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Sacral Neuromodulation for Lower Urinary Tract and Bowel Dysfunction in Animal Models: A Systematic Review With Focus on Stimulation Parameter Selection

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ABSTRACT

Objective: Conventional sacral neuromodulation (SNM) has shown to be an effective treatment for lower urinary tract and bowel dysfunction, but improvements of clinical outcome are still feasible. Currently, in preclinical research, new stimulation parameters are being investigated to achieve better and longer effects. This systematic review summarizes the status of SNM stimulation parameters and its effect on urinary tract and bowel dysfunction in preclinical research.

Materials and Methods: The literature search was conducted using three databases: Ovid (Medline, Embase) and PubMed. Articles were included if they reported on stimulation parameters in animal studies for lower urinary tract or bowel dysfunction as a primary outcome. Methodological quality assessment was performed using the SYRCLE Risk of Bias (RoB) tool for animal studies.

Results: Twenty-two articles were eligible for this systematic review and various aspects of stimulation parameters were included: frequency, intensity, pulse width, stimulation signal, timing of stimulation, and unilateral vs. bilateral stimulation. In general, all experimental studies reported an acute effect of SNM on urinary tract or bowel dysfunction, whereas at the same time, various stimulation settings were used.

Conclusions: The results of this systematic review indicate that SNM has a positive therapeutic effect on lower urinary tract and bowel dysfunction. Using low-frequency-SNM, high-frequency-SNM, bilateral SNM, and higher pulse widths showed beneficial effects on storage and evacuation dysfunction in animal studies. An increased variability of stimulation parameters may serve as a basis for future improvement of the effect of SNM in patients suffering from urinary tract or bowel dysfunction.

Keywords: Fecal, incontinence, sacral nerve stimulation, stimulation paradigms, voiding dysfunction

Conflict of Interest: Gommert A. van Koeveringe declares to have a conflict of interest for Medtronic and Axonics. All other authors declare that they have no conflict of interest.

INTRODUCTION

Since the introduction in the 1980's sacral neuromodulation (SNM) has been used in patients with lower urinary tract dysfunction (1, 2). Patients with urinary tract dysfunction reported not only a positive effect of SNM on their lower urinary tract symptoms but also on defecatory complaints. The latter resulted in the first electrical stimulation of sacral nerves for the treatment of fecal incontinence (3).

Nowadays, SNM is an established surgical intervention for urinary tract and bowel dysfunction, more specifically storage and evacuation disorders, intended to treat patients unresponsive to conservative treatment. In urinary tract dysfunction, conservative treatment includes physiotherapy or medication, and in bowel dysfunction, diet and fluid advice, medication, biofeedback therapy, and colonic irrigation. Storage disorders refer to an overactive bladder, a hyposensitive rectum, an underactive urethral or

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anal sphincter causing incontinence. Evacuation disorders refer to an underactive bladder, slow transit colon, and an overactive urethral or anal sphincter causing retention or constipation.

SNM is a minimally invasive therapy involving chronic electrical stimulation of the third sacral nerve root (S3). Successful SNM for both urinary tract and bowel dysfunction is often defined as an improvement in symptomatology of 50% or more compared to baseline. In an accompanying paper, we systematically reviewed the effect on stimulation parameters for sacral neuromodulation on lower urinary tract and bowel dysfunction related to clinical outcome (4). These results showed that the efficacy of SNM on both lower urinary tract and bowel dysfunction might be improved by changing stimulation parameters.

From the point of human ethical concerns, in addition to further understanding of the mechanisms of action, the effects and fine-tuning of SNM in the treatment of urinary tract and bowel dysfunctions is studied in animals. The reason to use preclinical animal studies on SNM is threefold: 1) finding the optimal balance between a positive effect of SNM and potential harmful side effects; 2) fully standardized research in patients with regard to the effect of SNM stimulation paradigms is limited due to ethical concerns and large clinical variability; and 3) implantable pulse generators (IPGs) currently used in clinics are restricted to only a limited range of SNM stimulation settings. In contrast, preclinical studies allow the use of SNM settings beyond conventionally used clinical stimulation paradigms and have previously provided valuable insights into the efficacy and working mechanisms of SNM. To date, no comprehensive overview of the effects of individual SNM parameters for treatment of urinary tract or bowel dysfunction in animal models is available. This systematic review of preclinical literature on SNM and its effect on urinary tract and bowel dysfunction with focus on stimulation parameters fills this gap in the literature. The combination of this systematic review on animal studies and a systematic review of the clinical studies of SNM in urinary tract and bowel dysfunction (4) serves as a basis for future improvement toward the effects of SNM in patients suffering from urinary tract or bowel dysfunction.

MATERIALS AND METHODS

Search Strategy

A systematic literature search was conducted using three databases: Medline (PubMed), Ovid (Embase) and PubMed. Search terms used for all databases are included in the Appendix. Results were uploaded to EndNote to assess for relevance. Reviewers were not blinded to author names, institution, or study title. One reviewer (PD) collected the following characteristics of the included studies: the first author, year of publication, species, sex and number of species, model of disorder, control condition, anesthesia used, stimulation settings, and results of the studies.

Study Selection and Inclusion Criteria

Two reviewers (P.D., R.A.) performed extensive searches of available literature up until January 14, 2020. This search was a shared search for the present preclinical review and a clinical review (see accompanying paper (4)) and results were allocated to each systematic review after the final study inclusion. Studies were eligible

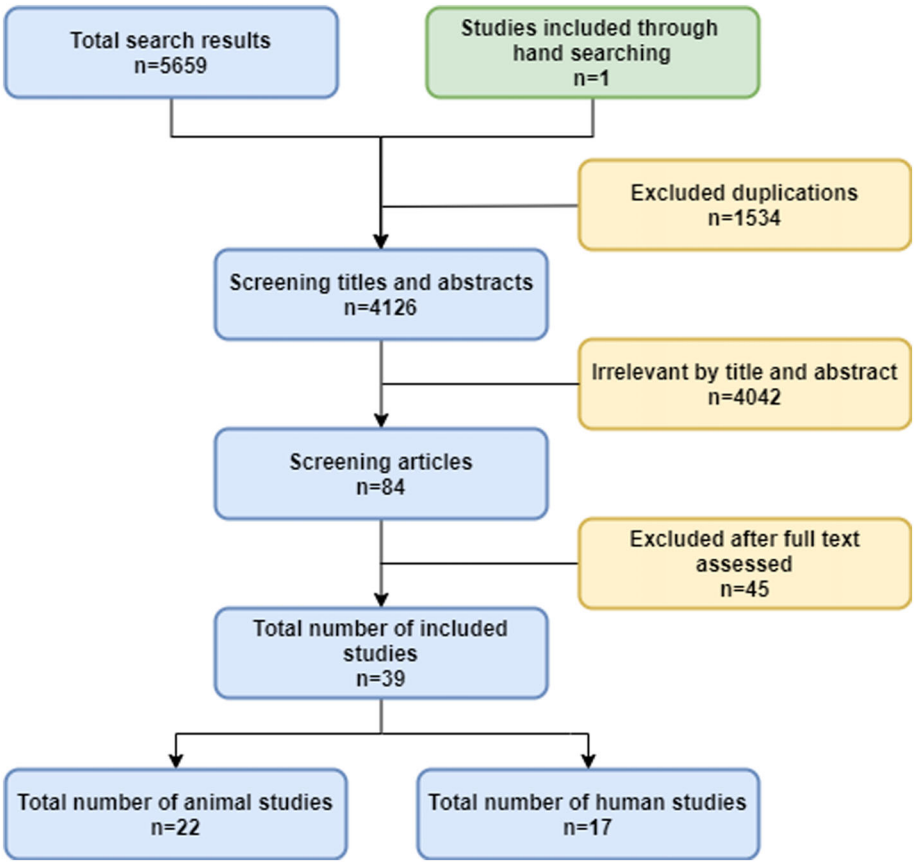

Figure 1 Flowchart of the included studies. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1 Study Characteristics.

