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Pudendal nerve stimulation for treatment of lower urinary tract symptoms: A systematic review of safety, technical feasibility and clinical efficacy

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ABSTRACT

Aim: Pudendal nerve stimulation (PNS) is a promising neuromodulation option. While sacral neuromodulation (SNM) and posterior tibial nerve stimulation (PTNS) are established third-line treatments for lower urinary tract dysfunction (LUTS), the pudendal nerve offers potential advantages that merit systematic review. The review aims to evaluate the safety, technical feasibility, and clinical efficacy of PNS for the treatment of urinary incontinence.

Methods: The review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported in accordance with the PRISMA guidelines. PubMed, Embase, and Cochrane Central were searched for studies on PNS, without time or language restriction. The final search date was 12th June 2024.

Results: Of 3,020 records screened, 14 studies were included. Two randomised crossover designs and 12 observational studies included a total of 292 patients, predominantly female (n=198; 68%). Safety data were reported by eight studies with a total of 24 adverse events reported in 199 patients (12.1%). These included infections (n=3; 1.5%), lead displacements (n=5, 2.5%) and unwanted stimulation effects including pain (n=10; 5.0%). All studies reported technical outcomes with varying results depending on approach. Operative duration ranged from 20-130min and conversion from percutaneous nerve evaluation to implant varied from 30%–100%. Seven studies included measures of clinical efficacy for LUTS and showed a reduction of 2.92 (5.57 to 2.65) in mean daily incontinence episodes (95% CI: 1.52 to 4.31), alongside improvements in voiding volumes and frequencies. Four studies reported physiological data, with increases in bladder capacity (factor 1.5-2) and effect on undesired detrusor contractions (UDC). Where directly compared, PNS demonstrated comparable or better outcomes than SNM in symptom reduction.

Conclusion: PNS appears to be a safe and technically feasible therapy. Clinical outcome data suggest beneficial effects in several LUTS populations including urinary incontinence.

1. Introduction

Neuromodulation is a standard third-line treatment option in patients with lower urinary tract dysfunction (LUTS). Sacral neuromodulation (SNM) and posterior tibial nerve stimulation (PTNS) have been extensively investigated with some high-quality studies leading to their global recognition as standard of care. However, in the search for alternative treatments and/or improved efficacy rates, other targets have been explored.

One of these is the pudendal nerve. The pudendal nerve originates from the sacral plexus, specifically S2, S3 and S4 nerve roots. After passing through the pudendal (Alcock's) canal, it divides into three distal branches: the inferior rectal branch, the perineal branch, and the dorsal genital nerve (DGN) of the penis and clitoris (with significant anatomical variation in the branching pattern) [1]. The composition of the pudendal nerve with afferent sensory, efferent motor, and autonomic fibres to and from the urethra and bladder provides physiological rationale as a target for neuromodulation for LUTS. The pudendal nerve can be accessed by transcutaneous (mainly stimulation of the DGN) and percutaneous approaches (electroacupuncture or lead implantation).

DGN stimulation has gained prominence in the field and generally entails the trans- or percutaneous stimulation of either the dorsal penile or clitoral nerve, offering potential applications for both overactive

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bladder (OAB) and neurogenic bladder dysfunction [2]. An advantage of DGN stimulation lies in the nerve's superficial position, which akin to the tibial nerve, enables transcutaneous methods using surface electrodes (although the use of subdermal needle electrodes is also significantly more manageable than the placement of electrodes deeper into the pelvis along the pudendal nerve). Stimulation is possible through continuous or conditional stimulation (e.g. activation upon unwanted detrusor contractions, or patient activation). Stimulation parameters include amplitudes that are typically twice the bulbocavernosus reflex, frequencies ranging between 5 and 25 Hz, and pulse widths of 200–250 μs [2].

The majority of DGN stimulation studies have focussed on patients with neurogenic bladder dysfunction. Within this context, several research groups have explored the efficacy of percutaneous DGN stimulation, employing either needle or wire techniques to deliver conditional (as opposed to continuous) stimulation. Reported outcomes include the suppression of unwanted detrusor contractions (UDCs) and an improvement of cystometric capacity by as much as 214% [3]. Transcutaneous DGN stimulation studies using surface electrodes have reported more variable results with some reporting increased cystometric capacity (by up to 177%), whereas others have shown little effect [4]. Where reported, some transcutaneous approaches have yielded successful suppression of UDCs with the time between the first detrusor contraction and the first desire to void increased, allowing patients sufficient time to reach the toilet [5]. Fewer studies have examined the impact of DGN stimulation on non-neurogenic urinary incontinence symptoms (e.g. detrusor overactivity, urge urinary incontinence). These also showed that MCC can be increased (by up to 55%) concomitant on reduced incontinence (up to 50%) and urgency episodes (up to 80%) [2,6].

Stimulation of the inferior rectal branch of the PN has been studied to a much lesser extent than DGN stimulation. Anogenital afferent stimulation (AGAS) delivers an electrical stimulus by an anal probe with reported improvements in incontinence episodes for both stress and urinary incontinence [7]. Studies in children also showed positive results, but the lack of large-scale studies means that little definitive conclusions can be drawn [8,9].

Despite the greater popularity of DGN stimulation, there have also been studies directed to stimulating the main PN trunk. While this is technically more challenging due to its deeper anatomical position and tortuous path, it is theoretical potential to invoke greater physiological effects on both bladder and sphincters is well established in preclinical literature [10,11]. Given these challenges, and with new technologies at a horizon stage [12,13], there is a need to appraise the current evidence base for key outcomes pertinent to future development.

1.1. Aims and objectives

This systematic review builds on previous narrative reviews [14–17] with specific focus on assessing safety, technical feasibility and clinical efficacy of PN trunk stimulation.

