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2. Running title: Neuromodulation for colonic disorders
3. Authors: Bridget R Southwell (BScHons, MSc, PhD, AGAF).
4. Institutional Affiliation: Surgical Research Group, Murdoch Children's Research Institute, Melbourne, Australia; Department of Urology, Royal Children's Hospital, Melbourne, Australia; Department of Paediatrics, University of Melbourne, Melbourne, Australia.
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8. Corresponding author: Dr. Bridget Southwell
Surgical Research Group
Murdoch Children's Research Group
50 Flemington Road
PARKVILLE, VICTORIA, 3052
Australia

Phone: +61 03 9345 5805
Email: bridget.southwell@mcri.edu.au

Off-label uses of devices- Use of transcutaneous electrical stimulation devices to treat fecal incontinence or constipation is off-label.

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CME aims

Understand the types of electrical stimulation used on the colon

Understand the advantages and costs of the different stimulation regimens

Understand the effectiveness for faecal incontinence and constipation

Abstract

Background. In the last 20 years, studies have shown that large bowel function can be modified by neural stimulation. While still in its infancy, this area of research is beginning to show promise. **Methods:** This overview brings together systematic reviews and meta-analyses of electrical stimulation used to treat colonic disorders (faecal incontinence, constipation, slow transit constipation (STC), irritable bowel syndrome (IBS-C), and spina bifida-neurogenic bowel). Different methods of electrical stimulation including through sacral nerves, paraspinal, transabdominal and using electro-acupuncture over the ankle or knee and direct stimulation of the bowel are reviewed. **Results and Discussion:** Most evidence is low level (pilot and small cohort studies) but with more RCTs appearing. Sacral nerve stimulation (SNS) does improve urinary dysfunction and faecal incontinence, but not constipation. It is expensive with high rates of reoperation. Transcutaneous stimulation with interferential current (IFC, alternating current at KHz frequency with 2 channels out of phase) does improve constipation and may provide benefit as an adjuvant to behavioural or exercise therapies. Acupuncture and electro-acupuncture (low/very low-level evidence) may have a benefit for constipation. **Conclusion:** SNS is effective but expensive and limited to extreme patients. Transcutaneous stimulation is non-invasive and cheap and IFC may be effective for constipation, but many parameters need to be optimised and higher-level evidence provided from studies (sham, blinding, and larger patient numbers). The next 20 years should be exciting in the field as higher level studies are performed.

Introduction: Colonic disorders and methods of stimulation

Electrical stimulation to treat bowel disorders is becoming increasingly common and a number of methods have been used. This review is confined to electrical stimulation to treat colonic disorders including faecal incontinence (FI), constipation, slow transit constipation (STC), irritable bowel syndrome with constipation (IBS-C), and spina bifida-neurogenic bowel. Electrical stimulation through sacral nerves, paraspinal, transabdominal and using electro-acupuncture over the ankle or knee and direct stimulation of the bowel are reviewed. Many of the techniques were developed for urinary disorders where the effects are more quickly apparent and objective outcome measures are better developed. Because of space limitations, studies on bladder will be mentioned briefly only, with the reader given some recent references for further information.

Methods for this review

Systematic reviews use a systematic process to define a research question, search for studies, assess their quality and synthesize findings qualitatively or quantitatively (1-3). They are designed to provide a complete, unbiased summary of current evidence relevant to the specified research question. Systematic reviews of randomised controlled trials (RCTs) are key to the practice of evidence-based medicine. They may include a meta-analysis component using statistical techniques to synthesize the data from several studies into a single quantitative estimate or summary effect size (2).

Rather than perform a systematic review of a specific research question, the aim of this review was to cover a wide scope to present the current position of a field. The scope of the review was defined as 'electrical stimulation of the colon'. The aim was to cover all modes of stimulation and effects on bowel motility, faecal incontinence and constipation and colonic disorders. Literature was searched for 'sacral nerve stimulation, sacral nerve modulation, neuromodulation, transcutaneous electrical stimulation, functional electrical stimulation, interferential, acupuncture, percutaneous tibial nerve stimulation, transcutaneous tibial nerve stimulation, vagal nerve stimulation, paraspinal, transabdominal', and 'intestine, bowel, bladder, constipation, faecal incontinence, incontinence, colonic disorders, slow transit constipation (STC), irritable bowel syndrome (IBS-C), and spina bifida-neurogenic bowel'. 'Reviews, systematic reviews and meta-analysis' were also identified. The literature was organised according to mode of stimulation. Systematic reviews and meta-analyses with their conclusions were given priority. Systematic reviews and meta-analyses are most useful when there is enough data to make conclusions, so they are presented from the most recent to the older studies. Reviews are summarised in tables and conclusions drawn together. RCTs and case studies published after most recent reviews are also included.

General reviews of electrical stimulation and the GI tract

There are a number of general reviews of electrical stimulation in the GI tract (4-6) including electrophysiology of the GI tract, history of GI electrical stimulation, various methods of electrical stimulation of the stomach and small bowel in healthy animals and models of GI diseases and clinical applications of electrical stimulation to GI disorders and their possible mechanisms.

Neural circuitry of bladder and bowel

Innervation and neural circuitry of the bowel is complex and because of space limits in this paper, the reader is directed to these reviews (7-9).

Terminology: stimulation and modulation

The term sacral nerve stimulation (SNS) and SN modulation (SNM) are used interchangeably within the literature. Amend et al. (2011) (10) listed the definitions. “**Stimulation** leads to an immediate reaction after activation of the impulse generator”, while “**Modulation** describes a sequence, which often needs processing”. Earlier Craggs and McFarlane (1999) (11) defined “**Neuromodulation** as the influence of activity in one neural pathway modulating the pre-existing activity in another, through synaptic interaction.” Brindley (1994) (9, 12) described “**sacral neuromodulation** as characterized by the use of low-amplitude stimulation, increasingly below the sensory threshold, with low modulation frequencies, and almost continuous activation of the impulse generator”.

Sacral nerve stimulation (SNS)/ Sacral nerve modulation (SNM)

In the last two decades since FDA approval, sacral nerve stimulation (SNS) has become an accepted intervention and is a well-established technique (over 300 papers (13)). Initially it was used for urinary incontinence, then for faecal incontinence and constipation. Electrodes are implanted on sacral nerves 2-4 and a stimulator is implanted in the skin of the buttocks (Figure 1). Patients undergo a period of temporary electrode placement to test effectiveness (percutaneous nerve evaluation, PNE), followed by permanent implantation if they have positive results.

Stimulation of the bladder is outside the scope of this review, but since the pioneer work was done on the bladder, the reader is directed to a recent review on this area (14). The authors conclude that “there is evidence of effectiveness of SNS for lower urinary tract dysfunction (LUTD), specifically overactive bladder (OAB) and non-obstructive urinary

Fig 1

retention, with both objective and subjective improvement in voiding symptoms in several randomized controlled trials (RCTs) when compared to sham or standard medical therapy". The main limitations for more extensive use include relatively high cost, implantation of a device and reoperation secondary to adverse events (AE).

In Physiology, electrical stimulation as a treatment has been termed 'Electroceuticals'. Horn et al 2019 (15) reviewed targeting of the autonomic nervous system using vagal nerve stimulation and SNS and included sections on functional GI disease (gastroparesis) and gastric electrical stimulation (GES), vagal nerve stimulation (VNS) and obesity and on bladder dysfunction and SNS as well as discussing the future developments of these technologies including selectivity, feed-back control, wireless electrodes and form-fitting electrodes.

SNS/SNM and Faecal incontinence

Table 1

SNS/SNM was first applied to treat FI in 1995 and the benefit is now well established. Since 2010, there have been 3 meta-analysis (MA) of SNS for FFI (16-18) and a number of reviews for FI and/or constipation (14, 18-34) (Table 1). MA conclude benefit with a decrease in FI episodes and symptom scores (16, 18). The mechanism is via complex spinal and supraspinal mechanisms, rectal compliance is improved, FI episodes are reduced and QOL restored. Tan et al (16) performed a meta-analysis in 2011 (34 studies, 944 temporary lead implants, 665 permanent implants) and concluded benefit of the treatment with significant improvement in objective and subjective measures for FI patients, a decrease in weekly incontinence episodes and incontinence scores, the ability to defer defecation was increased, SF-36 and FIQL domains improved and anal pressures increased. In 2017, Zhu et al (18) performed a meta-analysis of studies comparing SNS/SNM to control patients for FI (6 studies, 270 patients, 147 SNS, 123 control). SNS significantly improved the outcome of patients with FI compared to control with a significant reduction in FI episodes and in the Wexner Incontinence Score. For children, SNS may be effective for bowel and bladder disorders (BBD) in carefully selected children, with reoperation as a high risk (35). Individual sites continue to report their experience in cohorts (for example (32)) adding to the evidence base that permanent SNS/SNM is effective for FI. Two reviews of SNS for FI after surgery (Table 1B) conclude it is effective in patients with low anterior resection syndrome (LARS) (27), but more studies are needed for rectal surgery or radiotherapy (28).