Study ID	Species	Sex	Amount	Model	Anesthesia	Procedure
Boger et al. (14)	Cat	m	6	Detrusor sphincter dyssynergia; induced by S1/S2 stimulation	α-chloralose and isoflurane	Extradural cuff electrode
Braun et al. (21) and Seif et al. (22)	Minipig	n/a	12	Detrusor hyperactivity induced by 0.25% formalin solution	Anesthetized, without specification	Transforaminally
Brouillard et al. (17)	Rat	f	13	Healthy	Urethane and conscious	Transforaminally
Cong et al. (20)	Pig	both	7	Bladder overactivity induced by 2.5% acetic acid (control saline)	α-chloralose	Transforaminally
Evers et al. (25)	Rat	f	72	Healthy	Urethane	Transforaminally
Evers et al. (26)	Rat	f	32	Intra-pelvic balloon inflation	Urethane	Transforaminally
Huang et al. (27)	Rat	m	39	Constipation induced by 2 mg/kg ip loperamide (control saline)	Conscious	Transforaminally, extradural
Kaufman et al. (23)	Minipig	n/a	8	Detrusor hyperactivity induced by 0.25% formalin solution	α-chloralose	Laminectomy of segments, intradural
Li et al. (6)	Pig	both	13	Bladder overactivity induced by 5% acetic acid (control saline)	α-chloralose	Transforaminally, by localizing needle
Li et al. (7)	Cat	both	7	Pudendal nerve stimulation to mimic bladder underactivity	α-chloralose	Laminectomy of segments, intradural
Potts et al. (24)	Rat	f	24	Healthy	Urethane	transforaminally
Shaker et al. (15)	Dog	m	11	Detrusor sphincter dyssynergia; induced by spinal cord section at T10 level	Isoflurane	Laminectomy of segments, extradural cuff electrode
Sievert et al. (16)	Dog	m	20	Healthy	Atropine and pentobarbital	Laminectomy of segments, intra- and extradural
Snellings and Grill (8)	Cat	m	14	Healthy	α-chloralose	Extradural cuff electrode
Su et al. (9)	Rat	f	164	Healthy	Urethane	Removed S1 processes
Su et al. (10)	Rat	f	159	Healthy	Urethane	Not specified
Su et al. (11)	Rat	m	31	Bladder overactivity induced by 0.3% acetic acid (control saline)	Urethane	Removed S1 processes
Su et al. (12)	Rat	f	46	Healthy	Urethane	Removed S1 processes
Su et al. (13)	Rat	f	126	Healthy	Urethane	Removed S1 processes
Zhang et al. (18)	Cat	both	19	Healthy	α-chloralose	Dorsal laminectomy, intradural
Zhang et al. (19)	Cat	both	6	Bladder overactivity induced by 0.5% acetic acid (control saline)	α-chloralose	Dorsal laminectomy, intradural

f, female; ip, intraperitoneal; m, male; n/a, not available.

Table 2 Study Design and Outcome for Urinary Tract Dysfunction.

Study ID	Location	Duration	Frequency (Hz)	Pulse width (μsec)	Intensity	Extra information	Outcome
Boger et al. (14)	S2 S1 S1	60 or 90 sec	20 20 12500	100	7 ± 3 Vpp 3 ± 1 Vpp 15 ± 3 Vpp	Intermittent bilateral Continuous Continuous	HF-SNM (12.5 kHz) can prevent EUS activation and allow complete bladder voiding
Braun et al. (21) and Seif et al. (22)	S3	10 min interval	15	1000 210	2.0 V	Quasi-trapezoidal 2/40 signal Biphasic rectangular	Quasi-trapezoidal SNM inhibited unstable detrusor contractions more than rectangular SNM
Brouillard et al. (17)	S1 left	60 sec, started at the onset of the steep rise in bladder pressure signaling an imminent void.	1000 3000		1 mA	Sinusoidal waveform	HF-SNM can suppress imminent voiding for 35–262 sec
Cong et al. (20)	S3 left	During bladder filling	14	64 204 624	5.64 ± 0.76 V (T_{mot}) 3.11 ± 0.48 V 2.52 ± 0.49 V		All pulse widths inhibited bladder overactivity compared to acetic acid levels. Motor threshold for pulse width of 64 μsec was significantly higher than the other two thresholds
Kaufman et al. (23)	S3 DRT	Every 5 min	15	210	2.0 V	Unilateral left Unilateral right Bilateral	Bilateral SNM reduced overactive detrusor contractions better compared to unilateral SNM
Li et al. (6)	S3		5 15 30 50	210	4 V		SNM at 15, 30 and 50 Hz increased bladder capacity. Frequencies higher than 15 Hz did not lead to better outcomes
Li et al. (7)	S1/S2 DRT	During bladder filling	15 30	200	1–1.5x, 1.5-2x T_{mot} 1x, 1–1.5x, 1.5-2x T_{mot}		S1 SNM (15–30 Hz; 1–1.5x T_{mot} - 1.5-2x T_{mot}) blocked pudendal inhibition
Potts et al. (24)	L6/S1	During bladder filling	10	100	Just below T_{mot}	Bilateral, biphasic	SNM between 50–100% and 75–100% of bladder filling cycle increases bladder capacity over control fills
Shaker et al. (15)	S2 and S1 left and right	20 sec	30 600	180 60 175 150 60 20–500 100	1.8 mA 0.9 mA 0.3–1.5 mA 0.7–1.5 mA 0.7 mA 1.1–1.5 mA		HF-SNM reduced urethral pressure. Optimal blocking parameters are 600 Hz, 60 μs, 1,3 mA. Bilateral SNM did not increase the blocking effect
Sievert et al. (16)	S1/S2/S3		1–1000	220	0.08–10 V	Unilateral Bilateral	Bilateral S3 stimulation increased bladder pressure sign better than unilateral SNM
Snellings and Grill (8)	S1	For 30 sec after absolute bladder pressure	2, 5, 7.5, 10, 15, 20, 30	100	0.8, 1, 2x T_{mot}	Unilateral	S1 SNM at 7.5 or 10 Hz and 2x T_{mot} showed maximum inhibition of the normal number of bladder contractions
Su et al. (9)	L6	10 min	10 0.01, 0.1, 1, 20, 50, 100	100	2, 3, 4, 6x T_{mot} 6x T_{mot} (=0.6 mA)	Bilateral	SNM at 10 Hz and high intensity (2 - 6x T_{mot}) showed maximum inhibition of the number of bladder reflex contractions
Su et al. (10)	L6 left	10 min	0.5 10	100	0,6 mA (supra T) 0.6 mA, 1x T_{mot} 0.8, 1x T_{mot}	Bilateral, pulse match/mismatch	Bilateral L6 SNM was more effective than unilateral SNM using a bladder rhythmic contraction model
Su et al. (11)	L6	On every other void	1 10 50	100	1x T_{mot} 0.5, 1, 2x T_{mot} 1x T_{mot}		High-intensity SNM in most effective for altering bladder activities
Su et al. (12)	L6	10 min	10	30 60 90 120 210	0,11 ± 0.02 mA (T_{mot}) 0,12 ± 0.02 mA (T_{mot}) 0,19 ± 0.03 mA (T_{mot}) 0,12 ± 0.03 mA (T_{mot}) 0,16 ± 0.03 mA (T_{mot})		All pulse widths showed inhibition of bladder activity, and no significant differences where found between pulse widths tested. Optimal pulse width was 40 μs
Su et al. (13)	L6	15 min	0.01, 0.1, 1, 4, 10, 40, 100 interburst 0.01 - intraburst 0.1, 1, 10, 40, 1000 interburst 0.1 - intraburst 1, 10, 40, 100, 1000 interburst 1 - intraburst 10, 40, 100, 1000	100	1 T_{mot}	Bilateral biphasic	SNM in burst patterns reduced the number of bladder contractions with an optimum of a four-pulse burst interburst of 1 Hz and intraburst of 40 Hz, but this burst pattern did exceed a continuous stimulation of 10 Hz
Zhang et al. (18)	S1/S2/S3 DRT or VRT		5 15 30	200	0.25, 0.5, 1, 2x T_{mot} 1x T_{mot} 1x T_{mot}		SNM at 5 Hz was optimal for increasing bladder capacity. S1 DRT SNM was more effective than S2 DRT
Zhang et al. (19)	S1/S2/S3 DRT or VRT		5 15 30	200	0.25, 0.5, 1x T_{mot} 1x T_{mot} 1x T_{mot}		SNM at 5 Hz (S1/S2; 1x T_{mot}) inhibited bladder overactivity and increased bladder capacity

DRT, dorsal root; EUS, external urethral sphincter; HF-SNM, high frequency sacral neuromodulation; SNM, sacral neuromodulation; T_{mot}, motor threshold; VRT, ventral root.

for inclusion when in line with the following inclusion criteria: 1) preclinical or clinical study; 2) intervention of temporary or permanent SNM; and 3) comparison of various SNM stimulation parameters. In addition, no language limitations were used and both reviews and meta-analyses were excluded.