2. Material and methods

The systematic review for PNS was conducted in line with the protocol, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, and reported in accordance with the Preferred Reporting items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [18,19].

2.1. Inclusion and exclusion criteria

In accord with the review objectives, the review was limited to studies of PNS where the main nerve trunk was targeted with an implantable lead enabling chronic (defined as minimum of 4 weeks) stimulation. This excluded studies where branches of the PN were stimulated (e.g. DGN) and where intermittent stimulation was applied at intervals (such as electroacupuncture). While studies of PNS for any clinical indication were eligible for inclusion for safety and technical data, clinical and physiological outcome data were only extracted from studies of patients where the primary indication was the treatment of urinary incontinence (UI). No restriction was applied based on anatomical approach, type of implantable electrode(s) used or on stimulation parameters applied.

There were no restrictions based on study/trial design, study quality or on year of publication. However, eligibility required a minimum starting cohort of five patients on intent-to-treat i.e. case reports were not eligible. Comparison with a control group was not an inclusion criterion but where a comparator was included, clinical outcome data (UI only) were extracted for both PNS and comparator. Review articles, letters, abstracts and posters were excluded. No language restrictions were applied.

Table 1
Full search strategy for PNS articles.

Keywords	
1.	(stimulation) OR (neuromodulation) OR (neuroprosthesis) OR (neuroprostheses) OR (electrical) OR (electrode) *5,171,887 results*
2.	Pudendal *10,862 results*
3.	Both #1 and #2 *3020 results*

The duplicates from these 2 searches (3020 results) were removed (1984 results), were restricted to humans (1553 results) and excluded reviews (1368 results). These were screened against the eligibility criteria.

2.2. Outcome measures

Primary and secondary outcome data are shown in Table 2. The primary outcome measure was safety, as derived by frequency and type of adverse events. Technical data included device architecture, surgical approach, stimulation parameters and methods. Clinical (e.g. change in mean frequency of UI episodes) and physiological data (e.g. change in bladder capacity, impact on UDC) were also included.

2.3. Search strategy

PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched for eligible studies. No time or language restrictions were applied. The date of the final search was 12th June 2024. The full search strategy Table 1 included some unexpected descriptive interventional terms e.g. 'neuro-prostheses' derived from a basic search of previous reviews [2]. Population terms were dropped since all disease states treated by PNS were eligible for extraction of technical and safety data. Included studies from the review articles identified in the search were screened for additional eligible studies.

2.4. Article selection

One reviewer (SH) performed the search and imported all records into a spreadsheet (Microsoft Excel for Office 365 via CSV file export). After removal of duplicates, three reviewers (SH, CK & JK) independently screened the titles and abstracts against the eligibility criteria. Full-text articles of potentially eligible studies were retrieved and reviewed. Any disagreements were resolved through discussion with the senior author (SdW). Partial duplicates i.e. overlapping populations that nevertheless provided unique data in each paper were included to maximise data retrieval.

2.5. Data extraction

Data were extracted into the spreadsheet by SH. We adhered to the predefined outcome measures outlined in Table 2. Data on study

Table 2
Outcome measures from extracted data for PNS studies.

Safety[a]	Primary	Total of all adverse events
	Secondary	Total serious adverse events
		Total serious adverse device events
		Specific common adverse events (detail)
Technical[a]	Device architecture	Type of lead (manufacturer)
		Number of electrodes
		Type of implant (manufacturer)
		Fixation methods
	Surgical approach	Open or percutaneous
		Anaesthesia e.g. general, local, sedation
		Insertion route e.g. gluteal, posterior
		Insertion guidance – electrophysiological/radiological
		Anatomical location on nerve
		Number of needle attempts per successful lead placement
		Conversion rate: PNE to implant
	Stimulation	Parameters: mean amplitude, pulse width, frequency
		Cycling vs. continuous vs. conditional
		Amplitude tolerance
Clinical[b]	Primary	Change in UI episodes per week
	Secondary	Voiding frequency
		Total urgency episodes (dry + wet) per week
		Stress UI events per week
		Summative symptom scores
		Disease-specific QoL measures e.g. OABq
		Global patient ratings of success or satisfaction π
Physiological[b]	Cystometrogram	Change in bladder capacity (ml)
		Change in UDC frequency per unit time
		Other
	Barrier function	Urethral pressures
		Pelvic floor or sphincter EMG

Key:
[a] All PNS indications.
[b] UI indications only; π including patient preference; UDC: unwanted detrusor contractions; EMG: electromyogram; UI: urinary incontinence; QoL: quality-of-life; PNE: percutaneous nerve evaluation.

Table 3
Risk of bias assessment for randomised studies.

Study	Year	Journal	Type	Risk of bias	Domains
Peters et al. [20]	2005	Neurourol. Urodyn.	Crossover	High	
Peters et al. [21]	2007	BJU Int.	Crossover	High	

Level of risk
Low
Moderate
Serious
No information
Randomised studies bias domains: (1) Randomisation process; (2) Deviations from intended interventions; (3) Missing outcome; (4) Measurement of outcome; (5) Selection of reported result.

characteristics were also extracted, including publication year, study period, size of study population, participant demographic and baseline characteristics, follow-up schedule, and loss to follow-up rates. No authors were contacted to clarify data. Study design was determined using the approach published previously to differentiate case series from cohort studies [22].

2.6. Quality assessment

Risk of bias was assessed in randomised studies by a single reviewer (SH) using the Revised Cochrane risk-of-bias tool for randomised trials (RoB2) and assigning moderate risk of bias to domains where documentation of method was insufficient to reach a conclusion. Non-randomised studies were not assessed for risk of bias due to evident general deficiencies in design (case series).

