric bladder contractions	Cats - SCI	↓ / ↑	Wang (47)

EAS: External Anal Sphincter
EMG: electromyography
EUS: External Urethral Sphincter
IAS: External Anal Sphincter
PMC: Pontine Micturition Centre
SCI: Spinal Cord Injury


BLADDER
Urinary Incontinence
LUTS
Bladder Pain Syndrome
Constipation
Irritable Bowel Syndrome
Fecal Incontinence
BOWEL