Quality of the literature included was assessed by two reviewers (P.D., R.A.) using the SYRCLE Risk of Bias (RoB) tool for animal studies (5). The items in the RoB tool relate to performance bias, selection bias, attrition bias, detection bias, reporting bias, and other biases. Papers were marked as low risk, high risk, or unclear risk. RoB was rated "high" if there were expectations of bias; "unclear" if information was missing, incomplete, or not clear; and "low" if all items were explained clearly and no bias was found.

RESULTS

Based on the online search, 5659 papers were identified and one additional paper was included through hand searching (Fig. 1 for flowchart). Of which 1534 were excluded because of duplications. Due to irrelevance by title and abstract screening, 4042 papers were excluded and 45 more papers were excluded after full text screening. Finally, 39 studies were relevant for inclusion, of which 22 were preclinical studies.

Characteristics of Included Studies

Papers included and relevant characteristics are shown in Table 1. Within these, a large variability was noted with respect to both approach and use of specific stimulation parameters and outcome parameters as well as the animal species. To analyze the outcome, papers were sub-grouped based on type of SNM stimulation parameters: frequency, intensity, pulse width, stimulation signal, timing of stimulation, and unilateral vs. bilateral stimulation. Intensity was often expressed as a percentage of the motor threshold (T_{mot}). T_{mot} is defined as the lowest intensity to evoke pelvic floor muscle contractions, hind toe twitches, or tail twitches. Thereafter, a distinction was made based on outcome parameters: for urinary tract dysfunction: bladder activity, bladder capacity, external urethral sphincter (EUS) activity, and for bowel dysfunction: anal canal cortical evoked potentials (EPs) and rectal volume. Study design and primary outcome of the literature selected are shown in Table 2 (urinary tract dysfunction) and Table 3 (bowel dysfunction).

Risk of Bias Assessment/Methodological Quality

A methodological quality assessment was performed on all papers included (Table 4). In general, randomization (item 1, 4, 6), concealment (item 3), blinding (item 5, 7), and missing data (item 8) were poorly reported. Conversely, papers were free of selective reporting (item 9) and mentioned baseline characteristics (item 2). Other potential bias that could have led to high risk (item 10) regarded anesthesia used during the experiment and missing data about materials and stimulation parameters.

SNM and Urinary Tract Dysfunction

Effect of Frequency

Significant improvement of urinary tract dysfunction in animals has been found in several studies investigating SNM frequencies below 100 Hz (Table 5). Although not all studies on the effects of SNM frequency were performed with similar stimulation intensity or pulse width, stimulation seems to be optimal within a frequency range of 7.5–15 Hz (6–12). The use of SNM at various

Table 3 Study Design and Outcome for Bowel Dysfunction.

Study ID	Location	Duration	Freq (Hz)	Pulse width (μs)	Intensity	Extra information	Outcome
Evers et al. (25)	S1 left	30 min, 3 min, 18 s, 1.8 s	0.1, 1, 10, 100	1000	15 V	No of pulses is 180	Optimal frequency for anal canal cortical EPs is 2 Hz. SNM at 0.5x, 0.75x and 1x T_{mot} increased anal EPs compared to 0x and 0.25x times T_{mot} in rats
		3 min	0.1, 1, 10, 25, 100			No of pulses is 18, 180, 1800, 4500, 18000	
			2		0.25, 0.5, 0.75x T_{mot}	Optimal frequency	
Evers et al. (26)	S1 left	10 min	2 14	1000	1x T_{mot}		Optimal frequency for anal canal cortical Eps is 2 Hz
Huang et al. (27)	S3 right		5	100 210	90% of T_{mot}		SNM inhibited constipation best using 5 Hz, 100 μsec and 90% of T_{mot}
			15	100 210 500			
			30	210			

EPs, evoked potentials; SNM, sacral neuromodulation; T_{mot}, motor threshold.

Table 4 Quality Assessment SYRCLE's Risk of Bias.

SYRCLE's RoB		1	2	3	4	5	6	7	8	9	10
		Selection bias 1	Selection bias 2	Selection bias 3	Performance bias 1	Performance bias 2	Detection bias 1	Detection bias 2	Attrition bias	Reporting bias	Other potential bias
Boger et al. [14]	2012	✗	−	−	✗	−	−	−	✓	✓	✗
Braun et al. [21]	2003	✗	✓	−	✗	−	−	−	−	✓	✗
Brouillard et al. [17]	2019	✗	✓	−	✗	−	−	−	✓	✓	−
Cong et al. [20]	2019	✗	✓	−	✗	−	−	−	✓	✓	✗
Evers et al. [25]	2014	✗	✓	−	−	−	−	−	✓	✓	−
Evers et al. [26]	2016	✗	✓	−	−	−	✓	✓	✗	✓	−
Huang et al. [27]	2019	−	✓	−	−	−	−	−	✓	✓	−
Kaufmann et al. [23]	2009	✓	✓	−	✗	−	−	−	✓	✓	✗
Li et al. [6]	2017	✗	✓	−	✗	−	✓	−	✓	✓	✗
Li et al. [7]	2018	✗	✓	−	✗	−	−	−	✗	✓	✗
Potts et al. [24]	2019	−	✓	−	−	−	✓	−	✓	✓	−
Seif et al. [22]	2003	✗	✓	−	✗	−	−	−	−	✓	✗
Shaker et al. [15]	1998	✗	✓	−	✗	−	−	−	−	✓	✗
Sievert et al. [16]	2002	✗	✓	−	✗	−	✓	−	−	✓	✗
Snellings et al. [8]	2012	✓	−	−	✗	−	−	−	✗	✓	✗
Su et al. [9]	2012	✗	✓	−	✗	−	−	−	−	✓	✗
Su et al. [10]	2013	−	✓	−	✗	−	−	−	−	✓	−
Su et al. [11]	2016	✓	✓	−	✗	−	−	−	−	✓	✗
Su et al. [12]	2017	✗	✓	−	✗	−	−	−	−	✓	−
Su et al. [13]	2017	−	✓	−	✗	−	−	−	−	✓	−
Zhang et al. [18]	2013	✓	✓	−	✗	−	−	−	−	✓	✗
Zhang et al. [19]	2017	✗	✓	−	✗	−	−	−	✓	✓	✗

1: ✓ = adequate randomization; − = randomization but no details; ✗ = no evidence of randomization; **2**: ✓ = all baseline characteristics given; − = not all baseline characteristics given; ✗ = baseline characteristics not given; **3**: ✓ = evidence of allocation concealed; − = no information on concealment of allocation; ✗ = evidence of inadequate concealment of allocation; **4**: ✓ = evidence of random housing of animals; ✗ = no information on housing agreement at all; **5**: ✓ = evidence of caregivers/investigators were blinded to intervention; − = no information on blinding to intervention; ✗ = evidence of non-blinding to intervention; **6**: ✓ = evidence of random selection for assessment; − = no information on random selection for assessment; ✗ =evidence of non-random selection for assessment; **7**: ✓ = evidence of assessor blinded; − = no information on assessor blinding; ✗ = evidence of non-blinded assessor; **8**: ✓ = explanation of animal missing data; − = no information if all animals were included in final analysis; ✗ = no explanation of missing animal data; **9**: ✓ = free of selective reporting based on methods/results; ✗ = selective reporting; **10**: ✓ = free of other high bias risk; − = insufficient data to determine risk of other bias; ✗ = existence of problems with potential for high risk of bias

frequencies (0.01–100 Hz) was shown to significantly reduce the number of bladder contractions per minute (9, 10, 13) or bladder pressure (8) using frequencies from 0.05 to 50 Hz, with the best results applying 4, 7.5, and 10 Hz stimulation. SNM in burst patterns (4–6 pulse burst; interburst 0.01–1 Hz, intraburst 0.1–1000 Hz) reduced the number of bladder contractions per minute with an optimum of a four-pulse burst 1 Hz interburst and 40 Hz intraburst (13), although this burst pattern did not exceed a continuous stimulation of 10 Hz.