A recent MA compared SNS/SNM to percutaneous tibial nerve stimulation (PTNS) for treating FI (17). Evidence level was low with only 1 randomised controlled trial (RCT) and 3 non-randomised prospective studies (302 patients, 109 SNS, 193 PTNS). SNS resulted in significantly improved functional outcomes and quality of life, significantly greater reduction in FI episodes/week, greater improvement in the Wexner continence score, coping and depression on short-term follow-up compared to PTNS. But, further, high-quality, multi-centre RCTs with standardised outcome measures and long-term follow-up are required.

SNS for FI is effective and safe long-term, with >3-year follow-up data was reported in 2011 (20) (83 patients, and 86% ($p < 0.0001$) reported $\geq 50\%$ reduction in FI episodes/week compared with baseline, FI episodes/week decreased from mean 9.4 to 1.7, perfect continence in 40%). SNS/SNM improved FI severity index and all 4 scales of the FI Quality of Life (FIQOL) instrument at 12, 24, and 36 months follow-up. Major issues are adverse events (AE) and cost. AE are common (implant site pain, paraesthesia, change in the sensation of stimulation, infections, cable breaks and electrode displacements) (20, 21) with surgical revisions required in 1/3 of patients (36, 37) at significant resource costs to the surgical unit (38) (Table 2). Costs are approximately Euro€20,000 or £35,000 (39, 40), 2-3 times greater than conservative treatment (39), the lifespan is 5-7 years, with regular follow-up required (17). However, as alternatives may be costly, some argue that this may be justified (37).

Table 2

Studies on mechanism of action were reviewed by Carrington et al 2014 (23). They concluded it is likely that the effect of SNS on anorectal function occurs at a pelvic afferent or central level. An additional study on mechanism in rats (41), found SNS did not affect sphincter forces, recto-anal reflexes or slow wave frequency of anal canal smooth muscle. So the absence of effect on motor pathways of continence suggests the mechanism of action is predominantly on sensory feedback mechanisms from the anorectum, increasing cortical awareness of the pelvic floor (Table 3).

Table 3

Parameters that have been used were reviewed by Devane et al 2015 (26) and Dudding et al 2011 (19) (Table 3). They concluded that further research is needed into optimal settings (19) and this requires an understanding of the physiology (26).

SNS/SNM and Constipation

Bowel disorders treated with SNS/SNM include sphincter disruption, evacuation difficulty, neurogenic bowel dysfunction, irritable bowel syndrome (IBS) and constipation (13, 43). Three systematic reviews (29, 31, 34), 5 reviews (33, 43-46) (Table 4A) and 7 studies (47-53) (Table 4B) conclude the evidence is limited and that SNS is not effective for constipation. There may be some value in children (50), but more studies are required (35). Improvement in bowel frequency during PNE seemed to predict good response to permanent implantation and optimising patient selection appeared critical to the use of SNS in treating constipation (46), with evidence of efficacy in both slow transit and rectal evacuation difficulty. Good quality prospective, cross-over studies, and further research into patient selection, operative technique and stimulation parameters for existing indications are needed (43).

Table 4

Future developments (from presentations at International Neuromodulation Society Conference May 2019) include wireless electrodes with separate external stimulators that will greatly reduce problems with lead migration and infection. External stimulators can be

recharged and stimulation parameters changed without requiring surgical removal from the patient. Electrodes and devices that measure nerve activity are allowing feedback for stimulation. Stimulation parameters that are not continuous and stimulation for minimal periods during the day, are extending battery life for implanted devices. These developments are expected to improve success rates and reduce adverse events and surgical revision as well as reduce the need for device and battery replacement.

Transcutaneous electrical stimulation (TES) and functional electrical stimulation (FES)

Electrical parameters of TES and FES. TES and FES are stimulation on the skin using a pair of electrodes, with positive and negative poles with current delivered as spikes (pulsed direct current, DC) (Figure 2). Each spike has an on-time (in microseconds) and off-time and the repetition of spikes is the frequency (10 spikes per second = 10Hz). Pulses can be delivered in trains and the number of trains per second is the burst frequency. Typically current is delivered between 5-100 Hz (low frequency). Increasing the amplitude (voltage or current) successively activates sensory nerves, motor nerves and then pain nerves (54)(page 65). Generally electrical current flows through the skin rather than deep into the tissue. At lower frequencies, stimulation makes skeletal muscle twitch. Frequencies of 1-2 Hz allow skeletal muscle fibres time to relax between pulses. This is known as FES (54). At higher frequencies, the twitch responses fuse and at 20-50Hz contraction becomes tetanic with no relaxation occurring. For a steady sustained contraction, the upper limit of the firing rate is about 30Hz in human skeletal muscle. For transcutaneous stimulation, electrodes are flat pads placed on the skin. They may be carbon rubber or silicon adhesive ((54) page 52). The term TENS (transcutaneous nerve stimulation) is often used in place of TES where stimulation does not produce muscle contraction.

TES and FES for constipation

A number of general reviews of electrical stimulation (ES) mention treatment of bowel dysfunction. Bosques et al 2016 reviewed the effects of ES on posture and motion and also noted use of ES for bowel dysfunction (55). Two recent reviews specifically of neurostimulation in the treatment of GI disorders include transcutaneous stimulation and concluded that evidence quality is low and understanding of the mechanisms of each modality are needed (5, 6) (Table 5).

Table 5

Recent studies using TES or FES to treat bowel dysfunction are summarised in Table 6. TES improved constipation symptoms in children with lower urinary tract dysfunction (LUTD) (Veiga et al 2013) (56) and with overactive bladder and dysfunctional voiding (Tugtepe et al. (2015) (57). Patients with multiple sclerosis with constipation given FES on the abdomen had significant improvements in PAC-QOL (58), whole gut transit time (WGTT) and colonic

Table 6

transit time (CTT), and laxative use (59). Larger studies with controls are needed to determine the potential of FES to treat constipation. TES for 12 hours a day to mimic SNS was not effective for chronic constipation (60), while treatment for 20 min per day, 3 time per week increased BM/week more than sham stimulation (61).

Interferential Current (IFC)

What is IFC: Rather than DC, interferential stimulation uses alternating current. Each cycle consists of a positive and negative phase, producing a balanced charge (Figure 3). Current frequencies are much higher than TES, in the 1000-10,000Hz range. For IFC, two currents of slightly different frequency are crossed, and interfere to create summation and subtraction currents (54). Two pairs of electrodes can be positioned so that the currents intersect deep within the tissue. Current spread occurs under the electrodes, reducing the intensity at depth but IFC is expected to penetrate deeper than TES. IFC can be delivered through 4 electrodes on the belly or back so that currents cross through the skin (transcutaneous), or 2 electrodes on the belly and 2 on the back so that the currents cross within the body (transabdominal) (Figure 4). For Urinary disorders, 2 electrodes are placed over the symphysis pubis, and under the ischial tuberosity; so currents cross through the pelvic floor and bladder (62).

Fig 3

Fig 4

A common misinterpretation is that there is only a maximum stimulation in the region of intersection of the currents, but Ward (2009) presented a detailed discussion of the current (63). Ward argues that “the stimulus experienced by a nerve fibre depends on the orientation of the nerve fibre relative to the current (electrodes), and may be continuous (unmodulated), fully modulated or partially modulated depending on the fibre location and orientation relative to the electrodes. In addition, the stimulation intensity experienced by nerve fibres has a maximum modulation if the fibres are oriented optimally and zero modulation when fibres are oriented along one of the current pathways “(63). So positioning of the electrodes could greatly change the effect. Most of the effects of IFC have been studied on skeletal muscle where visible contractions provide a quantifiable outcome measure. Ward and Robertson 2000 (64) showed that stimulation of nerves that innervate striated muscle at 100 Hz or more, results in fatigue and reduction in torque in the muscle and can also inhibit the release of acetylcholine [21]. Similar studies on gastrointestinal smooth muscle have not been performed and little is known of the effects of specific stimulation frequencies within the abdomen. Methods to measure contraction of bladder or bowel in intact animals are needed to optimise the electrical frequency. Most studies on bladder used stimulation at 4000Hz and studies on bowel have followed this pattern.

IFC and Incontinence

IFC is widely used in women with stress incontinence to treat urinary incontinence resulting from an overactive bladder (OAB) (65, 66) and in children with primary nocturnal enuresis and non-neuropathic underactive bladder (62, 67).

IFC and Constipation

There is one SR and one review of IFC and constipation. Southwell (68) reviewed the use of IFC to treat constipation with emphasis on the current, devices used and mechanism of action. Moore et al 2018 (6) systematically reviewed the literature on IFC and GI motility (17 studies, 13 paediatric, 11 RCTs, 3 in adults). All studies found statistically significant improvement in symptom reduction but there were weaknesses in study design (especially in earlier studies) and the need to develop adequate placebo/sham treatment. The types of problems that can occur using IFC were reviewed, identifying design and engineering requirements to deliver TES at home for treating chronic constipation, and educational material required to train clinicians, patients, and users (69).