2.7. Synthesis of results

Meta-analysis was not performed due to heterogeneity of study designs, which included randomised trials, prospective and retrospective observational studies, and differences in inclusion criteria, diagnostic criteria, and outcome measures. On this basis, a narrative synthesis was carried out for the pre-specified outcomes.

2.8. Notes on surgical approach

The literature describing anatomical approach to reach the pudendal nerve is confused by multiple descriptions that variably attribute an approach to an author or to the skin entry point, the latter being subject to varying anatomical descriptions. Table 4 summarises the terminology used for this review.

2.9. Appraisal and analysis plan

Results are presented descriptively as tables with limited narrative description.

3. Results

3.1. Search and study selection

The PRISMA flow diagram Fig. 1 shows the systematic literature search and study selection process with reasons for exclusions [19]. A

Table 4
Surgical approaches to the pudendal nerve.

Preferred descriptor	Synonyms	Author attributions	Notes
Ischiorectal	Perineal Infragluteal	Peters (2005) (based on historic nerve block methods) [20]	Entry medial to ischial tuberosity (a point between anus and IT). Usually, trans-vaginal or trans-anal palpation of ischial spine and electrophysiological ± fluoroscopic guidance.
Posterior	Transgluteal Supragluteal	Schmidt (1989) [23]	Surface marking of ischial spine. Insertion perpendicular to skin with intra-rectal palpation (att. Bock 2010) [24] or electrophysiological ± fluoroscopic guidance (att. Spinelli 2005) [25]
STAR	Midgluteal	Heinze (2015) [26]	Four fixed anatomical landmarks used to draw a triangle. Defined point inside triangle is used for entry with some angulation in and up to reach ischial spine.
LION [a]technique	Laparoscopic transperi-toneal	Possover (2014) [27]	A pocket is made in the retroperitoneal space to expose distal sacral, sciatic and pudendal nerves. A bespoke curved introducer is used to place the lead.
ENTRAMI technique	Endoscopic subgluteal	Jottard (2019) [28]	A laparoscope is inserted by a lateral incision in the buttock and the sub-gluteal space insufflated to identify the pudendal nerve under direct vision.

Key:
ENTRAMI: Endoscopic trans gluteal minimal-invasive.
[a] Laparoscopic Implantation of Neuroprosthesis.

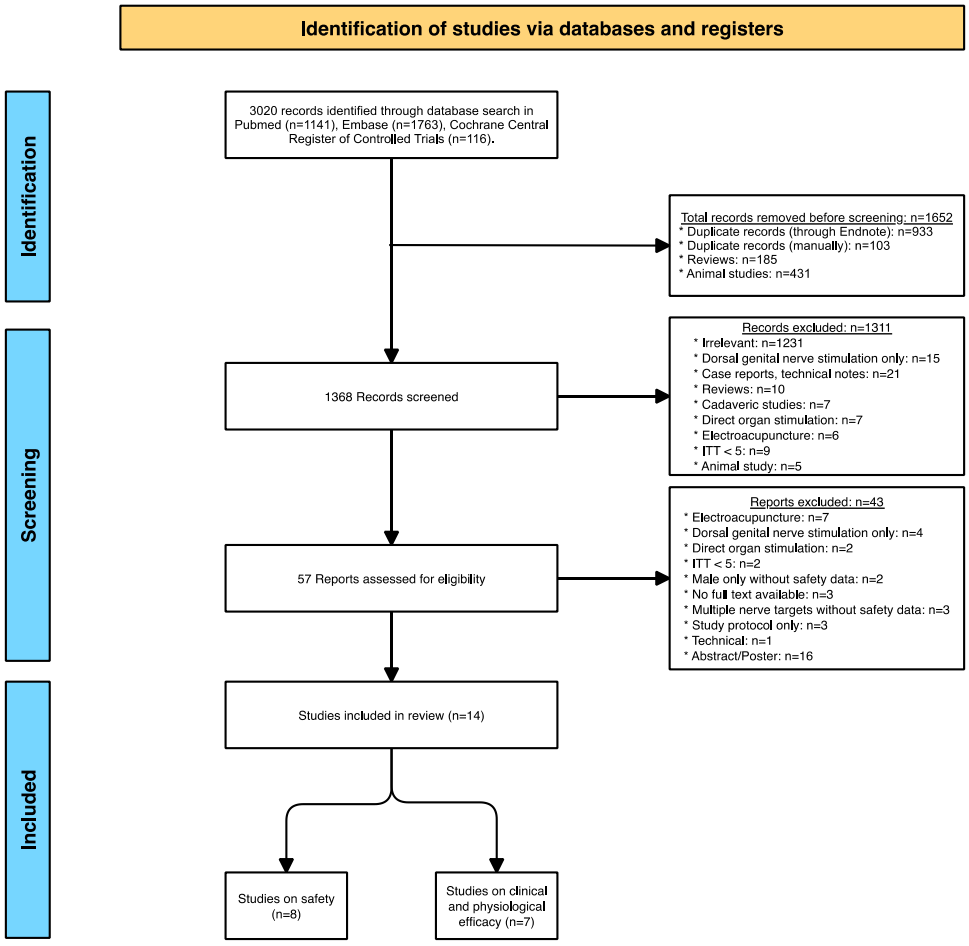

Fig. 1. PRISMA flow diagram for PNS systematic review.

total of 3020 records were identified by database searches. Of these, 14 were included in the final review. All provided some information on implantation technique, 7 provided some clinical and/or physiological outcome data related to UI and 8 documented data on safety outcomes. There were no exact duplicates, but some populations clearly overlapped in serial publications [29,30].