Contradictory effects were reported (14–16) as low-frequency (LF)-SNM (10–30 Hz) was shown to affect voiding in dyssynergic reflexive EUS activity and showed elevated bladder and EUS pressure. The best SNM frequencies that inhibit EUS for voiding were 20 and 100 Hz, which resulted in the most optimal bladder response and the lowest EUS pressure and the fastest EUS fatigue, respectively (16). Stimulation at 30 Hz was applied to evoke maximal bladder pressure. Nonetheless, this stimulation also evoked EUS pressure, since the intensity threshold for EUS pressure is lower than the intensity threshold for bladder pressure (15). With focus on uncoordinated contractions of bladder and EUS, detrusor sphincter dyssynergia was induced by providing intermittent bilateral S2 SNM at 20 Hz to evoke bladder pressure and continuous S1 SNM at 20 Hz to evoke EUS pressure (14). The use of high-frequency (HF)-SNM (12.5 kHz, 600 Hz or 200 Hz) allowed voiding, caused by a possible EUS blockade (14, 15) or stimulation related EUS fatigue, which seemed closest to normal voiding (16). The optimal blocking parameters (600 Hz; 60 µsec; 1.3 mA) caused a maximum blocking of EUS pressure and a minimal blocking of bladder pressure (15). HF-SNM at 1 or 3 kHz was reported to suppress imminent voids for 35–262 sec when SNM was applied for 60 sec after the onset of an imminent void. Bladder pressure continued to rise steeply after the SNM onset and reduced rapidly to a lower level for the remaining 60 sec SNM until a void occurred (17).

Table 5 Frequency and Outcome in Urinary Tract Dysfunction.

Frequency (Hz)	Bladder activity	Bladder capacity	EUS activity	Reference
0.01 - 5	0	?		6, 8-11, 13, 18, 19
7.5 - 15	−	+	+	6-11, 13, 16, 18, 19
20 - 40	?	?	+	6-11, 13-16, 18, 19
50	−	?		6, 9, 11
100 - 200	0		−	9, 13, 16
600 - 12500	−		−	14, 15, 17

− = inhibition or decrease; 0 = no changes; + = excitation or increase; ? = ambiguous outcome

The effect of different frequencies on bladder capacity in healthy and acetic acid (a.a.) induced overactive bladder (OAB) animals was investigated (6, 7, 11, 18, 19). SNM at 5 Hz increased bladder capacity (defined as inhibition of isovolumetric bladder contractions) in healthy and a.a. induced OAB in cats, whereas SNM at 15 and 30 Hz did not change bladder capacity (18, 19). Contrarily, SNM at 15, 30, and 50 Hz was shown to increase bladder capacity (defined as infused volume) in a.a. induced OAB pigs equally effective while SNM at 5 Hz did not change bladder capacity (6, 7). Conversely, the use of SNM at 10 Hz increased bladder function significantly as compared to sham, while at the same time, 1 Hz and 50 Hz SNM were ineffective (11).

Effect of Intensity

Stimulation intensities ranging from 0x to 6x T_{mot} (Table 6) were studied in animals with an overall optimal intensity of at least 1x T_{mot}. Higher intensity (2x T_{mot}) SNM caused significantly greater reductions in bladder activity than 0.8x or 1x T_{mot} (8). Stimulation at T_{mot} caused a delayed inhibition of the number of bladder reflex contractions per minute and stimulation at high intensity (2x to 6x T_{mot}) resulted in a prolonged inhibition in rats (9). Furthermore, the intensity required to cause significant inhibition of bladder activity was higher for unilateral SNM (2x T_{mot}) compared to bilateral SNM (0.8x T_{mot}), suggesting that bilateral SNM at the same intensity results in more/prolonged inhibition (10).

SNM increased bladder capacity at 1x and 2x T_{mot} as compared to 0x, 0.25x, and 0.5x T_{mot} (18, 19). Similar results were reported and showed that bladder capacity during 1x T_{mot} was significantly larger than sham, while bladder capacity during 2x T_{mot} was significantly larger than sham, 0.5x, and 1x T_{mot} (11). SNM at S1 (1–1.5x T_{mot}) applied together with pudendal nerve stimulation (PNS), used as a model to partly mimic bladder underactivity, blocked PNS inhibition and decreased bladder capacity to control levels, whereas SNM alone did not increase bladder capacity. SNM applied at 1.5–2x T_{mot} increased bladder capacity compared to control, and together with PNS, SNM blocked PNS inhibition. These results were not seen for SNM at S2, which only showed a significant increase when SNM alone at 1.5–2x T_{mot} was applied (7).

Effect of Pulse Width

SNM pulse widths significantly affected bladder capacity and inhibited bladder activity in animals. In order to detect the

Table 6 Intensity and Outcome in Urinary Tract Dysfunction.

Intensity (x T_{mot})	Bladder activity	Bladder capacity	Reference
0.25 - 0.4		0	18, 19
0.5 – 0.9	0	0	8, 10, 11, 18, 19
1 – 1.9	?	+	7-11, 18
2 - 6	−	+	8-11, 18

− = inhibition or decrease; 0 = no changes; + = excitation or increase; ? = ambiguous outcome

Table 7 Frequency and Outcome in Bowel Dysfunction.

Frequency (Hz)	Anal canal EPs	Rectal volume	Reference
0.1 - 5	+	+	25-27
10 - 15	+	+	25-27
25 - 30	?	+	25, 27
100	0		25

0 = no changes; + = excitation or increase; ? = ambiguous outcome

optimal pulse widths that achieve the best clinical effects, pulse widths of 64, 204, and 624 μsec (F = 14 Hz) were analyzed and shown to significantly increase bladder capacity as compared to the a.a. control level (20). Pulse widths between 30 μsec and 210 μsec (F = 10 Hz) were shown to significantly inhibited bladder activity (12). In neither of the studies, significant differences were noted between the pulse widths tested. The latter may be related to the various stimulation intensities used, which were provided at T_{mot}. An inverse exponential correlation was found between pulse width and corresponding T_{mot} (intensity) and the optimal pulse width determined by T_{mot} was 40 μsec in one study (12). The other study concluded that for a clinical approach, a pulse width of 204 μsec might be more appropriate for SNM in patients to optimize battery life and maintain patient comfort during stimulation (20).

Effect of Stimulation Signal

Several stimulation signals can be delivered to modulate the effect of SNM in animals. Sinusoidal SNM almost doubled the EUS pressure when compared to rectangular SNM using similar amplitudes (16). Using rectangular SNM, evoked bladder pressure decreased with an increased amplitude (higher than 6 V) which did not occur using sinusoidal SNM. It was concluded that rectangular SNM has many harmonics that stimulate other nerve fibers and that "cleaner" sinusoidal SNM may result in a more organ-specific stimulation (16, 21, 22). Further analysis of the effect of stimulation signal revealed that quasi-trapezoidal SNM inhibited induced detrusor overactivity significantly more than the conventional rectangular SNM (21, 22).

Effect of Unilateral Versus Bilateral SNM

Bilateral SNM in animals was shown to significantly increase bladder pressure (16) and decreased the number of hyperactive detrusor contractions more than unilateral SNM (10, 23). Interestingly, the intensity threshold for bilateral SNM was 0.8x T_{mot}, and for unilateral SNM 2x T_{mot}. No significant differences were found in bilateral stimulation using balanced (time-matched pulses) and unbalanced (time-mismatched pulses) current intensities (10).

Effect of Timing

One study focused on the timing of SNM in relation to a specific phase of the bladder filling cycle. SNM delivered between 50–100% and 75–100% of the bladder filling cycle increased bladder capacity with 32% and 43%, respectively, over control fills. SNM delivered in the first 50% of the bladder filling cycle had no effect on bladder capacity (24).

Table 8 Intensity and Outcome in Bowel Dysfunction.

Intensity (x T_{mot})	Anal canal EPs	Reference
0.25	0	25
0.5	+	25
0.75	+	25
1	+	25

0 = no changes; + = excitation or increase

SNM and Bowel Dysfunction

Effect of Frequency

A few studies focused on analysis of SNM parameters for bowel dysfunction (25–27). It was noted that frequency of SNM on amplitude of anal canal EPs is highly significant in healthy rats (25). Various frequencies (0.1–100 Hz) were tested and showed that 1 and 10 Hz stimulation significantly increased the amplitude of EPs compared to other frequencies (Table 7). Using a graph of nonlinear curve fitting for each time point, a frequency-potentiation relationship parabolic in form with a clear optimum at 2 Hz in these healthy rats was reported (25). These findings were further substantiated in a rodent model of fecal incontinence where SNM restored the decreased EPs after pudendal nerve injury and 2 Hz SNM also enhanced the decreased EPs more than 14 Hz (26).