Two early RCTs comparing active stimulation with no current sham showed only a small effect of IFC over sham stimulation (70-76). Prospective cohort studies found there are larger effects when stimulation is given more often using a battery-operated stimulator at home allowing daily treatment for an hour and if treatment continues for longer (2-6 months) (77-81). IFC using electrodes placed lower down (sacral rather than lumbar) was also effective for constipation due to anorectal retention (82). Comparing IFC to sham treatment (no current) in children with myelomeningocele showed improved sphincter pressure and recto-anal inhibitory reflex in the IFC group with defecation/week increased significantly compared to sham (65) (Table 7). When the currents are not crossed, interference does not occur and improvement does not occur (83). An abstract report of an RCT showed IFC with currents crossed within the abdomen is more effective than stimulation with currents not crossed suggesting this could be an effective sham (84) (Table 7).

Recent studies showed that using IFC may be an effective adjuvant therapy to medical and rehabilitation programs and significantly boosted the effects of treatment. Behavioural therapy (high fibre diet, hydration, toilet training and pelvic floor muscles exercises (PFM)) with IFC produced a significantly higher increase in defecation/week, significantly lower mean pain score and improved symptoms in significantly more patients, than behavioural therapy alone in 30 postoperative HD patients (85). In an RCT on 90 children with FC (86), PFM exercises with IFC compared with PFM alone produced treatment success in more patients (88% vs 43%) significantly reduced the constipation score and normalised stool form in significantly more patients (76 vs 46%).

Studies in adults have been more delayed. The protocol for the CON-COUR RCT using IFC to treat chronic constipation in adults was published in 2015 (87), but no results have been reported yet. Pilot cohort studies in adults with refractory constipation (88, 89) report improved symptom scores and reduced laxatives. Preliminary results using a purpose built device in children with refractory constipation are also promising (90).

Studies on mechanism of action are essential but studying the mechanism of action of IFC in animals is difficult as electrodes need to be placed each day, handling of animals is extensive and outcome measures are not established. Studies in pigs showed that a short period of stimulation (30 mins/day for 5 days) is not enough to produce an effect on whole gut transit (91, 92) while stimulation for slightly longer (2 weeks) made the stools softer and transit faster (83). Methods to measure contractions of the bowel daily in intact animals are needed to advance animal studies.

Acupuncture

Acupuncture originates from traditional Chinese medicine with a number of stimulation sites (points) defined to treat bowel conditions (Lee et al 2018 (95)). Traditionally, metal needles are inserted into the site and twisted to activate (96). Acupuncture points were standardised by Chinese, Japanese and Korean practitioners under a World Health Organisation (WHO) standard in 2008 (97). Acupoints most commonly used for CC include ST25, ST37, BL25, ST36, TE6, CV6, CV4, BL33, and BL34 (98). There is limited data for acupuncture effects on bowel due to methodological flaws, no standard assessment tools and no placebo or comparators, so conclusions cannot be drawn from early studies (99).

Four major acupoints for CC (98) are:

- **ST25:** upper abdomen, lateral to umbilicus above small intestine. EA at ST25 enhanced small intestinal motility in rodent model of slow transit constipation [38]. However, in normal/fasted rats, EA at ST25 produced inhibitory effects on jejunum electrical and mechanical activities suggesting that EA at ST25 exerts different effects under different conditions.
- **ST36 and ST37:** anterior aspect of leg, above tibialis anterior muscle with ST36 above ST37. Commonly used for gastrointestinal discomfort, nausea and vomiting, stress and fatigue. Acupuncture stimulation of ST36 increased intragastric pressure and gastric peristaltic frequency in rats with gastric hypomotility. In patients after abdominal surgery, stimulation at ST36 shortened time of first flatus passage and improved gastrointestinal functions. Significant acceleration of colonic transit with EA at ST36 was mediated via the sacral parasympathetic efferent pathway. Acupuncture at ST37 altered rectal motility with the effect appearing one hour after needling.

- **BL25:** located on lumbar region, at level of inferior border of spinous process of the fourth lumbar vertebra (L4), laterally to the posterior-median line. Acupuncture at BL25 reduced early postoperative inflammatory small bowel obstruction, improved symptoms of ulcerative colitis and irritable bowel syndrome.
- **TE6:** located on posterior aspect of forearm, midpoint of the interosseous space between radius and ulna, proximal to dorsal wrist crease. EA at TE6 and ST36 was effective for adhesive ileus, improved abdominal pain and distention, and accelerated intestinal peristalsis.

Acupuncture and Bowel:

Table 8

There are 2 SR for acupuncture and bowel (Table 8). For CC, a SR (100) (15 studies, 1256 participants) concluded acupuncture may improve weekly spontaneous bowel motions (SBM), QOL, and symptoms. However, evidence was low level and limited by small sample sizes and low methodological quality. Xu et al 2014 (101) reported a protocol for a trial. A SR For IBS (102) (17 RCTs, 1806 pts) concluded no benefits of acupuncture relative to a credible sham acupuncture control on IBS symptom severity or QOL. In comparative effectiveness Chinese trials, patients self-reported greater benefits from acupuncture than pharmacological therapies. Future trials may help clarify whether this is due to patients' preferences for acupuncture or greater expectations of improvement from acupuncture relative to drugs.

Limitations of studies include not using standard assessment tools and not having a placebo control. Depth and angle of needling affects outcomes (98) and shallow needling has been used as a comparator/control as well as needling away from the active point. In a recent RCT, parallel design pilot trial comparing acupuncture to sham (95), acupuncture produced clinically meaningful improvements in SCBMs occurring more than 3 times per week with these improvements maintained for 4 weeks after treatment completion. Combining acupuncture with other treatments may be effective.

Acupuncture mechanism

Gao et al 2015 (103) studied the mechanism of action of acupuncture on colonic motility in rats using a manometry balloon inserted 5-6 cm into the rectum of anesthetized normal rats or rats with diarrhea or constipation. They found that acupuncture at heterotopic acupoints increased distal colonic motility regardless of normal or pathological conditions mainly by activating C-fibers of somatic afferent nerve and M3 receptors.

Electroacupuncture (EA)

EA and Constipation

There are 2 SR of EA and constipation (100, 104) with the more recent concluding EA is effective (104) (Table 8). The overall efficacy rate of EA for chronic FC (CFC) was 57% to 94% (98) with increased defecation frequency and increased number who had ≥ 3 defecations/week, decreased stool property, constipation symptoms and GI transit time. Several articles reported that acupuncture outperformed conventional medicine (lactulose, plantain, senna granules) but the earlier SR indicated they were equally effective (100).

Ischemic stroke patients are predisposed to autonomic function imbalance. In a recent RCT, applying TENS at acupoints (TEA, 86 patients randomly assigned to 2 weeks TEA or sham-TEA) was effective in the prevention of stroke-induced constipation, with the effect possibly mediated via autonomic function (105). TEA decreased the incidence of stroke-induced constipation, increased bowel movements and SBM/week, improved stool consistency and QOL and decreased straining defecations and laxative use more than sham TEA. TEA increased vagal activity and decreased sympathetic activity (vs. baseline).

EA mechanism

Studies suggest that acupuncture ST36 (knee) and PC6 (wrist) alters sympathetic activity, resulting in an inhibitory effect on blood pressure in humans (106) and heart rate in rats (107). Studies in rats suggest EA at ST36 (knee) is affecting sympathovagal activity (108). 5-HT and of tryptophan hydroxylase (TPH) (109), TRPV1 receptors (110) and muscarinic M3 receptors (103) have been implicated. Afferent nerve A delta- and C-fibers mediate the transduction of the acupuncture signal and C-fibers are essential for enhancing the effect of acupuncture on distal colonic motility (103). In dogs, rectal distension (RD) inhibits colonic contractions and delays colonic transit. EA at ST36 restored the RD-induced impairment in both colonic contraction and transit by enhancing vagal activity with the effect mediated via a cholinergic pathway (111). In humans, TES at acupoints PC6 (wrist) and ST36 daily for 2 weeks improved gastric function, lowered plasma VIP, motilin and IL-6 levels and improved association between gastric myoelectrical activity (GMA) and sympathovagal balance (112). Acute TENS application at PC6 and ST36 also increased sympathetic and vagal components of HRV in scleroderma (SSc) patients (107) while prolonged TENS normalized the sympathovagal balance, decreased GI symptom scores and increased the physical functioning score (SF36), which strongly correlated with the change in the sympathovagal balance (113). Eight weeks EA resulted in activation of the parasympathetic nervous system in patients given active but not sham treatment (107). Thirty min of daily TEAS treatment at PC6 is partially effective in maintaining orthostatic tolerance with the effect thought to be partially due to activation of the peripheral sympathetic nervous system (106).

Percutaneous tibial nerve stimulation (PTNS) and transcutaneous tibial nerve stimulation (TTNS)

Percutaneous tibial nerve stimulation (PTNS) is derived from acupuncture and was first described in the 1980s (121). Needle electrodes are inserted into the leg above the ankle or around the knee and current supplied across the needles with stimulation pulsed around 20Hz. TTNS uses adhesive electrodes in place of needles and so allows patients to perform stimulation at home without a clinician (Figure 5).

Fig 5

PTNS has been well used to modulate bladder function and facilitate bladder storage. There are a number of SR of the use of PTNS for bladder dysfunction (17, 122-131). Current conclusions are that PTNS has a success rate of 40-80%, it is effective short term, but data on long term effects are needed.