3.2. Notes on exclusions

Some techniques were deemed to be out of scope for the review including numerous studies of dorsal genital nerve stimulation (usually employing surface, but occasionally needle electrodes) [2]. Studies on electro-acupuncture were also excluded due to transient (non-implant)

Table 5
Full-text articles excluded.

Reference		Reason
1	Janneck C. Electric stimulation of the bladder and the anal sphincter – a new way to treat the neurogenic bladder. Prog Pediatr Surg. 1976;9:119-39 [31].	Intravesical not pudendal stimulation.
2	Juenemann KP, Lue TF, Schmidt RA, Tanagho EA. Clinical significance of sacral and pudendal nerve anatomy. J Urol. 1988;139:74-80 [32].	Only 2 electrodes inserted both at S3.
3	Rogers J, Henry MM, Misiewicz JJ. Disposable pudendal nerve stimulator: evaluation of the standard instrument and new device. Gut. 1988;29:1131-3 [33].	Intra-rectal stimulation.
4	Ohlsson BL, Fall M, Frankenberg-Sommar S. Effects of external and direct pudendal nerve maximal electrical stimulation in the treatment of the uninhibited overactive bladder. Br J Urol. 1989;64:374-80 [34].	Only 2 pudendal implants amongst large mix of transvaginal, transanal and needle stimulations.
5	Binnie NR, Kawimbe BM, Papachrysostomou M, Smith AN. Use of the pudenda-anal reflex in the treatment of neurogenic faecal incontinence. Gut. 1990;31:1051-5 [35].	Dorsal genital nerve stimulation.
6	Ishigooka M, Hashimoto T, Izumiya K, Katoh T, Yaguchi H, Nakada T, Handa Y, Hoshimiya N. Electrical pelvic floor stimulation in the management of urinary incontinence due to neuropathic overactive bladder. Front Med Biol Eng. 1993;5:1-10 [36].	Direct needle neuromuscular stimulation to pelvic floor.
7	Lemos, N. et al. Rehabilitation of people with chronic spinal cord injury using a laparoscopically implanted neurostimulator: Impact on mobility and urinary, anorectal, and sexual functions. Neuromodulation: Technology at the Neural Interface, 26(1), pp. 233-245 [37].	Leads implanted across pudendal, sciatic and femoral nerves.
8	Li T, Feng X, Lv J, et al. Short-term Clinical Efficacy of Electric Pudendal Nerve Stimulation on Neurogenic Lower Urinary Tract Disease: A Pilot Research. Urology 2018;112:69-73 [38].	Electroacupuncture.
9	Wang S, Lv J, Feng X, et al. Efficacy of Electrical Pudendal Nerve Stimulation in Treating Female Stress Incontinence. Urology 2016;91:64-9 [39].	Electroacupuncture.
10	Wang S, Zhang S, Zhao L. Long-term efficacy of electrical pudendal nerve stimulation for urgency-frequency syndrome in women. Int Urogynecol J 2014;25:397-402 [40].	Electroacupuncture.
11	Wang S, Lv J, Feng X, et al. Efficacy of Electrical Pudendal Nerve Stimulation versus Transvaginal Electrical Stimulation in Treating Female Idiopathic Urgency Urinary Incontinence. J Urol 2017;197:1496-1501 [41].	Electroacupuncture.
12	GU Y, Lv T, Jiang C, Lv J. Neuromodulation of the Pudendal Nerve Assisted by 3D Printed: A New Method of Neuromodulation for Lower Urinary Tract Dysfunction. Front Neurosci. 2021;15:619672 [42]	No safety data reported. Leads implanted across sacral and pudendal nerves

characteristics of such techniques [38,41]. A list of the most important studies excluded at full text review is included in Table 5.

3.3. Characteristics of included studies [Table 6]

From 14 studies, there were two randomised crossover designs [20,21]. The remaining 12 studies were a mix of 7 prospective and 5 retrospective observational designs. Information on ethics (or equivalent) approval was available for all studies claiming to be prospective in design.

Numbers of included patients ranged from 13 to 84 per study. In addition, the study of Schmidt documented a clinical experience of approximately 200 patients but the majority of these (exact number unstated) were needle insertions only [23]. The total number of patients (excluding these 200) was 292 of whom the majority (n = 198) were female (where stated). Clinical indications varied with the majority (n = 8) of studies performed for urinary indications. The remaining 6 studies provided treatment for bowel and chronic pelvic and perineal pain indications (n = 3 each). Follow-up was poorly reported and generally short-term (6–12 months). Several studies reported outcomes at end of treatment while others reported longer-term follow up on a subset of the starting population.

3.4. Risk of bias and quality of included studies

The paucity of information on study design in almost all reviewed papers made any assessment of quality difficult. Both randomised studies were judged as having a high risk of bias using the ROBINS-I or RoB2 assessment tools Table 3.

3.5. Safety [Table 7]

Safety outcomes were reported in 8 studies. The primary literature review outcome (total of all adverse events) could only be based on anecdotal recording of individual events. A total of 24 adverse events were reported in 199 patients (12.1%). Events rates per study varied from 7.1 to 50.0% of patients. Reported events included infections (n = 3; 1.5%), lead displacements (n = 5, 2.5%) and unwanted stimulation effects including pain (n = 10; 5.0%). Only one study cited direct consequences of lead insertion such as bleeding but did not document rate of occurrence [23].

3.6. Technical feasibility outcomes [Table 8]

Technical outcomes varied greatly between studies depending on general approach. Nine studies repurposed InterStim™ devices used for SNM (introducer, quadripolar electrode lead and IPG) with a further two studies using the InterStim™ leads but through alternative approaches (LION and ENTRAMI) [46,49]. Of the nine using a percutaneous method, two used the posterior approach, four used the ischiorectal approach and the remainder included a mix of the two, excepting Heinze et al. who also used the STAR approach (4 anatomical landmarks creating a triangle targeting the pudendal nerve) [26]. All techniques are listed in Table 4.