In the treatment of constipation, SNM significantly increased rectal volume. All frequencies tested increased rectal volume in rodents, with a reported optimal frequency of 5 Hz and an optimal pulse width of 100 μsec (27).

Effect of Intensity

Using the reported optimal frequency of 2 Hz, various stimulation intensities (0.25x, 0.5x, 0.75x, 1x T_{mot}, and sham) were investigated in healthy rats (25). SNM stimulation at 0.5x, 0.75x, and 1x T_{mot} significantly increased the amplitude of EPs compared to sham stimulation (Table 8).

DISCUSSION

This systematic review aimed to investigate the effects of various stimulation parameters of SNM for urinary tract and bowel dysfunction in animals. In general, all studies reported an acute effect of SNM on urinary tract or bowel dysfunction while various stimulation settings were used.

LF-SNM of 7.5–15 Hz appeared to be optimal in inhibiting bladder contractile activity and increasing bladder capacity, which is useful for patients with urinary incontinence, whereas HF-SNM inhibited EUS activity and caused voiding. It is important to note that some SNM frequencies within this range have only been studied to a limited extent, which might over- or underestimate the effect. Ambiguous results were reported using LF-SNM. Three studies reported that LF-SNM increased bladder activity (14–16) and three studies reported that SNM inhibited bladder activity (8–10). No clear explanation for these contradictory results was given causing the underlying mechanisms to warrant further research. Interestingly, studies that reported an increase in bladder activity applied SNM at L6 in female Sprague Dawley rats (9, 10) and S1 in male cats (8), whereas studies that reported a decrease in bladder activity applied SNM at S2 in male cats (14) and S1-S3 in male dogs (15, 16). These results may be caused by the various animal species used. But these results may also suggest that location of SNM is important as SNM at L6-S1 may increase the EUS activity and concomitantly inhibit bladder activity, whereas SNM at S1-S3 may shift the balance in the opposite direction.

HF-SNM was reported to block or fatigue EUS pressure and allow voiding (14–16). At the same time, HF-SNM was reported to suppress acute imminent voids (17). All studies reported low bladder pressure when HF-SNM was applied. It is highly probable that HF-SNM first increases EUS pressure and therefore suppresses voiding and after a short period decreases EUS pressure due to fatigue and thereafter allows voiding.

SNM at low frequencies that seem to be optimal in inhibiting bladder activity and increasing bladder capacity are similar to the conventional frequencies used in the clinic. Similarly, high frequencies that seem to cause voiding are not used. These high frequencies may have clinical utility for patients with voiding dysfunction. Moreover, in clinically related areas like anesthesiology and pain management, the use of spinal cord stimulation in treatment of chronic neuropathic (low back) pain has been shown to benefit from HF (10 KHz) (28). As the spinal network underlying bladder control and defecation has similarities with the nociceptive spinal network it is not unreasonable to speculate that similar HF paradigms may also achieve significant effects for lower urinary tract and bowel dysfunction (29).

For bowel dysfunction, the preferred SNM frequencies to increase anal canal EPs and rectal volume are lower than the conventional frequencies used in clinical settings. In addition, the preferred pulse width to increase rectal volume is lower, whereas the stimulus intensity seems equal to clinical settings.

For urinary tract dysfunction, values above 1x T_{mot} were optimal in achieving a positive acute effect. Only two papers showed an effect of sub-T_{mot} SNM (10, 24), and it is noteworthy that inhibition of bladder activity was reported in animals that received bilateral SNM (10, 24) but not in animals that received unilateral SNM (8, 10). In additional papers, it was concluded that bilateral stimulation increased bladder pressure and decreased the number of hyperactive detrusor contractions more than unilateral SNM with similar stimulation settings (16, 23). This may suggest that bilateral SNM is more effective at lower intensities than unilateral SNM. However in clinical studies, bilateral SNM was not reported to be more effective than unilateral SNM (30) and chronic SNM in clinical setting is always applied at (sub)sensory threshold, which is significantly lower than the motor threshold (31).

Preferred SNM frequencies for bowel dysfunction (2–5 Hz) are lower compared to urinary tract dysfunction (10 Hz) in animal models, whereas bowel dysfunction (31 Hz) in clinical settings is treated with higher SNM frequencies compared to urinary tract dysfunction (16 Hz). In contrast, experimental studies on bowel dysfunction apply lower intensities to achieve a positive effect compared to urinary tract dysfunction. In this respect, it should be noted that most experimental studies were performed under anesthesia which has been shown to affect outcome measurements. Under conscious conditions, stimulation at T_{mot} may cause an unpleasant perception or paresthesia.

The majority of the SNM pulse widths applied in the experimental studies on urinary and bowel dysfunction are similar to conventional settings used in clinical settings. The inverse exponential correlation and the optimal pulse width based on T_{mot} (40 μsec) was later reported to be the identical in anesthetized and awake sheep (32). This inverse exponential correlation suggests that the SNM total charge per second is relevant for a positive effect (20). However, when the total number of pulses for each frequency-duration combination was fixed at 180, not all combinations presented the same outcome in anal canal EPs. This suggests that SNM total charge is not important for the outcome. Only 0.1 and 1 Hz showed a significant effect, whereas 10 and 100 Hz did not. It is worth noting that the settings with a significant effect had the longest SNM duration; 30 min and 3 min, respectively. Other settings had a SNM duration of 18 and 1.8 sec (25). This may suggest that a minimal SNM duration is required to detect a significant outcome and that SNM total charge is still important for clinical outcomes.

Furthermore, SNM during the last 50% of bladder filling appeared to be the most optimal (24). In addition, a sinusoidal and quasi-trapezoidal signal seemed to be more organ-specific and inhibited induced detrusor overactivity more, respectively (21, 22). Both results were only reported in one study making it hard to draw definite conclusions from this data.

Previous research in the field of urology improved the understanding of the mechanisms of action behind SNM. It was once thought that an efferent EUS motor response causing detrusor relaxation was involved in the mechanisms of action underlying SNM. This theory solely is unlikely as SNM has shown to work when no EUS contractions are observed (33). Another theory supports activation of sensory nerves; research into the latency of the motor response (i.e., anal sphincter contraction) measured in women implied that the response is reflex mediated (34). In this context, it is also important to note that, although with use of intravaginal electrical stimulation in cat, the involvement of reflex pathways when recording efferent nerves to the bladder was noted (35). Research into cortical changes showed increased cortical activity after acute SNM and reduced cortical activity after chronic SNM. These observations were seen in both urinary and fecal incontinence (36). In addition, areas involved in micturition, awareness, and alertness showed changes in regional cerebral blood flow (rCBF) in the brain following SNM. This results display an increased awareness of bladder filling and pelvic floor contraction after SNM suggesting SNM restores normal urinary continence (37).

In line with this hypothesis, in cats dorsal root SNM (afferent pathways) at intensity threshold inhibited bladder activity more than ventral root SNM (efferent pathways) (18). Moreover, low-intensity SNM in rodents showed increased bladder capacity which was reported to be afferent mediated, whereas high-intensity SNM additionally attenuated the bladder contraction amplitude and was reported to be efferent mediated (9). These results suggest that low-intensity SNM only activates large myelinated fibers while high-intensity SNM additionally activates unmyelinated C-fibers (9, 10, 38).

Limitations within the reviewed studies for both urinary tract and bowel dysfunction were, mainly, the methodological quality assessment (5). Due to poor reporting most RoB items were scored with "unclear" risk for all studies. Only a few studies reported randomization or blinding while most studies did not report such details. Likewise, data required for replication of the experiment was missing, such as stimulation settings, device specification, and animal characteristics. More precise reporting is required to achieve higher quality animal studies during future investigations.

Furthermore, the diversity in outcome parameters and SNM settings made it difficult to compare studies. Primary outcome parameters (bladder activity, bladder capacity, EUS activity, and anal canal EPs) were not one on one comparable making it challenging to determine an optimal effect. Moreover, stimulation settings often differed. For example, stimulations with similar frequencies noted various results, which could be due to the large variability in other stimulation settings, such as intensity, duration, and location. Furthermore, use of heterogeneous animals across studies may result in differential effects of stimulation using similar stimulation settings. Looking forward, a more standardized methodological approach is needed for further research.