PTNS and TTNS for faecal incontinence and constipation

Table 9

There are 2 SR for FI and PTNS (132, 133) (Table 9). In 2014 (132) there was only one RCT for TTNS and TTNS was not superior to sham and no adequate RCT of PTNS versus sham had been conducted. Since then there are 2 RCTS of PTNS to treat FI in adults (134, 135) (Table 9) and both found little/no benefit over sham for FI. Van der wilt et al (135) felt the key challenge is to identify the patients who may benefit most from this procedure. In 2019, PTNS has been identified as a treatment that is not effective for FI (136).

Table 10

Results for PTNS and constipation are variable (Table 10). For constipation, PTNS had little success (137, 138) or some effect (139) and stimulation at ST36 (knee) may be more effective than across the ankle (140). PTNS enhanced healing of anal fissures (141-143).

Costs of PTNS

Martinson et al 2013 (144) measured costs for bladder treatment using PTNS compared to SNS. Of course, PTNS is much cheaper, but the paper does provide data on costs. The costs of initial therapy were \$1,773 for 12 weekly PTNS treatments and \$1,857 for test SNS. For ongoing therapy the cost of the SNS surgical implant was \$22,970. Cumulative discounted 2-year costs were \$3,850 for PTNS and \$14,160 for SNS. In both groups 48% remained on therapy. The incremental cost-effectiveness ratio was \$573,000 per additional patient on sacral nerve stimulation. When considering only patients who completed initial stimulation

successfully, the costs were \$4,867 and \$24,342 with 71% and 90%, respectively, remaining on therapy for an incremental cost-effectiveness ratio of \$99,872.

Direct stimulation of the intestine:

Studies of electrodes implanted onto the bowel wall have been performed in dogs. Location of electrodes and parameters of stimulation affect the outcomes. Electrical stimulation via the serosa or mucosa of the small intestine increased the speed of small intestine transit (155). In contrast, single-channel ES inhibited intestinal motility within a distance of at least 2 m (156) with the inhibitory effect mediated via sympathetic but not nitrergic, serotonergic (5-HT) and opiate pathways in that study. ES with long pulses significantly inhibited intestinal motility by 60-74%. Hexamethonium, guanethidine, phentolamine, propranolol partially, but not N (omega)-nitro-L-arginine (L-NNA), ondansetron and naloxone prevented the inhibitory effect of IES on intestinal motility. Using electrodes surgically implanted in the seromuscular layer in dogs (157), at different stimulation sites, ES exerted different effects on stool frequency and food intake. Proximal colon electrical stimulation (PCES), rectosigmoid colon electrical stimulation (RCES), and sequential CES sessions (seq CES) significantly accelerated GITT compared to sham stimulation, RCES and seq CES increased stool frequency while PCES and RCES inhibited food intake.

Vagal Nerve stimulation (VNS):

VNS may be useful for colonic disorders involving inflammation (158-160). VNS has been tested for Crohn's disease with off-target effects limiting use (161). Cervical VNS has a number of unwanted, off-target effects (changes in heart rate, respiration rate or blood pressure). However, Payne et al 2019 (162) have shown in rats that VNS with electrodes placed on the nerve near the distal oesophagus has beneficial effects on inflammation without unwanted side effects. These findings are in agreement with reports of abdominal VNS in anaesthetized pigs and for the treatment of post-operative ileus (163, 164). Transcutaneous vagal nerve stimulation is now being developed (164).

Future requirements:

Optimal Parameters: Most of the parameters used for treating bowel dysfunction have come from bladder treatment with the hope that they will work for the bowel. Transcutaneous stimulation can take weeks to months to produce improvement in bowel function. This may be because the parameters used are a long way from optimal. For SNS, the effect can be seen immediately on stimulation, making it is easier to determine optimal parameters. It is also difficult to perform frequency or dose response studies when it takes a long time for the stimulation to have an effect on the bowel. To inform optimal parameters for stimulation, we need studies of mechanism of action, position to place electrodes,

electrical parameters (frequency, time per day, months required), and type of electrodes/pads to optimise treatment.

There is a need for RCTs with well-defined sham or comparator groups. These take some time to develop as each new treatment develops and require optimised methods as described above. Studies to define parameters to use for sham stimulation (considering months of stimulation required for effects) are also required. What placebo can be used, is no electrical current adequate, what position of electrodes can be used to provide current and still act as a sham? Is another treatment (such as behavioural therapy or PFM exercise) with and without ES a better design?

High level evidence comes from blinded studies. This has been developed for SNS by turning the device On or OFF with the patient blinded to the order. But this is not easy for transcutaneous stimulation where patients apply the device themselves. The issues that affect blinding include that the 'treatment is felt by the patient, stimulation is done for months and is delivered at home by the patient' (68). Questions to address are 'How can you blind the person delivering the treatment and how can you blind the patient?'

What features can be measured to get a subjective measure of improvement? Patients can record through diaries and a number of questionnaires are available. PAC-QOL and PAC-SYM are most commonly used for adults (165, 166), (Officially distributed by Mapi Research Trust – ePROVIDE: <https://eprovide.mapi-trust.org/instruments/patient-assessment-of-constipation-symptoms>, <https://eprovide.mapi-trust.org/instruments/patient-assessment-of-constipation-quality-of-life-questionnaire>). For children, PedsQL has released a gastrointestinal symptom scale which may become commonly used (167-170). Rome IV recently released questionnaires (<https://theromefoundation.org/>), but we have found they are very long for paediatric use. Unfortunately, while new measures may provide better distinction of changes in symptoms, as new measures evolve, it makes it difficult to compare to previous studies. Thus the evidence base may not evolve to meta-analyses level.

For the evidence-base it is preferable to have objective measures. Those used so far include transit studies, gastric emptying, anorectal manometry or colonic manometry to measure the rate of movement through the bowel or strength or frequency of contractions.

Another consideration is the complexity of the innervation of the bowel. Pathology is likely to affect many aspects of the peripheral and central nervous systems. It may be that months of stimulation are required because the mechanism of action is neuromodulation and repairing multiple sites within the nervous system takes time.

Summary

Neuromodulation of the bowel has been developing over the last 20 years. Most evidence is low level (pilot and small cohort studies) but with more RCTs appearing. The longest experience is with SNS/SNM. Using this stimulation, there are multiple RCTs, systematic reviews and meta-analysis concluding SNS **does** improve urinary dysfunction, **does** improve faecal incontinence, but it **is not** effective for constipation (2RCTs) and is very expensive with high rates of reoperation. Using transcutaneous stimulation, for FES and TES- there are 2 case studies and 1 RCT- concluding TES is effective for urinary disorders, but evidence is not clear for constipation. TES- IFC (AC, KHz, phase shifted) **does** improve urinary dysfunction and for constipation, it is significantly better than control and may provide benefit as an adjuvant to behavioural or exercise therapies. Acupuncture has low/very low level evidence showing no effect for urinary incontinence, possibly an effect for OAB and for constipation and no benefit for IBS. For electro-acupuncture (also low/very low level evidence) we can't say for urinary dysfunction but it is effective for constipation. PTNS is effective for bladder dysfunction, not effective for faecal incontinence and the effect is not clear for constipation. Direct stimulation or vagal nerve stimulation are still in experimental studies in animals. Many parameters need to be optimised and study designs need to include sham and blinding with larger patient numbers. The next 20 years should be exciting in the field as higher level studies are performed.

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Interferential Current (IFC)

A. Stimulator with leads and electrodes

B. Electrode position on abdomen

C. Electrode position for Slow Transit Constipation

Yik 2018

D. Electrode position for Anorectal Retention

Yik 2016

NER_13099_IFC device and location of electrodes hair 30-10-19.jpg

A. Channel 1: Alternating current at 4000 Hz
(4000 pulses per second)

B. Channel 2: Alternating current at 4100 Hz
(4100 pulses per second)

C. Interference of the two currents-
frequency 4050 Hz, beat frequency 100 Hz

NER_13099_ifc waveform 3 graphs 30-10-19.jpg

Author's name: ...Bridget R Southwell..

Author's address:

Murdoch Children's Research Institute, Level 5, Royal Children's Hospital, Parkville, Victoria, Australia
3052.....

Title of article ("Article"): Electro-Neuromodulation for Colonic Disorders- Review of meta-analyses, systematic reviews and RCTs

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Sample authorship description and acknowledgement:

Drs. A, B and C designed and conducted the study, including patient recruitment, data collection, and data analysis. Dr. A prepared the manuscript draft with important intellectual input from Drs. B and C. All authors approved the final manuscript. [Insert name of organization] provided funding for the study, statistical support in analyzing the data with input from Drs. A, B and C, and also provided funding for editorial support. Drs. A, B and C had complete access to the study data. We would like to thank Dr. D for her editorial support during preparation of this manuscript

Single Author- BS designed the review outline and protocol, performed literature search, collection of articles, read and analysed articles, wrote all drafts and final version of the manuscript. BS typed the review. There was no funding for the review. The topic was presented as an invited talk at the International Neuromodulation Society Meeting in Sydney Australia in May 2019.

3) Was this research or its publication assisted by any non-financial or 'in-kind' contributions? (e.g. provision of study design, data collection, data analysis, writing assistance, literature searching, administrative support, supply of materials).