All used varying combinations of surface markings, intraluminal digital palpation of the ischial spine, electrophysiological and radiological guidance with one using anorectal manometry [29]. The Bion-r was also inserted by an ischiorectal approach using a small incision for the larger introducer (applicator) required to place a 3.3 mm wide

Table 6
Characteristics of 14 included studies.

Study	Year	Country	Design	Main procedure	N	N female	Main diagnostic indication (s)	Follow Up (months)	Outcomes
Schmidt [23]	1989	USA	RCS	PNS	~200	NS	Mixed undocumented	NS	S,T
Bosch [43]	2005	Netherlands	RCS	Bion®	15 (5 implanted)	15, 5	DO (4 failed SNM)	6	C,T
Groen et al. [44]	2005	Netherlands	PCHTS	Bion®	14 (6 implanted)	14	DO failing conservative management; 12 failed previous neuromodulation (SNM, PNE or PTNS)	6	All
Spinelli et al. [25]	2005	Italy	PCS	PNS	15	7	Neurogenic UI failing medical management (3 failed SNM)	N = 7 at 6 months	C,T
Peters et al. [20]	2005	USA	RXOT	PNS	30	NS	Voiding dysfunction (22 UFS; 5 UI; 5 retention syndromes)	2 × 7 days crossover	All
Peters et al. [21]	2007	USA	RXOT	PNS	22	19	Interstitial cystitis (IC)	2 × 7 days crossover then cohort to 6 months	All
Peters et al. [45]	2010	USA	RCS	PNS	84 (some duplicate Peters 2005)	66	42 IC (BPS); 26 UFS; 13 retention syndromes; 13 other [12 neurological diagnosis] [most failed SNM]	24 (9–56)	All
George et al. [30]	2012	UK	PCS	PNS	20	18	13 cauda equina syndrome with constipation/FI; 7 FI only	12	S,T
George et al. [29]	2014	UK	PCS	PNS	13 may be duplicate 2012	11	13 cauda equina syndrome with constipation/FI	12 (9–22)	S,T
Possover [46]	2014	Switzerland	RCS	LION	14	12	OAB, UUI (9 fail SNM)	'several months'	C,T
Thomas et al. [47]	2014	UK	PCS	PNS	10	10	FI	N = 5 to min 6 months (range 6–36)	T
Heinze et al. [26]	2015	Germany	PCHTS	PNS	20	NS	Chronic pelvic pain syndrome	NS	T
Peters et al. [48]	2015	USA	RCS	PNS	19	12	Chronic pelvic pain syndrome; 13 also UUI (6 failed SNM)	0–60	C,T
Jottard et al. [49]	2021	Belgium	PCS	ENTRAMI	16	14	Chronic pelvic pain syndrome	1	S,T

Key: RCS: retrospective case series; PCS: prospective case series; PCHTS: prospective cohort study; RCT: randomised comparison trial; RXOT: randomised crossover trial; LION: laparoscopic implantation of neuroprosthesis; DO: detrusor overactivity; SNM: sacral neuromodulation; UI: urinary incontinence; UUI: urge urinary incontinence; MUI: mixed urinary incontinence; OAB: overactive bladder; UFS: urgency frequency syndrome; FI: faecal incontinence; AES: anal electrical stimulation; BF-assist PFMT: biofeedback-assisted pelvic floor muscle training; outcomes: C = clinical; S = safety; T = technical.

implant. The introducer was guided by transvaginal palpation, electrophysiological (it has some form of electrode at the tip) and radiological feedback. The cylindrical implant was pushed into position using an obturator within the introducer which was then removed leaving the Bion-r *in situ*.

Numbers of patients progressing from some form of percutaneous nerve evaluation to implant varied from 30% (Bion-r) to 100%. However, in some studies, the denominator was not stated. Only one study documented the number of attempted needle insertions required to site the PNE lead. Heinze et al. [26], documented that the ischiorectal approach required 15 or 8 passes to site the electrode based on whether intra-rectal palpation [24] was used compared to 22 for the posterior approach [25] and a mean of 3.5 using their own STAR technique.

Where stated, procedures were performed under LA or GA. Some operative durations for PNS quadripolar electrode lead insertion were very short (mean 20 min) [21] but ranged to 83–130 min in one study [26]. The Bion-r procedure took a mean of 67 min (15–123) [44].

3.7. Stimulation parameters

Parameters varied depending on procedure. For studies using InterStim™ devices, the default pulse width of 210 μs and frequency 14–15 Hz were employed (Spinelli used 5–15 Hz) [25] with amplitudes limited by the device between 0–10 mA. The Bion-r device used very similar parameters (0–10 mA, 200 μs, 20 Hz) but with cycling roughly 5 s on and off [43]. No study documented tolerances to stimulation parameters although the ENTRAMI study of patients with chronic pain found that three patients that could not tolerate stimulation at all [49].

3.8. Clinical outcomes [Table 9]

Clinical outcomes were extracted for effect of PNS on LUTS symptoms in 7 studies. Symptom recording and use of summative scoring instruments varied between studies based on population studied and author preference. In general, the starting populations were older adults with mean ages ranging from 38 to 63 years (median of means:

Table 7
8 studies reporting safety outcomes.