In summary, in animal studies, we found that LF-SNM of 7.5–15 Hz appeared to be optimal for storage dysfunction. HF-SNM is shown to facilitate bladder evacuation. Bilateral SNM and pulse widths above conventional settings allow a reduction in stimulus intensity to diminish aberrant perceptions. For bowel dysfunction, it was difficult to make any firm conclusions, but studies showed that a frequency of 2–5 Hz and a stimulus intensity below 1x T_{mot} was preferred for both storage and evacuation dysfunction. The findings of this review should be interpreted with caution since the methodologies within the studies analyzed were assessed with "unclear" risk of bias and too diverse to present comprehensive and precise conclusions toward optimal settings in clinical practice. A more standardized methodological approach is needed for further research.

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Authorship Statements

Perla Douven, Gommert A. van Koeveringe, Elbert A. Joosten, Stephanie O. Breukink, Jarno Melenhorst, and Roman Assmann designed and conceptualized the study. Perla Douven wrote the manuscript. Perla Douven, Roman Assmann, and Jos Kleijnen determined the systematic literature search strategy and performed the search. Perla Douven and Roman Assmann critically filtered and quality assessed the manuscripts. All authors have approved the final version of the manuscript.

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APPENDIX: SEARCH TERMS

All search strategies are based on work published in Riemsma et al.[39]

Embase (ovid): 1974–2020/01/13

Searched 14.1.2020

1. incontinence/
2. continence/
3. (incontinen$ or continen$ or obstipat$).ti,ab,ot.
4. urine incontinence/ or mixed incontinence/ or stress incontinence/ or urge incontinence/
5. ((Urine$ or urinary or urinat$ or micturat$ or bladder$) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or escaping or uncontrolled or trickl$ or "lack of control" or "no control" or "out of control" or "not voluntary" or involuntary or wetting or leaked or seeped or retention$ or retain$ or dysfunct$ or malfunct$ or obstruct$ or block$ or overactiv$ or over-activ$)).ti,ab,ot.
6. (bladder$ adj3 control$).ti,ab,ot.
7. (SUI or OAB or BPS).ti,ab,ot.
8. "giggle enuresis".ti,ab,ot.
9. "enuresis risoria".ti,ab,ot.
10. (incontinentia urinae or enuresis ureterica or ureter enuresis or enuresis diurnal).ti,ab,ot.
11. ((Unable or inabilit$ or abilit$ or able) adj3 control$ adj3 (urine$ or urinat$ or urinary or micturat$)).ti,ab,ot.
12. neurogenic bladder/.
13. ((neurogenic$ or neurologic$ or spinal or spastic$) adj4 bladder$).ti,ab,ot.
14. neurogenic vesical dysfunct$.ti,ab,ot.
15. (Bladder sphincter dys?ynergia or detrusor sphincter dys?ynergia or neurogenic detrusor overactiv$).ti,ab,ot.
16. feces incontinence/.
17. (Encopresis or incontinentia alvi).ti,ab,ot.
18. ((bowel$ or rectum or rectal$) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or uncontrolled or trickl$ or "lack of control" or "no control" or "out of control" or "not voluntary" or involuntary or control$)).ti,ab,ot.
19. ((Unable or inabilit$ or abilit$ or able) adj3 control$ adj3 (faeces or faecal$ or feces or fecal$ or stool$ or rectum or rectal$ or bowel$ or bladder$ or anal$ or anus or urine or urinary or diarrh$ or soiling)).ti,ab,ot.
20. ((feces or faeces or fecal$ or faecal$ or stool or stools or defecat$ or soiling) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or escaping or uncontrolled or trickl$ or "not voluntary" or involuntary or control$)).ti,ab,ot.
21. ((diarrh$ or Pseudodiarrh$ or Pseudo-diarrh$) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or uncontrolled or trickl$ or "not voluntary" or involuntary or control$)).ti,ab,ot.
22. ((Unable or inabilit$ or abilit$ or able) adj3 control$ adj3 (diarrh$ or Pseudodiarrh$ or Pseudo-diarrh$)).ti,ab,ot.
23. ((bowel$ or rectum or rectal$ or defecat$) adj4 (disorder$ or malfunction$ or dysfunction$ or evacuat$ or obstruct$ or block $)).ti,ab,ot.
24. ((feces or faeces or fecal$ or faecal$ or stool or stools or defecat$ or soiling) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or escaping or uncontrolled or trickl$ or "not voluntary" or involuntary or control$)).ti,ab,ot.
25. (urinary tract adj3 (dysfunct$ or disorder$ of syndrome$)).ti,ab,ot.
26. (LUTD or LUTS).ti,ab,ot.
27. (pelvic floor adj3 (dysfunct$ or disorder$ of syndrome$)).ti,ab,ot.
28. ((feces or faeces or fecal$ or faecal$ or stool or stools or defecat$ or soiling) adj2 (store or stored or storag$) adj2 (disorder $ or dysfunct$ or malfunct$ or syndrome$)).ti,ab,ot.
29. ((disorder$ or difficult$ or syndrome$) adj4 (urine$ or urinat $ or urinary or micturat$ or bladder$)).ti,ab,ot.
30. overactive bladder/.
31. (detrusor adj2 (overactiv$ or over-activ$)).ti,ab,ot.
32. cystitis/ or interstitial cystitis/.
33. ((pain$ or discomfort$ or inflamm$ or infect$) adj4 (urine$ or urinat$ or urinary or micturat$ or bladder$ or pelvis or pelvic)).ti,ab,ot.
34. (megacystitis or cystitis or pericystitis).ti,ab,ot.
35. (detrusor adj2 (overactiv$ or over-activ$)).ti,ab,ot.
36. ((bladder$ or hunner or hunneri or submucos$ or submucos$) adj2 (ulcus or ulcer$)).ti,ab,ot.
37. or/1-36
38. sacral nerve stimulation/
39. InterStim.ti,ab,ot.
40. (SNS or SNM).ti,ab,ot.
41. (sacral adj3 (neuromodulat$ or neuro-modulat$ or deafferent$ or de-afferent$ or neurostimulat$ or neuro-stimulat $)).ti,ab,ot.
42. medical electrical stimulation therap$.ti,ab,ot.
43. ((bladder$ or sacral$) adj2 (Autoaugment$ or Auto-augment $)).ti,ab,ot.

44. (sacral nerve$ adj3 (modulat$ or stimulat$)).ti,ab,ot.
45. or/38-44.
46. 37 and 45