☐ YES ☒ NO

If yes, state the identity of the individuals who provided this assistance and disclose the source of any material or financial support:

Corresponding Author: Bridget Southwell Date: 6 Aug 2019

A Location of Tibial Nerve

Tibial Nerve Stimulation Across Ankle

B Percutaneous

C Transcutaneous

NER_13099_PTNS stim 29-10-19.jpg

Table 1. Reviews on Sacral nerve stimulation (SNS)/sacral nerve modulation (SNM) and Faecal Incontinence (FI) (MA= meta-analysis, SR= systematic review, R= review, S= study)

A: SNS/SNM and FI			
Reference	Compared	Number of studies, patients	Conclusion
Simillis et al 2018 (17) MA	SNS vs PTNS	4 stud, 302 pt	Benefit, decrease in FI episodes and scores. SNS superior to PTNS. SNS costly
Zhu et al 2017 (18) MA	SNS vs control	6 stud, 270 pt	Benefit, decrease in FI episodes and scores
Tan et al 2011 (16) MA	Temp vs perm SNS	34 stud, 944 pt	Benefit, decrease in FI episodes and scores.
Gelos and Niedergethmann 2018 (33) R	SNS for FI and Const		SNS is a suitable therapeutic option for nearly all causes of FI refractory to conservative treatment. By complex spinal and supraspinal mechanisms, rectal compliance is improved and anal FI episodes reduced. Not effective for Constipation.
Nordenstam et al 2015(30) R	FI and other common indications		Common indications for SNS, patient selection, technical details of procedure, published outcomes, and complications. SNS is an effective treatment option for FI (reduce clinical symptoms and restore QoL.
Thaha et al 2015 (29) SR	FI, ON vs OFF. 2 trials const	6 FI stud crossover, parallel. 2 constip stud	Limited evidence, SNS can improve FI. Did not improve const. AE occurred. Rigorous RCTs needed.
Maeda et al 2015 (25) R	European consensus statement		Evidence base for almost all questions was poor. Expert opinion only
Liu and Wang 2014 (24) R			Reviewed the current application of SNS (in chinese)
Thin et al 2013 (22) SR	SNS vs PTNS/TTNS Effects to 5 year	11 st, 7 PTNS, 4 TTNS	Success rates for SNS were 33-81 %. SNS, PTNS and TTNS resulted in improvements in Cleveland Clinic Incontinence Score and QoL measures. Still no consensus on outcome reporting: measures used, aetiologies

			assessed, length of follow-up or assessment standards.
Goos and Ruf 2012 (21) SR	Indications, complications, revisions		Success with Idiopathic, muscular and neurogenic disorders. Infections, cable breaks and electrode displacements occur. Some patients require surgical revision or removal.
Ratto et al 2010 (42) R			First line treatment after failing conservative therapy
Mellgren et al 2011 (20) S			Long-term effectiveness and safety of SNS for FI patients
B: Post surgery			
Reference	Indication	Number of Studies	Conclusion
Ramage et al 2015 (27) R	FI in Low anterior rectum resection syndrome (LARS)-post surgery	1 case report and 6 prosp case series, 43 pts, permanent implantation in 34. 32 had improved symptoms.	Success rates comparable to FI. 94.1% s experienced improved symptoms
Thomas et al 2015 (28)R	FI after rectal surgery or rectal radiotherapy	8 studies on patients with anterior resection or pelvic radiotherapy. 57 pts, all single group series from 1 to 15 pts. Follow-up 1-36 mth.	Improved symptoms and some QOL. Success 47% to 100%. Larger studies and better patient selection needed.

Table 2. Costs of Sacral nerve stimulation (SNS)/sacral nerve modulation (SNM) for Faecal Incontinence (FI) and constipation

Authors	Reference	Covers	Conclusion
Simillis et al 2018 (17)	(17)	SNS vs PTNS	SNS costly, lifespan 5-7 years, need regular follow-up, reprogramming and battery changes
Van der Wilt et al 2017 (39)	(39)	Costs of SNS in Netherlands	3 year period/patient: SNS €17,789 (SD €2492), Conservative treatment €7,574 (SD €4332)
Zeiton et al 2016 (36)	(36)	Costs of revision in 125 pts with permanent SNS	Surgical revisions required in 29% of patients. Explanted in 6 pts. Substantial unexpected costs for the surgical group.
McMullin et al 2014 (38)	(38)	85 pts, 24 mth FUp.	Significant resource implications. 30% with unsatisfactory outcome requiring revision. Costs £37,000 (50% of FUp costs for 30% of patients).
Van Wunnik et al 2012 (37)	(37)	Costs of SNS for children in Netherlands	Less costly and more effective than artificial sphincter and so justifies use in children with incontinence. ~30% with unsatisfactory outcome requiring revision.
Dudding et al 2008	(40)	Costs in UK	£25,000-£35,000-(2008) per QALY (UK)

Table 3. Mechanism of action of sacral nerve stimulation (SNS)/sacral nerve modulation (SNM) (S=study, SR=systematic review, R=review)

A: Mechanism of action of SNS				
Type	Authors	Number of Studies	Studied	Conclusion
S	Devane et al 2016 (41)	1 st rat model SNS, 18 rats S1 or L6	Determine SNS effect on external and internal anal sphincter forces, recto-anal inhibitory (RAIR) and excitatory reflexes, (RAER) and the slow wave (SW) frequency of the internal anal sphincter.	Did not affect sphincter forces, recto-anal reflexes or slow wave frequency of anal canal smooth muscle. Absence of effect on motor pathways of continence suggests mechanism of action is predominantly on sensory feedback mechanisms from the anorectum, increasing cortical awareness of the pelvic floor.
SR	Carrington et al 2014 (23)	53 clinical, 9 exp	Changes in cortical, gastrointestinal, colonic, rectal, and anal function.	Likely influence of SNS on anorectal function occurs at a pelvic afferent or central level.
B: Parameters used				
Ref	Type	Studied		Conclusion
Devane et al 2015 (26)	R	Parameters for FI. Evidence for stimulation parameters and potential electrophysiological effects of changing these		Need for understanding of physiology to determine parameters.
Dudding et al 2011 (19)	R	Methods improvement. Neurostimulator programming		An improved outcome of SNS can be achieved by selecting the best possible stimulation parameters individualized to each patient. Further research into the optimal settings is needed.

Table 4. Sacral nerve stimulation (SNS)/sacral nerve modulation (SNM) for constipation
(constip= constipation, CBM= complete bowel motions, FC= functional constipation, FI= faecal incontinence, R=review, SR= systematic review)

A: Reviews- SNS/SNM and constipation				
Indication	Author	Type	Number of Studies and patients	Conclusion
Paed FC	Mills et al 2019 (45)	R	3 studies	Discuss evidence for new treatments in children, including SNS. For SNS reviewed 3 studies- At follow-up, 68% of patients fulfilled the predefined criteria for successful response and 24% fulfilled criteria without concurrent laxative or ACE use.
FI and Constip	Gelos and Niedergethmann 2018 (33)	R		Efficacy of SNM in constipation is not well established. May be considered in patients who fail to respond to conservative measures. Further potential indications are discussed.
Constip	Pilkington et al 2017(34)	SR	7 articles- 2 cochrane reviews, 2 RCTs, 375 pts	Great caution. Evidence is limited. Pooled treatment success 57-87%. Retrospective and prospective studies have different results and drop-out rates are high.
Bowel and constip	Baron et al 2016 (french) (31)	SR		Improves intestinal bowel symptoms scores (level 4 evidence). For constipation, there are contrasting results. <ul style="list-style-type: none"> • If symptoms scores improve, QOL scores not significantly changed. • Some people reported aggravation of constipation symptoms. • Discordant results may be due to multiple causes of constipation involving different pathophysiological mechanisms.
FI and Constip	Thaha et al 2015 (29)	SR	6 crossover trials and 2 parallel group trials	Limited evidence <ul style="list-style-type: none"> • SNS did not improve symptoms in patients with constipation. • adverse events occurred in some patients. • Rigorous high quality RCTs needed
ES for GI tract	Abell et al 2015 (13)	R		SNS and constipation. Optimising patient selection is critical for constipation. Some

				evidence of efficacy in slow transit and rectal evacuation difficulty.
Constip	Thomas et al 2013 (44)	R	13 studies, 3 paed, 10 adult.	Test stim successful in 42-100%. Permanent stim in 87%. May be effective for constipation. Need larger prospective studies with longer FUp.
Constip and SNS	Sharma et al 2013 (46)	R	10 studies, 125 permanent implants from 225 PNE procedures	Bowel diaries showed improvement in > 50% of patients on PNE and 90% permanent implantation over medium to long-term follow-up. The rate of adverse effects was high, mostly related to electrode position.
FI, Const, IBS,	Dudding et al 2011 (43)	R		Paucity of high quality evidence to support the use of SNS for the majority of novel indications (faecal incontinence, constipation, irritable bowel syndrome, mixed urinary and bowel disorders, spinal injury and neurodegenerative disease, pain syndromes, and sexual dysfunction). Need good quality prospective, cross-over studies to determine the true benefits of SNS. Further research into patient selection, operative technique and stimulation parameters for existing indications.
B: Studies SNS/SNM and diarrhea				
Ref	Patients	Number of patients		Conclusion
Fassov et al 2019 (47)	IBS-D	21, allocated to SNS On or OFF for 2 weeks, then crossover.		Compared to placebo, subsensory SNM significantly reduced pain and number of bowel movements (most common and troublesome symptoms of IBS-D). Other domains in GSRS-IBS questionnaire did not change. Improvement of primary endpoint was borderline significance (<i>P</i> = 0.057).
C: Studies- SNS/SNM and constipation				