Study	Classified reporting (Y/N)	AEs/N	SAE	SADE	DD	Specific adverse events reported (frequency)
Schmidt [23]	N	NS	NS	NS	NS	Vascular absorption of LA; bleeding — veins and artery but no complications stated; advises avoid aspirin for 48h; pain due to local bruising
Groen et al. [44]	Table only for 6/14 patients	7/14: all in 6	NS	NS	NS	1 allergy, 1 vaginal dryness, 1 vaginal fungal infection, 1 IPG mechanical irritation on bicycle riding, 3 altered bowel function
Peters et al. [20]	N	3/30	NS	NS	NS	2 sterile seromas around IPG; 1 forward migration of lead
Peters et al. [21]	N	2/22	NS	NS	NS	2 sterile seromas around IPG
Peters et al. [45]	N	6/84	NS	NS	NS	3 lead migrations; 2 pain (all revised); 1 localised wound infection treated by antibiotics
George et al. [30]	N	1/20	NS	NS	NS	1 infection with explantation
George et al. [29]	N	2/13	NS	NS	NS	1 infection with explantation; 1 lead migration
Jottard et al. [49]	N	3/16	NS	NS	NS	Pain in 3 patients

Key: * no full article published on date of literature search.

Table 8
14 studies reported technical outcomes.

Study	Device architecture				Surgical approach						Stimulation				
	Lead	N Electrode	IPG	Fixation	Anaes.	Skin	Approach	Guidance	Conversion	Duration (mins)	Amp	PW (μs)	Freq (Hz)	Cycling	Tolerance
Schmidt [23]	NS	NS	NS	NS	LA	P	Posterior	EP and also mentions haptic by perforation of STL	NS	NS	NS	NS	NS	NS	NS
Bosch [43]	Bion-r	1 integrated	Bion-r	NS	LA,S	P, small incision	IRF	TV palp, EP, Rad	15 PNE for 5 implants	NS	0–10 mA	200	20	4.92/4.9 2 on off	NS
Groen et al [44]	Bion-r	1	Bion-r	NA	LA, S	P, small incision	IRF	TC palp, EP, Rad	14 PNS for 6 implants	6 (15–123)	NS	NS	NS	NS	NS
Spinelli et al [25]	InterStim	4	InterStim 3023	Tines	LA	P	Mix IRF & posterior	IRF: TV palp, EP; Posterior: EP	15 PNE for 12 implants NS	NS	<sensory threshold	210	5 to 15	Some nocturnal some conditional	NS
Peters et al [20]	InterStim	4	InterStim	Tines	NS	P	IRF	EP, rad, motor and sensory	30 PNE for 24 implants	24 vs. SNM 26	0–10 mA	NS	NS	NS	NS
Peters et al [21]	InterStim	4	InterStim	Tines	NS	P	IRF	EP, rad, motor and sensory	22 PNE for 17 implants	20 vs. SNM 27	0–10 mA	NS	NS	NS	NS
Peters et al [45]	Stim	4	InterStim	Tines	NS	P	IRF	EP, rad, motor and sensory	54/84 in FU with PNS	NS	0–10 mA	NS	NS	NS	NS
George et al [30]	3093–28	4	InterStim 3625 or 3058	Tines	GA	P	Posterior	TR palp, rad, EMG in first 4 pts	20/20		NS	NS	NS	NS	NS
George et al [29]	3093–28	4	InterStim 3625 or 3058	Tines	GA	P	Posterior	TR palp, rad, ARM	13/13		0–10 mA	210	14	Continuous	NS
Possover [46]	NS	NS	NS	One suture to abdominal fascia	GA	Lap	LION technique (n = 7 with bespoke curved applicator)	Direct vision	14 PNE for 11 implants	79 then 18 with bespoke introducing	<1.5 V	210	15	NS	NS
Thomas et al [47]	3093–28	4	InterStim 3625 or 3058	Tines	GA	P	Posterior IRF (n = 1) TR palp, EP, rad	TR palp, EP, rad	13/13	NS	0–10 mA	210	14	Continuous	NS
Heinze et al [26]	3995 bilat in 12	4	NS	Tines	NS	P	IRF Posterior STAR	4 fixed anatomical landmarks, rad	20/20	83–130	NS	NS	NS	NS	NS
Peters et al [48]	3995	4	InterStim 3058	Tines	NS	P	IRF	EP only	19 implants: denominated not provided	NS	NS	NS	NS	NS	NS
Jottard et al [49]	PNE 3995	4	NA	Tines and skin level	GA	Lap	Lat. Gluteal	Direct vision	14/14	NA[a]	NS	NS	NS	NS	3 unable to tolerate

Key: IPG: implantable pulse generator; PW: pulse width; NS: not stated; LA: local anaesthetic; GA: general anaesthetic; P: percutaneous; Lap: laparoscopic; IRF: ischiorectal fossa; STL: sacrotuberous ligament; EP: electrophysiological; TV: transvaginal; TR: trans-rectal; rad: radiological; PNE: percutaneous nerve evaluation.

[a] Includes neurolysis.

49.5 years). Symptom duration reflected a treatment refractory population with a median of approximately 5 years. Intractability was also reflected by previous failure of other therapies including SNM (high proportions of patients in 6 studies). The primary clinical outcome — change in daily urinary incontinence episodes (UIE) was reported 6 studies with a further 1 study reporting proportion of patients who were dry after treatment.

All studies reporting UIE showed that PNS roughly halved daily incontinence episodes from about 6 to 3 UIE/day. In the two crossover studies of Peters et al. the effect size parallelled SNM in patients with

Table 9
7 studies reported clinical outcomes.