Medline (Ovid): 1946–2020/01/13
Searched 14.1.2020

1. Fecal Incontinence/
2. exp Urinary Incontinence/
3. Urinary Bladder, Neurogenic/
4. Urinary Bladder, Overactive/
5. cystitis/ or cystitis, interstitial/
6. urination disorders/or urinary retention/
7. (incontinen$ or continen$ or obstipat$).ti,ab,ot.
8. ((Urine$ or urinary or urinat$ or micturat$ or bladder$) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or escaping or uncontrolled or trickl$ or "lack of control" or "no control" or "out of control" or "not voluntary" or involuntary or wetting or leaked or seeped or retention$ or retain$ or dysfunct$ or malfunct$ or obstruct$ or block$ or overactiv$ or over-activ$)).ti,ab,ot.
9. (bladder$ adj3 control$).ti,ab,ot.
10. (SUI or OAB or BPS).ti,ab,ot.
11. "giggle enuresis".ti,ab,ot.
12. "enuresis risoria".ti,ab,ot.
13. (incontinentia urinae or enuresis ureterica or ureter enuresis or enuresis diurnal).ti,ab,ot.
14. ((Unable or inabilit$ or abilit$ or able) adj3 control$ adj3 (urine$ or urinat$ or urinary or micturat$)).ti,ab,ot.
15. ((neurogenic$ or neurologic$ or spinal or spastic$) adj4 bladder$).ti,ab,ot.
16. neurogenic vesical dysfunct$.ti,ab,ot.
17. (Bladder sphincter dys?ynergia or detrusor sphincter dys?ynergia or neurogenic detrusor overactiv$).ti,ab,ot.
18. (Encopresis or incontinentia alvi).ti,ab,ot.
19. ((bowel$ or rectum or rectal$) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or uncontrolled or trickl$ or "lack of control" or "no control" or "out of control" or "not voluntary" or involuntary or control$)).ti,ab,ot.
20. ((Unable or inabilit$ or abilit$ or able) adj3 control$ adj3 (faeces or faecal$ or feces or fecal$ or stool$ or rectum or rectal$ or bowel$ or bladder$ or anal$ or anus or urine or urinary or diarrh$ or soiling)).ti,ab,ot.
21. ((feces or faeces or fecal$ or faecal$ or stool or stools or defecat$ or soiling) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or escaping or uncontrolled or trickl$ or "not voluntary" or involuntary or control$)).ti,ab,ot.
22. ((diarrh$ or Pseudodiarrh$ or Pseudo-diarrh$) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or uncontrolled or trickl$ or "not voluntary" or involuntary or control$)).ti,ab,ot.
23. ((Unable or inabilit$ or abilit$ or able) adj3 control$ adj3 (diarrh$ or Pseudodiarrh$ or Pseudo-diarrh$)).ti,ab,ot.
24. ((bowel$ or rectum or rectal$ or defecat$) adj4 (disorder$ or malfunction$ or dysfunction$ or evacuat$ or obstruct$ or block $)).ti,ab,ot.
25. ((feces or faeces or fecal$ or faecal$ or stool or stools or defecat$ or soiling) adj4 (leak or leakage or leaks or leaking or seep or seepage or seeps or seeping or accident$ or escap$ or escaping or uncontrolled or trickl$ or "not voluntary" or involuntary or control$)).ti,ab,ot.
26. (urinary tract adj3 (dysfunct$ or disorder$ of syndrome$)).ti,ab,ot.
27. (LUTD or LUTS).ti,ab,ot.
28. (pelvic floor adj3 (dysfunct$ or disorder$ of syndrome$)).ti,ab,ot.
29. ((feces or faeces or fecal$ or faecal$ or stool or stools or defecat$ or soiling) adj2 (store or stored or storag$) adj2 (disorder $ or dysfunct$ or malfunct$ or syndrome$)).ti,ab,ot.
30. ((disorder$ or difficult$ or syndrome$) adj4 (urine$ or urinat $ or urinary or micturat$ or bladder$)).ti,ab,ot.
31. (detrusor adj2 (overactiv$ or over-activ$)).ti,ab,ot.
32. ((pain$ or discomfort$ or inflamm$ or infect$) adj4 (urine$ or urinat$ or urinary or micturat$ or bladder$ or pelvis or pelvic)).ti,ab,ot.
33. (megacystitis or cystitis or pericystitis).ti,ab,ot.
34. (detrusor adj2 (overactiv$ or over-activ$)).ti,ab,ot.
35. ((bladder$ or hunner or hunneri or submucos$ or submucos$) adj2 (ulcus or ulcer$)).ti,ab,ot.
36. or/1–35.
37. InterStim.ti,ab,ot.
38. (SNS or SNM).ti,ab,ot.
39. (sacral adj3 (neuromodulat$ or neuro-modulat$ or deafferent$ or de-afferent$ or neurostimulat$ or neuro-stimulat $)).ti,ab,ot.
40. medical electrical stimulation therap$.ti,ab,ot.
41. ((bladder$ or sacral$) adj2 (Autoaugment$ or Auto-augment $)).ti,ab,ot.
42. (sacral nerve$ adj3 (modulat$ or stimulat$)).ti,ab,ot.
43. or/37–42.
44. 36 and 43

Pubmed (NLM): 1947–2020/01/13
Searched 14.1.2020

#52 Search (#41 AND #46 AND #51)
#51 Search (#50 OR #49)
#50 Search (((pubstatusaheadofprint OR publisher[sb])))
#49 Search (#47 OR (#47 AND #48))
#48 Search human*[tiab]
#47 Search (((rat[tiab] or rats[tiab] or mouse[tiab] or mice[tiab] or murine[tiab] or rodent[tiab] or rodents[tiab] or hamster[tiab] or hamsters[tiab] or pig[tiab] or pigs[tiab] or porcine[tiab] or rabbit [tiab] or rabbits[tiab] or animal[tiab] or animals[tiab] or dogs[tiab] or dog[tiab] or cats[tiab] or cow[tiab] or bovine[tiab] or sheep [tiab] or ovine[tiab] or monkey[tiab] or monkeys[tiab])))
#46 Search (#42 OR #43 OR #44 OR #45 OR)
#45 Search ("sacral nerve"[Title/Abstract]) AND (modulat*[Title/Abstract] OR stimulat*[Title/Abstract])
#44 Search ((sacral[Title/Abstract] OR Bladder*[Title/Abstract])) AND (neuromodulat*[Title/Abstract] OR neuro-modulat*[Title/Abstract] OR deafferent*[Title/Abstract] OR de-afferent*[Title/Abstract] OR neurostimulat*[Title/Abstract] OR neuro-stimulat* [Title/Abstract] OR Autoaugment*[Title/Abstract] OR Auto-augment*[Title/Abstract])
#43 Search (medical electrical stimulation[Title/Abstract]) AND therap*[Title/Abstract]
#42 Search (InterStim[Title/Abstract] OR SNS[Title/Abstract] OR SNM[Title/Abstract] OR PTNS[Title/Abstract])
#41 Search (#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40)
#40 Search (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)

#39 Search ((bladder*[Title/Abstract] OR hunner[Title/Abstract] OR hunneri[Title/Abstract] OR submucos*[Title/Abstract] OR submucos*[Title/Abstract])) AND (ulcus[Title/Abstract] OR ulcer*[Title/Abstract])

#38 Search ((pain*[Title/Abstract] OR discomfort*[Title/Abstract] OR inflamm*[Title/Abstract] OR infect*[Title/Abstract])) AND (urine*[Title/Abstract] OR urinat*[Title/Abstract] OR urinary[Title/Abstract] OR micturat*[Title/Abstract] OR bladder*[Title/Abstract] OR pelvis[Title/Abstract] OR pelvic[Title/Abstract])

#37 Search ((disorder*[Title/Abstract] OR difficult*[Title/Abstract] OR syndrome*[Title/Abstract])) AND (urine* or urinat* or urinary or micturat* or bladder*)

#36 Search (((feces[Title/Abstract] OR faeces[Title/Abstract] OR fecal*[Title/Abstract] OR faecal*[Title/Abstract] OR stool[Title/Abstract] OR stools[Title/Abstract] OR defecat*[Title/Abstract] OR soiling[Title/Abstract])) AND (store[Title/Abstract] OR stored[Title/Abstract] OR storag*[Title/Abstract])) AND (disorder*[Title/Abstract] OR dysfunct*[Title/Abstract] OR malfunct*[Title/Abstract] OR syndrome*[Title/Abstract])

#35 Search ((“urinary tract”[Title/Abstract] OR “pelvic floor”[Title/Abstract])) AND (dysfunct*[Title/Abstract] OR disorder*[Title/Abstract] OR syndrome*[Title/Abstract])

#34 Search (OAB[Title/Abstract] OR BPS[Title/Abstract] OR LUTD [Title/Abstract] OR LUTS[Title/Abstract])

#33 Search (((cystitis[Title/Abstract]) OR “overactive bladder”[Title/Abstract]) OR (“over-active detrusor”[Title/Abstract] OR “overactive detrusor”[Title/Abstract])) OR (megacystitis[Title/Abstract] OR pericystitis[Title/Abstract])

#32 Search ((((Unable[Title/Abstract] OR inabilit*[Title/Abstract] OR abilit*[Title/Abstract] OR able[Title/Abstract])) AND control* [Title/Abstract]) AND (diarrh*[Title/Abstract] OR Pseudodiarrh* [Title/Abstract] OR Pseudo-diarrh*[Title/Abstract]))

#31 Search (((diarrh*[Title/Abstract] OR Pseudodiarrh*[Title/Abstract] OR Pseudo-diarrh*[Title/Abstract])) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking[Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract] OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident*[Title/Abstract] OR escap*[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR “not voluntary”[Title/Abstract] OR involuntary[Title/Abstract] OR control*[Title/Abstract]))

#30 Search (((feces[Title/Abstract] OR faeces[Title/Abstract] OR fecal*[Title/Abstract] OR faecal*[Title/Abstract] OR stool[Title/Abstract] OR stools[Title/Abstract] OR defecat*[Title/Abstract] OR soiling[Title/Abstract])) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking[Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract] OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident*[Title/Abstract] OR escap*[Title/Abstract] OR escaping[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR “not voluntary”[Title/Abstract] OR involuntary[Title/Abstract] OR control*[Title/Abstract]))