Patients	Number of patients	Conclusion	
Lu et al 2017 (48)	Children with severe constipation dependent on Antegrade Continence Enema (ACE)	22 Children	Steady decrease in ACE usage. 1/2 receiving ostomy closure within 2 years.
Maeda et al 2017 (49)	Intractable Constipation	62 pts, 45 permanent implants. Prosp multi-centre open label.	Benefit in long-term in small minority. Caution due to high dropout and complication rate during the follow-up period.
van der Wilt et al 2016 (50)	Children and adolescents with chronic constipation not responding to intensive oral and/or laxative therapy	30 girls, mean age 16 yrs (range 10-20) 3 weeks test treatment	Benefits sustained over prolonged period of time. Mean defecation frequency increased 6 to 17 /21 days. Abdo pain and Wexner score decreased. Improvement sustained during follow-up (12-37 mth) in 43%.
Patton et al 2016 (51)	2 yr followup of Dinning trial	53 pts entered long term f-up. 44 withdrew because of treatment failure.	Very few patients for long term followup. SNS not effective.
Dinning et al 2015 (52)	Slow transit constipation	59 pts	SNS did not improve frequency of CBM over 3 weeks stim (PNE). Only 16 had positive PNE, but 55 went onto permanent SNS.
Graf et al 2015 (53)	Chronic constipation Uncontrolled	44 pts treated for 3 weeks,	Limited efficacy in unselected patients with CC. Not recommended for treatment on routine basis. 15 (1/3) experienced 50% reduction of symptoms and received a permanent implant. Only 5 reported sustained relief after 4-81 mths.

Table 5. Reviews of neurostimulation in the treatment of GI disorders. (CC= chronic constipation, FI= faecal incontinence, GI= gastrointestinal, IFC= interferential current, RCT= randomised controlled trial, TES= transcutaneous electrical stimulation, PTNS= percutaneous electrical stimulation).

Ref	Review of	Number of studies	Conclusion
Moore 2017 (6)	IFC to treat GI symptoms	17 studies, incl 11 RCT	Sig improvement in symptoms, weakness in design, need placebo.
Bosques et al 2016 (55)	Elect stim in youths	37 articles	Reviewed effects on body and motion. Electrical stimulation may be useful for chronic constipation.
Lu and Di Lorenzo 2016 (5)	Neurostim for GI disorders esp paed	Current Opinion 44 articles	SNS can be effective for refractory constipation and FI. TES and PTNS may be effective but evidence is low quality.

Table 6. Studies using standard transcutaneous electrical stimulation (TES) or functional electrical stimulation (FES) for bowel disorders (constip= constipation, LUTD= lower urinary tract disorder, PTES= parasacral transcutaneous electrical stimulation, STC= slow transit constipation. Pulse duration in msec or μ sec are as described in each paper).

Ref	Pt group	Stim sessions	Electrical Frequency	Electrode position	# of Pts	Effects
Street et al 2019 (58)	Multiple Sclerosis with constip	FES 2 x 30 min /day 6 weeks	40 Hz, 300 μ sec pulse width, 40–50 mA	Abdomen-transverse abdominus	20	PAC-QOI pre vs post 6 weeks Sig improvement in all subscales. Long-term therapeutic effect, reduction in laxative use and improved sexual functioning.
Yang et al. 2017 (61)	STC Adult	20 min, 3/wk, 4 weeks			14 TES, 14 sham TES	Increased bowel motions/wk in TES not sham. Decreased CAS score and abdominal pain in both.
Singleton et al 2016 (59)	Multiple sclerosis-constip	30 min, 2/day for 6 weeks	40Hz, 330 μ sec pulse width, 40–50mA	2 pairs around belly button over the external oblique and transverse abdominis muscles	FES Pilot 4 pts	Reduced whole gut and colonic transit time, improved PAC-QOL.
Iqbal et al. 2016 (60)	Chronic Constipation	12 hrs/day 4 wks mimic SNS	40 Hz pw 220 us, below sens threshold	2 pairs, 1 left and 1 right of Sacrum	16 TES	Ineffective
Tugtepe et al (2015) (57)	Child overactive bladder or dysfunctional voiding	20 min, daily, 3 mth	10 Hz, pw 350 us	S3 dermatome	27 all TES 11 OAB, 16 DV	Constip symptoms improved.
Veiga et al 2013 (56)	Children LUTD with Constipation	20 min, 3/wk, clinic	10 Hz, pw 700 us, max level tolerated	2 either side S2-S4	14 all TES	All urinary improved. Constip improved in 86% of patients

Table 7. Interferential current (IFC) stimulation for constipation (abd= adominal, BM= bowel motions, Constip= constipation, dec=decreased, freq= frequency, HD= Hirschsprung disease, Hr QOL= health related quality of life, IBS-C= irritable bowel syndrome- constipation predominant, inc= increased, PFME= pelvic floor muscle exercises, RAIR= recto-anal inhibitory reflex, sig=significantly STC= slow-transit constipation)

A: Studies- not RCTs						
Pt Group	Location	Sessions	Stim Freq Hz	# of Pts	Ref	Effects
STC Adult	home	1 hr, daily 4 mth	4080-4160	17	Talley 2018 (abst) (89)	Impr symptoms in most pts. Sig impr PAC-SYM and PAC-QOL pre vs post.
Constip Child	home	1 hr, daily 4 mth	4080-4160	10	Gunawan et al 2017 (abst) (90)	Preliminary, improvement in bm/wk, stool vol, urge, straining,
Constip Adult	home	1 hr, daily 6 wks	4080-4160	7- 3 STC, 4 CIC	Moore 2017 (abst) (88)	Impr symp score, Reduced lax.
STC Child	home	1 hr, daily 6 months	4080-4160	62	Yik et al 2018 (81)	>50% improved- Inc BM/wk, urge to defecate and QOL, decr soiling and abd pain,
AR Child	home	1 hr, daily 3 months	4080-4160	10	Yik et al 2016 (82)	Inc defec freq, dec soiling, dec laxatives, Hr QOL impr, >50% pts improved
STC Adult	home	1 hr/day 3 mths	4080-4160	11	Queralto et al 2013 (94)	64% improved- inc BM/wk, symptom score, QOL, faster transit,
STC Child	home	1 hr, daily, 3-6 mths	4080-4150	32	Yik et al 2012 (93)	Inc in def freq and urge, dec in soiling and abd pain. Colonic transit faster. HrQOL impr.
STC Child	home	1 hr, daily, 2 mths	4080-4160	Pilot 11	Ismail et al 2009 (77)	Inc defec freq, dec soiling, no effect on abd pain
STC Child	clinic	20 min, 3/wk, 4 wk	4080-4150	Pilot 8	Chase et al 2005 (70)	Small- incr defec freq and dec soiling

B: RCTs						
Pt Group	Location	Stim sessions	Stim Frequency Hz	# of Pts	Clinician	Effects
STC Adult	home	1 hr, daily 6 wks	4080-4150	16 Crosse d vs 15 not crosse d	Moore et al 2018 (abs) (84)	Crossed IFC sig > uncrossed, 60 vs 13% Inc BM/wk, impr PAC-SYM, VAS. Decr laxatives. No effect on anorectal manometry or transit.
Constip Child	home	20 min, 2/wk, 10 sess	4005-4055 Vs no current	PFME +/- stim, 45 per group	Sharifi-Rad et al 2018 (86)	IFC sig boosts PFME, 80 vs 45% Inc bm/wk, dec const severity, soiling, pain
HD Child postoperative	clinic	20 min 2/wk, 15 sess, 6 mth Follow up	4005-4025	30 HD Behav therap +/- stim, 15/group	Ladi-Seyedian et al 2017 (85)	IFC sig > control, 66 vs 27% of pts Imp constip symp, BM\wk & pain score
Child neurogenic bowel-spina bifida-constip	clinic	20 min, 3/wk, 15 sess	4005-4025	30 pts, 15 IFC, 15 sham	Kajbafzadeh et al 2012 (65)	IFC sig > sham. BM/wk inc Sphinct press & RAIR imp
IBS-C Adult	clinic	15 min, 12 sess, 4 wk	Vacuum 4080-4150	vacuum +/- IFC 29 IFC, 29 sham (vacuum - IFC)	Coban et al 2012 (76)	Symptoms impr in both during, Continued impr 1 mth after in IFC group
STC Child	clinic	20 min, 3/wk, 4 wk	4080-4150	16 Active vs 17 no current,	Clarke et al 2009 (72), Yik 2011 (74), Clarke et al 2009 b (71), Leong	Small-faster transit, impr QOL Long lasting in 1/3

				subsen sory	et al 2011 (73)	
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Table 9. Percutaneous tibial nerve stimulation (PTNS) and transcutaneous tibial nerve stimulation (TTNS) for faecal incontinence (FI). (PTNS= percutaneous tibial nerve stimulation, TTNS=Transcutaneous tibial nerve stimulation)