Study	Indication	Age	Symptom duration (years)	UIE pre (per day)	UIE post (per day)	VV pre	VV post	VF pre	VF post	Validated scores	GRA
Bosch [43]	DO (4 failed SNM)	NS	NS	6.9	2.9	139	154	NS	NS	NS	NS
Groen et al [44]	DO failing conservative management; 12 failed previous neuromodulation (SNM, PNE or PTNS)	55 (28–73)	8 (1–24)	6.2	2.4	140	161	NS	NS	LSI: 9.9 to 4.0	NS
Spinelli et al [25]	Neurogenic UI failing medical management (3 failed SNM)	38 (21–66)	NS	7 ± 3.3	2.6 ± 3.3	NS	NS	NS	NS	NS	NS
Peters et al [20]	Voiding dysfunction (22 UFS; 5 UI; 5 retention syndromes)	51 (25–80)	NS	5.1	2.7 (2.7 SNM)	89	154 (147 SNM)	22	12 (13 SNM)	NS	63% (vs. 46% SNS); Preference 79% vs. 21% SNS)
Peters et al [21]	Interstitial cystitis (IC)	48 (26–70)	~5 since diagnosis	~2	0.3 (~2 SNM)	85	155 (100 SNS)	26	15 (18 SNS)	NS	Preference for PNS (n = 13) vs. SNS (n = 4)
Peters et al [45]	42 IC(PBS); 26 UFS; 13 retention syndromes; 13 other [12 neurological diagnosis] [most failed SNM]	52 ± 17	NS	6.2 ± 5.2	5.0 ± 5.1	127	158	15	10	ISS: 3.3 to 2.8	60% improved, 30% same, 10% worse
Possover [46]	OAB, UUI (9 fail SNM)	47 [13]	NS	8.1	6 pts dry	NS	NS	25 (SD 112)	10 (SD 3)	NS	NS

Key: DO: detrusor overactivity; SNM: sacral neuromodulation; UI: urinary incontinence; UUI: urge urinary incontinence; MUI: mixed urinary incontinence; OAB: overactive bladder; UIE: urinary incontinence episodes; VV: voiding volume; VF: voiding frequency; UUIE: urge urinary incontinence episodes; SUIE: stress urinary incontinence episodes; NS: not stated; LSI: leakage severity index; ISS: incontinence severity score; UUIS: urge incontinence severity score; ISQoL: incontinence severity quality-of-life score; ICIQ-LUTS: international consultation incontinence questionnaire-lower urinary tract symptom score; ICIQ-LUTSqol: internation consultation incontinence questionnaire-lower urinary tract symptom quality-of-life score.

Table 10
4 studies reported physiological outcomes.

Study	Bladder capacity pre (ml)	Bladder capacity post (ml)	Undesirable detrusor contractions pre	Undesirable detrusor contractions post	Other
Bosch [43]	272	419	NS	NS	NS
Groen et al [44]	301 +/137	429 ± 60	NS	NS	1st involuntary DC 191 ml pre to 341 ml post
Spinelli et al [25]	153 ± 50	331 ± 111	NS	NS	NS
Possover [46]	159 (SD 53)	312 (SD 105)	NS	NS	NS

Key: UDC: undesirable detrusor contractions; * abstract only includes data from 2 patients.

voiding dysfunction (both therapies reduced from 5.1 to 2.7 UIE/d) but PNS was more efficacious for interstitial cystitis with no effect of SNM vs. a marked reduction with PNS [20,21].

Voiding volumes increased after PNS in all studies reporting this outcome with increases in mean volume varying from 15–70 ml. Voiding frequencies were only reported by 4 studies, but these decreased from the order of 20 voids per day to approximately 10 per day. Where PNS was studied in comparison with SNM, changes in voiding volumes and frequency were either similar or superior for PNS [20,21].

Several validated questionnaire-based scoring instruments showed changes in summative symptom scores with PNS (e.g. SF-36 health survey, generic QoL-questionnaires, ICSPI, PUF, Patient Overall Rating of Improvement). Reductions in scores were evident for Bion-r and PNS using InterStim™ for various urinary indications [44,45]. Global ratings of success were reported by several studies. These included preference for PNS over SNM in the two randomised crossover studies of Peters et al. In patients with voiding dysfunction, an overall reduction in symptoms was reported by 63% patients with PNS and 46% with SNM leading to a preference for PNS in 79% patients (vs. 21% SNM) [20]. In 17 patients with interstitial cystitis, 13 preferred PNS compared to 4 SNM [21].

3.9. Physiological outcomes [Table 10]

Only 4 studies contributed with data limited to bladder capacity [25,43,44,46]. Bladder volumes increased markedly in all, with changes that were close to a doubling of cystometric capacity in two studies [43,44] and 50% increases in the other two [25,46]. Other outcomes sought such as quantitative changes in UDC frequency and effect of stimulation on urethral pressures or pelvic floor/sphincter EMG were not reported by any study.

4. Discussion

PNS represents a valid alternative to existing neuromodulation therapies (SNM, PTNS) for patients with a range of urinary (DO, neurogenic dysfunction, IC) and faecal (FI) problems. In addition, the principle of applying electrical charge to the pudendal nerve to affect functionally restorative changes in bladder and urethral functions is well established in animals [50,51] and man using acute, and to a lesser extent, chronic and adaptive stimulation paradigms (see introduction). Such changes include stabilisation of undesirable bladder contractile activity [2] and augmentation of the guarding reflex through changes in sphincter/pelvic floor function [52–54].

This poses the question of why PNS has not caught on in the way that SNM has become a dominant treatment for medically refractory urinary complaints. Possible reasons might be the tortuous 3D anatomy of the PN and therefore the difficulty of accurate electrode placement (which requires electrophysiological ± radiological guidance), uncertainty regarding which section of the nerve to target (trunk vs. branches), difficulties with lead fixation (SNM has bony anatomy of sacrum to provide this) and a concern that direct targeting of a peripheral nerve might be limited by issues of stimulation tolerability. On this basis, we reviewed the state-of-the-art based on previous clinical application of PNS. We adopted co-primary outcomes of safety (frequency of adverse events) and efficacy (reduction in daily UIE). We also extracted information on technical approach and on other selected clinical and physiological outcomes. The review included a final count of 15 papers using several different approaches and for several indications (mainly urinary but some populations with chronic pain syndromes or bowel symptoms).