#29 Search ((((Unable[Title/Abstract] OR inabilit*[Title/Abstract] OR abilit*[Title/Abstract] OR able[Title/Abstract])) AND control* [Title/Abstract]) AND (faeces[Title/Abstract] OR faecal*[Title/Abstract] OR feces[Title/Abstract] OR fecal*[Title/Abstract] OR stool*[Title/Abstract] OR rectum[Title/Abstract] OR rectal*[Title/Abstract] OR bowel*[Title/Abstract] OR bladder*[Title/Abstract] OR anal*[Title/Abstract] OR anus[Title/Abstract] OR urine[Title/Abstract] OR urinary[Title/Abstract] OR diarrh*[Title/Abstract] OR soiling[Title/Abstract]))

#28 Search ((rectal[Title/Abstract]) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking[Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract] OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident*[Title/Abstract] OR escap*[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR “lack of control”[Title/Abstract] OR “no control”[Title/Abstract] OR “out of control”[Title/Abstract] OR “not voluntary”[Title/Abstract] OR involuntary[Title/Abstract] OR control*[Title/Abstract]))

#27 Search ((rectum[Title/Abstract]) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking[Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract] OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident*[Title/Abstract] OR escap*[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR “lack of control”[Title/Abstract] OR “no control”[Title/Abstract] OR “out of control”[Title/Abstract] OR “not voluntary”[Title/Abstract] OR involuntary[Title/Abstract] OR control*[Title/Abstract]))

#26 Search ((bowel*[Title/Abstract]) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking[Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract] OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident*[Title/Abstract] OR escap*[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR “lack of control”[Title/Abstract] OR “no control”[Title/Abstract] OR “out of control”[Title/Abstract] OR “not voluntary”[Title/Abstract] OR involuntary[Title/Abstract] OR control*[Title/Abstract]))

#25 Search ((Encopresis[Title/Abstract] OR “incontinentia alvi”[Title/Abstract]))

#24 Search ((“Bladder sphincter dyssynergia”[Title/Abstract] OR “detrusor sphincter dysynergia”[Title/Abstract] OR “Bladder sphincter dysynergia”[Title/Abstract] OR “detrusor sphincter dyssynergia”[Title/Abstract] OR “neurogenic detrusor overactivity”[Title/Abstract]))

#23 Search ((SUI[Title/Abstract] OR “giggle enuresis”[Title/Abstract] OR “enuresis risoria”[Title/Abstract] OR “incontinentia urinae”[Title/Abstract] OR “enuresis ureterica”[Title/Abstract] OR “ureter enuresis”[Title/Abstract] OR “enuresis diurnal”[Title/Abstract]))

#22 Search ((bladder*[Title/Abstract]) AND control*[Title/Abstract])

#21 Search “neurogenic vesical dysfunction”[Title/Abstract]

#20 Search ((bladder*[Title/Abstract]) AND (neurogenic*[Title/Abstract] OR neurologic*[Title/Abstract] OR spinal[Title/Abstract] OR spastic*[Title/Abstract]))

#19 Search ((((Unable[Title/Abstract] OR inabilit*[Title/Abstract] OR abilit*[Title/Abstract] OR able[Title/Abstract])) AND control* [Title/Abstract]) AND (urine*[Title/Abstract] OR urinat*[Title/Abstract] OR urinary[Title/Abstract] OR micturat*[Title/Abstract]))

#18 Search ((bladder*[Title/Abstract]) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking [Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract] OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident* [Title/Abstract] OR escap*[Title/Abstract] OR escaping[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR “lack of control”[Title/Abstract] OR “no control”[Title/Abstract] OR “out of control”[Title/Abstract] OR “not voluntary”[Title/Abstract] OR involuntary[Title/Abstract] OR wetting[Title/Abstract] OR leaked[Title/Abstract] OR seeped[Title/Abstract]))

#17 Search ((micturat*[Title/Abstract]) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking [Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract]

OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident*[Title/Abstract] OR escap*[Title/Abstract] OR escaping[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR "lack of control"[Title/Abstract] OR "no control"[Title/Abstract] OR "out of control"[Title/Abstract] OR "not voluntary"[Title/Abstract] OR involuntary[Title/Abstract] OR wetting[Title/Abstract] OR leaked[Title/Abstract] OR seeped[Title/Abstract]))

#16 Search ((urinat*[Title/Abstract]) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking[Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract] OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident*[Title/Abstract] OR escap*[Title/Abstract] OR escaping[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR "lack of control"[Title/Abstract] OR "no control"[Title/Abstract] OR "out of control"[Title/Abstract] OR "not voluntary"[Title/Abstract] OR involuntary[Title/Abstract] OR wetting[Title/Abstract] OR leaked[Title/Abstract] OR seeped[Title/Abstract]))

#15 Search ((urinary[Title/Abstract]) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking[Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract] OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident*[Title/Abstract] OR escap*[Title/Abstract] OR escaping[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR "lack of control"[Title/Abstract] OR "no control"[Title/Abstract] OR "out of control"[Title/Abstract] OR "not voluntary"[Title/Abstract] OR involuntary[Title/Abstract] OR wetting[Title/Abstract] OR leaked[Title/Abstract] OR seeped[Title/Abstract]))

#14 Search ((Urine*[Title/Abstract]) AND (leak[Title/Abstract] OR leakage[Title/Abstract] OR leaks[Title/Abstract] OR leaking[Title/Abstract] OR seep[Title/Abstract] OR seepage[Title/Abstract] OR seeps[Title/Abstract] OR seeping[Title/Abstract] OR accident*[Title/Abstract] OR escap*[Title/Abstract] OR escaping[Title/Abstract] OR uncontrolled[Title/Abstract] OR trickl*[Title/Abstract] OR "lack of control"[Title/Abstract] OR "no control"[Title/Abstract] OR "out of control"[Title/Abstract] OR "not voluntary"[Title/Abstract] OR involuntary[Title/Abstract] OR wetting[Title/Abstract] OR leaked[Title/Abstract] OR seeped[Title/Abstract]))

#13 Search ("bladder* control*"[Title/Abstract] OR SUI[Title/Abstract] OR "giggle enuresis"[Title/Abstract] OR "enuresis risoria"[Title/Abstract] OR "incontinentia urinae"[Title/Abstract] OR "enuresis ureterica"[Title/Abstract] OR "ureter enuresis"[Title/Abstract])

#12 Search (incontinen*[Title/Abstract]) OR continen*[Title/Abstract]

#11 Search (((((((("Urinary Incontinence"[Mesh]) OR "Fecal Incontinence"[Mesh:NoExp]) OR "Urinary Bladder, Neurogenic"[Mesh:NoExp]) OR "Urinary Bladder, Overactive"[Mesh]) OR "Cystitis"[Mesh:NoExp]) OR "Cystitis, Interstitial"[Mesh:NoExp]) OR "Urination Disorders"[Mesh:NoExp]) OR "Urinary Retention"[Mesh])

COMMENTS

This is a systematic review that addresses various aspects of sacral neuromodulation stimulation parameters in animal studies. The findings of this review should be interpreted with caution since it only relates to animal studies and the methodologies within the studies analyzed were assessed with 'unclear' risk of bias and too diverse to present comprehensive and precise conclusions toward optimal settings in clinical practice.

Jerzy Gajewski, MD
Halifax, Nova Scotia, Canada

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Sacral neuromodulation is a well-established therapy for bowel and urinary disorders management since the 1990's. The usual criticism of this therapy is how it works and which are the best parameters for chronic stimulation. Animal models are imperfect and lacking. Companies usually promote their own parameters to make it more simple based on past publications not cited here. The authors tried to compile published data even if correlation with routine and human use cannot always correlate to it. As a researcher, this publication may help to plan new experiments. As a clinician, it may help to understand how to modify parameters in everyday life of implanted patients, even if sometimes changes are not related to efficiency but to side effects (pain, neurological target,…).

Emmanuel Chartier-Kastier, MD
Paris, France

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This literature review on the effect of stimulation parameters of sacral neuromodulation on lower urinary tract and bowel dysfunction gives a clear overview of the preclinical animal data. It provides valuable information for researchers as well as for clinicians to get more insight in sacral neuromodulation.

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Antwerpen, Belgium