A: Reviews		
Pt Group	# of Pts	Conclusion
Simillis et al 2018 (17) PTNS vs SNS SR- MA	4 stud, 302 pts (109 SNS, 193 PTNS)	All studies noted improvement in symptoms after treatment, with similar efficacy for SNS and PTNS. Meta-analysis- Wexner score improved significantly with SNS compared to PTNS (WMD 2.27). SNS was also associated with a significant reduction in FI episodes/week and a greater improvement in the FIQOL coping and depression domains, compared to PTNS on short-term follow-up. No serious adverse events with either. Further, high-quality, multi-centre randomised controlled trials with standardised outcome measures and long-term follow-up are required in this field.
Horrocks et al 2014 (132) PTNS or TTNS SR	12 articles 6 PTNS, 5 TTNS, 1 both. 10 case series and 2 RCT.	PTNS and TTNS result in significant improvements in some outcome measures; however, TTNS was not superior to sham stimulation in a single large, adequately powered, RCT. As no adequate RCT of PTNS versus sham has been conducted, conclusions cannot be drawn regarding this treatment.
Thomas et al 2013 (133) PTNS SR	273 patients, 13 studies. 4 TTNS, 8 PTNS, 1 compared both with a sham. 1 FI with spinal cord injury and 1 FI with inflammatory bowel disease (IBD)	PTNS is effective for FI. However, many studies are poor quality. >50% improvement in FI episodes in 63-82% of patients. Improvement in urgency (1-5 min), in Cleveland Clinic FI score in 8 studies. Patients with urge and mixed incontinence benefit more than passive incontinence. Treatment regimens ranged in duration from 1-3 months. A residual therapeutic effect is seen after completion of treatment. Follow-up ranged from 1-30 months. Comparison between studies is difficult owing to differences in the outcome measures used, technique of PTNS and the timing and duration of treatment.
Thin et al 2013 (22) PTNS SR		PTNS as effective as SNM to 12 months. Little evidence for TTNS. Need to standardise outcome measures.
George et al (145) PTNS Opinion Rev		Reviews available information on PTNS and focuses on needs for evidence base and comparison to SNS.
B: Studies		

Pt Group	Sessions	Stim Frequency Hz	# of Pts	Ref	Effects
FI RCT	30 min	Hz, 200 us vs no current	29 PTNS, 30 sham	Van der Wilt et al 2017 (135)	FI- Slightly more effect of PTNS than sham, mostly not sig.
FI Adult RCT	1/wk, 12 wks	Transcutaneous	115 PTNS vs 112 sham	Knowles et al 2015 (134)	No benefit over sham in FI ISRCTN88559475
FI RCT		30 min, 12 treatments	115 PTNS vs 112 Sham	Horrocks et al 2015 (146)	No benefit over sham in FI Report to NIH ISRCTN88559475
FI PTNS compared with SNS during same time			PTNS in 21 and SNS in 57 patients.	Al Asari et al 2014 (147)	A 50% or more improvement in Wexner score was seen at 6 and 12 months in 47% and 30% of PTNS patients and in 50% and 58% of SNS patients with no significant difference between the groups. PTNS is easier, simpler, cheaper and less invasive than SNS with a similar short-term outcome.
FI daily vs 2 per week			30 patients randomised once daily vs twice weekly PTNS for a 6-week period at home	Thomas et al 2013 (148)	Little change in incontinence or BM frequency. little difference between groups but daily treatment maybe slightly more effective than twice weekly treatment. Larger studies needed.
		Pilot 2 weekly, 6 weeks	22 patients 18 continued at 6 weeks	Govaert et al 2010 (149)	18 continued the treatment; 13 patients had a > 50% decrease in incontinence episodes. Overall incontinence episodes/wk fell from 20 at baseline to 10 at 6 weeks and to 4 at 1 year. Postponement time and quality of life increased significantly during follow up. Percutaneous tibial nerve stimulation is simple and can be used in the outpatient setting. Good results can be obtained and sustained during maintenance treatment.
C: Mechanism of action					

Mechanism rats	Gao et al 2015 (103)	Acetylcholine M3 rec, afferent nerve a-delta and C-fibers mediated signal.
Mechanism human cortical effects	Finazzi-Agro et al 2009 (150)	Show effects of PTNS on cortical network. The P80 and P100 amplitude increase might reflect long-term modifications in synaptic efficiency through the somatosensory pathway. The plastic reorganization of cortical network triggered by peripheral neuromodulation can be hypothesized as a mechanism of action of PTNS. Further studies are needed to correlate LL-SEP modifications after PTNS with the success of the treatment.

Table 10. Percutaneous tibial nerve stimulation (PTNS) and transcutaneous tibial nerve stimulation (TTNS) for constipation. (FES= functional electrical stimulation, SNS= sacral nerve stimulation, SNM= sacral nerve modulation, STC= slow transit constipation, TENS= transcutaneous electrical nerve stimulation).

Reviews	
Wright and Haddad 2017 (8) Children bladder or bowel dysfunction. Gen Rev	Non-invasive and invasive electroneurostimulation (ENS) modalities for bladder/bowel dysfunction in children. Summary of proposed mechanisms of action and commonly used and recently reported techniques, including TENS, FES, intravesical electrical nerve stimulation, PTNS and SNM in conditions including overactive bladder, enuresis, dysfunctional voiding, constipation, combined bladder bowel dysfunction and neuropathic bladder and bowel dysfunction.
Bharucha et al 2017 (151) Surgical methods FI and defecatory disorders. Expert review and best practice advice	SNS should be considered for patients with moderate or severe FI in whom symptoms have not responded after a 3-month or longer trial of conservative measures and biofeedback therapy and who do not have contraindications to these procedures. Best Practice Advice 5: Until further evidence is available, PTNS should not be used for managing FI in clinical practice. For defecatory disorders, biofeedback therapy is the treatment of choice. Based on limited evidence, SNS should not be used for managing defecatory disorders in clinical practice.
Lu and Di Lorenzo 2016 (5) General review neurostim for GI disorders in children	SNS can be effective in the treatment of children with refractory constipation or FI. Patient satisfaction with treatment remains high despite the risk of complications requiring further surgery. Abdominal TES and PTNS are noninvasive and may be effective in the treatment of children with constipation and FI. (Evidence for benefit in children remains limited). High-quality studies demonstrating safety and efficacy and a better understanding of the mechanism of each modality are needed before there is more widespread acceptance.
Tong and Wang 2016 (152) Surgical chinese literature	SNS therapy and PTNS in managing refractory constipation have brought expected outcomes in recent years. (Not clear what this means).
De Groat and Tai 2015 (7) General review and nerve innervation	Summarises (a) neural control of the lower urinary tract and distal bowel, (b) clinical use of neuromodulation in the treatment of bladder and bowel dysfunctions. Although detailed mechanisms underlying the effects of neuromodulation are still to be elucidated, it is generally believed that effects are due to stimulation of action potentials in somatic afferent nerves. Afferent nerves project to the lumbosacral spinal cord, where they release excitatory neurotransmitters that activate ascending pathways to the brain or spinal circuits that modulate visceral sensory and involuntary motor mechanisms. Studies in animals revealed that different types of neuromodulation (for example, stimulation of a sacral spinal root, pudendal nerve or posterior tibial nerve) act by releasing different inhibitory and

	excitatory neurotransmitters in the central nervous system. In addition, certain types of neuromodulation inhibit visceral smooth muscle by initiating reflex firing in peripheral autonomic nerves or excite striated sphincter muscles by initiating reflex firing in somatic efferent nerves.	
B: Studies and trials		
Wu et al 2019 (140)	Constipation. Stim at ST36 (knee) vs PTNS. 8 pt, 2 wks each tx, crossover	Stim at ST36 was more potent and improved constip symptoms and rectal sensation more than PTNS.
Kumar et al 2017 (137)	Constipation. 34 pts, 11 STC, 14 rectal evac disorders (RED) and 9 BOTH, 30 min, 12 sess	PTNS is of no benefit to patients with constipation. Response in only 4/34 pts.
Madbouly et al 2017 (153)	Rectal evac disorders 36 pts, 30 min bilateral stim, 3 per week, 6 weeks	Successful outcome in 47%. More effective in patients with a less-modified obstructed defecation score. Additional studies needed to discover predictive factors for success.
Iqbal et al 2016 (138)	TTNS for constip. 15 pt, 30 min/day, bilateral at home, 6 weeks	Little effect. PAC-QOL improved sig but no change to PAC-SYM. 2 pts complete cure, 2 others improved. Careful selection of patients may assist.
Zhang et al 2014 (139)	ES at TTNS and ST36 for constip. 12 pts, 2 weeks of TTNS and 2 weeks sham in crossover design.	PTNS and ST36 are effective in CC. Effect possibly via autonomic mechanism. (1) ES inc SBM. After 2-week ES therapy, 83% patients had >3 BM/week, significantly different from sham-ES (P = 0.01). (2) ES improved PAC-SYM and PAC-QOL scores (P < 0.001, resp.). (3) ES significantly decreased threshold volume to elicit RAIR, ameliorated rectal sensory threshold, and maximum tolerance. (4) ES, but not sham-ES, increased the vagal activity and decreased the sympathetic activity.
Collins et al 2012 (154)	PTNS for STC pilot. 8 pts, 12 sess, 30 min,	Wexner constipation score and PAC-QOL improved significantly with treatment. Stool frequency increased and use of laxatives decreased. No change in colonic transit time.
C: PTNS and Anal Fissure		
Aho Falt et al 2019 (141)	9 pt, 30 min, 10 days.	PTNS enhanced healing of chronic anal fissure and reduced pain and bleeding with an associated improvement in bowel function.

Youssef et al 2015 (142)	Ptns vs sphincterotomy, 73 pts, 36 PTNS, 37 shincterotomy	All sphincterotomy pts had improvement at 1 months and 75% of PTNS. Anal fissure recurred in 3% of sphinct and 4% of PTNS. Lateral internal sphincterectomy remains the gold standard.
Altunrende et al 2013 (143)	10 pts, 10 days	Pain and bleeding resolved in all patients 2 days after the treatment, and mucosal healing was observed in 6 patients, 10 days after treatment. Wexner's constipation and visual analog scale scores for pain and Hamilton anxiety and depression scores decreased significantly. Among Short Form-36 subscales, only mental health score increased significantly.

Table 8. Acupuncture and Electro-acupuncture (EA) for constipation

(CC=chronic constipation, EA= electroacupuncture, FC=functional constipation, MA= meta-analysis, QOL= quality of life, R=review, S=study, SCBM= spontaneous complete bowel motions, SR=systematic review, T=trial, UI=urinary incontinence)

Pt Group	Effects	Pts
A: Acupuncture and FC		
T Zheng et al 2018 (114) Chronic FC	The 3 acupuncture treatments were as effective as mosapride in improving stool frequency and consistency. Magnitude of treatment effect cannot be determined due to lack of sham acupuncture control.	RCT 684 patients with CFC; Acupuncture at He (n = 172), Shu-mu (n = 171), He-shu-mu (n = 171) points, or oral administration of mosapride (n = 170). 16 sessions in 4 wks.
Pilot T Lee et al 2017 (95) FC	Acupuncture showed clinically meaningful improvements in SCBMs occurring >3 times per week and maintained for 4 weeks after treatment.	Pilot trial. 30 pts randomly assigned to real acupuncture (RA) or sham acupuncture (SA) group. RA consisted of 8 fixed acupuncture points (bilateral ST25, ST27, BL52 and BL25) and four additional points targeted to the individual based on Traditional Korean medicine (TKM). SA consisted of shallow acupuncture insertion at 12 non-acupuncture points. 12 sessions in 4 wks.
R Wang and Yin 2015 (98) CC review of range of therapies	17 articles on acupuncture for constipation. Control groups include medication, other stimulation, and acupuncture with medications. Medications include mosapride, PEG 4000, lactulose and Chinese medicines Fuzhengliqi mixture, plantain or senna. Sham acupuncture, shallow acupuncture, regular electrical stimulation were used as control. Suggest that acupuncture or electroacupuncture are effective in treating constipation.	
SR, MA Zhang et al 2013 (100) FC	Acupuncture was probably as effective as conventional medical therapy in the change of bowel movements and colonic transit activity (could be better than sham acupuncture for transit) (MA). Deep	15 RCTs, 1256 participants. All conducted in China and published in Chinese journals.

	acupuncture was better than normal depth acupuncture in abdominal region. Evidence limited by small sample size and low methodological quality.	
SR, MA Manheimer et al 2012 (102) IBS	No benefit of acupuncture relative to sham on symptoms severity or QOL. Patients report greater benefit but further trials required.	17 RCTs, 1806 pts
B: Electro-acupuncture and constipation		
R Chen et al 2018 (115) Gastro-esophageal reflux, functional dyspepsia, IBS and constipation	Review of studies. Important issues described: choice of stimulation parameters, frequency of therapy, choice of placebo, mechanisms of action involved in the therapeutic effects of EA for gut dysmotility and future research directions.	
SR Zhou et al 2017 (104) FC vs medication	EA was significantly more effective than medication at improving spontaneous bowel movements and total response rate, and reducing the symptoms of FC.	7 studies.
T Wu et al 2017 (116) FC EA at different current intensities vs mosapride. Protocol Zheng et al 2013 (117)	Primary outcome reached by 53.45%, 66.15%, and 52.24% of patients given LCI, HCI, and mosapride, resp. EA is effective and safe at both current intensities for FC; therapeutic effects of LCI and HCI are not superior to mosapride. EA is superior to mosapride in improving patients' life quality and satisfaction level of treatment; EA has fewer adverse events than mosapride.	4 weeks treatment and 4 weeks follow-up. 190 patients randomly divided into low current intensity group (LCI, 58), high current intensity group (HCI, 65), and mosapride group (MC, 67). 16 sessions of 30 min: 5/week for first 2 weeks and 3/ week during following 2 weeks. 2/50 Hz 5 mg mosapride citrate, 3 times daily for 4 weeks. Primary outcome (≥ 3 SBMs/ week and an increase of ≥ 1 SBMs from baseline during at least 3 of the 4 weeks).
T Liu et al 2016 (118)	The proportion of patients having >3 mean weekly CSBMs in the EA group was 31% and 38% over the	28 sessions of EA at traditional acupoints or sham EA (SA) at

FC	treatment and follow-up periods, compared with 12.1% and 14.1% in the SA group ($P < 0.001$).	nonacupoints over 8 weeks. 1075 patients (536 EA and 539 SA).
R Wang and Yin 2015 (98) CC review of range of therapies.	Suggest that acupuncture/EA are effective in treating constipation. More well-designed clinical trials are needed; mechanistic studies are also discussed. Different current frequencies and different numbers of treatments per week (best every day or every second day).	11 trials of EA for constipation. Review of acupuncture, moxibustion, massage, and herbal medicine. Efficacy, safety, influence factors, sham control design, and mechanisms of these therapies are discussed and evaluated.
T Xiong et al 2014 (119) FC	Statistically significant increase in stool frequency every week ($P < 0.01$), but no significant difference among the 3 groups. Low and high intensities of EA improved the FC patient's anxiety and depression, reduce the serum levels of CORT, and increase the serum levels of SP and VIP effectively with no significant difference between the low and high intensities of EA.	111 pts – 3 groups-EA groups (low and high intensity of EA groups) and medicine-controlled (MC) group.
T Shang et al 2013 (120) FC	Decreased defecation interval, stool property, constipation symptom grade, accompanying symptom grade, and GITT at the end of treatment in every group. Combined therapy is much better in long-term efficacy and the safety is good.	560 pts, 4 groups. Combining Fuzhengliqi mixture (FLM) with acupuncture in treating functional constipation (FC).
SR Zhang et al 2013 (100) CC	Acupuncture is as effective as conventional medicine. Acupuncture may improve weekly SBM, QOL and symptoms. Evidence limited by small sample size and methodological quality.	15 studies, 1256 pts
C: Rats- mechanism- all levels of bowel		
S Zhou et al 2017 (108)	Stress-induced gastric hypersensitivity can be prevented or suppressed by EA at ST36 via the	Rats treated with neonatal iodoacetamide mimicking functional dyspepsia (FD) are more vulnerable to stress.

EA- Rats-stress-induced gastric hypersensitivity (FD)	restoration of sympathovagal balance.	Effect of EA on sympathovagal balance: EA at ST36 (ZuSanLi) was performed during the acute stress or 30 min after the stress.
S Yu et al 2016 (110) EA- Rats ST25- jejunal motility	EA at ST25 inhibited jejunal motility in an intensity-dependent manner, via a mechanism in which sympathetic nerves and TRPV1 receptors play an important role.	EA at ST25
S Gao et al 2015 (103) Acupuncture Rats normal/constipation/diarrhea	Increased distal colonic motility in normal rats and rats with constipation or diarrhea. Acetylcholine M3 receptors played an important role in the facilitation of distal colonic motility. Afferent nerve Adelta- and C-fibers mediate the transduction of the acupuncture signal and C-fibers are essential for enhancing the effect of acupuncture on distal colonic motility.	Acupuncture at heterotopic acupoints
S Zhu et al 2015 (109) EA Rat constipation (cold gavage)	Positive effect on objective markers of constipation in a rat model (cold saline gavage). In addition, EA increased 5-HT and TPH in the colonic tissues. Faecal water content, defecation frequency, and gastrointestinal (GI) transit were measured, as well as the expression of tryptophan hydroxylase (TPH) in colonic tissues (by Western blot analysis) and 5-HT in faeces and colonic tissues (by ELISA).	EA at LI11 and/or ST37

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TES or FES- direct current

A Direct current

B Single Pair of electrodes C Two pairs of electrodes

Veiga 2013

Iqbal 2016

NER_13099_TES or FES hair 30-10-19.jpg

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Author/s:

Southwell, BR

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