4.1. Safety

The most striking observation was the derisory nature of adverse event reporting with no paper adhering remotely to CONSORT guidance on reporting of harms [55]. Although the CONSORT extension strictly only applies to RCTs, none of the provided checklist of 10 items were completed by any study. This seems inadequate for a therapy that requires surgical placement of an implantable active device (this being high risk by medical device classification: class 3, rule 8) [MDCG 2021]. On this basis, we were only able to list any adverse events as documented *ad hoc* within the body narrative of manuscripts (only one study of the Bion-r device included a table) [44].

Taking the extracted data at face value, these suggest that PNS is very safe with a small number of relatively minor adverse events only. This noted, Schmidt in his 1989 technical paper, does note the potential for complications arising from pudendal access e.g. vascular and nerve injury resulting in some patients having bruising [23]. As read, it appears that all such events were however self-limiting. Some confidence in the general concept of using larger diameter introducers in provided by the Bion-r studies where the external diameter of the device is 3.3 mm but no complications of use of a large introducer were reported [43,44]. Other adverse events are those well-established for SNM including infection, seroma formation around the IPG, lead migration and unwanted stimulation effects. The most serious of these complications — device infection was only reported in 2 patients out of 183 (1.1%) using a standard pudendal approach making this less common than accepted rates for SNM (2%–5% in large series). Lead migration was reported in 4/169 patients in whom a quadripolar tined lead (InterStim™) had been employed.

4.2. Technical factors

The review outlines the various anatomical approaches to the pudendal nerve. The two main approaches are via the ischiorectal fossa lateral to the anus, which allows the lead to be placed parallel to the nerve, and the posterior approach, where the lead crosses the trunk at a steep angle and therefore has a lower proportion of lead close to the nerve. Whether the difference between the two approaches (and the difference in the position of the lead relative to the nerve) leads to different outcomes could not be deduced from the review, but parallel placement should theoretically provide more stimulation opportunities. Both techniques were employed with no clear differences in ease of access or success although higher proportions (nearly 100%) of patients undergoing the posterior approach passed PNE and received implants compared to about 80% of those undergoing ischiorectal fossa-based access. Operative durations were very short — in some studies faster than SNM providing confidence that the procedure is not technically challenging, at least with experience. Data on the number of needle passes to locate the nerve were available in only one paper that compared approaches [26]. Using the ischiorectal approach required 15 or 8 passes to site the electrode based on whether intra-rectal palpation was used compared to 22 for the posterior approach and 3.5 using their own STAR technique [24,25].

Considering the low rate of lead migration, it was interesting to note that no fixation technique other than the pre-fixed tines on InterStim™ leads was employed. It seems unlikely that the tines (designed for fixation in bone and periosteum) convey much useful fixation in the soft tissues around the pudendal nerve but it is possible that some retraction is prevented by tines abutting the sacrotuberous ligament. Schmidt mentions the haptic feedback provided to the operator as this ligament is perforated and it may also be a useful landmark to guide correct insertion and to provide fixation [23]. Two very different surgical approaches both use direct anatomical localisation of the pudendal nerve trunk proximal to the sacrotuberous ligament. The LION technique creates a retroperitoneal pocket in the pelvis having used a laparoscope via the peritoneal cavity [46]. The ENTRAMI technique approaches the nerve under the gluteal muscles using a laparoscope and insufflation to expand tissues [28,49]. Neither are straightforward and while undoubtedly of value when neurolysis is required for pudendal neuralgia are unlikely to be scalable or cost effective for common indications such as urinary incontinence.

Choice of stimulation parameters for PNS appeared to be governed by prior art from SNM and the limits imposed by existing InterStim™ technology. Thus 0–10 mA, 14 Hz and 210 μs pulse width were common. These parameters are not necessarily the optimal for PNS. Uncertainty also exists as to whether these are actually optimal for SNM having been carried forward from historic animal studies into man [56]. The Bion-r system adopted similar parameters but with 5 s on–off cycling [43]. Electro-acupuncture studies (outside of this review) used higher amplitudes but much lower frequencies and pulse widths (~2 μs and 2 Hz). At the current time, it is simply impossible to comment on optimal parameters across varying techniques. No study in the literature used any form of adaptive stimulation paradigm.

4.3. Clinical and physiological outcomes

The primary clinical outcome (reduction in daily UIE) was reported by several studies and indicated beneficial effects of PNS with halving of UIE frequency (or better) in most studies. These data compare favourably with SNM even considering that the PNS populations often included patients who might be deemed neuromodulation refractory (having already failed SNM). Further, two randomised crossover studies in which a quadripolar lead was placed on both the pudendal and sacral nerves showed greater global symptom reductions leading to greater patient preference for PNS [20,21]. Other variables were improved by both PNS and SNM.

Useful data on physiological outcomes were limited to measurements of bladder capacity in patients with predominantly OAB/DO phenotypes. Five studies all showed increases in capacity with two showing a near doubling in cystometric capacity [25,46].

4.4. Future prospects

Recent research highlights (only published in abstract form) show a continued interest in PNS for treating urinary symptoms and pain. Moore et al. conducted a study using implanted leads, likely repurposed sacral nerve modulation materials, on ten female patients demonstrating promising results [57]. In another prospective study, De Wachter et al. assessed a novel closed loop PNS system in women with urgency urinary incontinence (UUI) and mixed urinary incontinence (MUI). The findings were positive for both groups, with particularly notable improvements in MUI patients [12]. While these results are encouraging, final publications are still pending.

4.5. Limitations

The selection of included manuscripts followed the PRISMA guidance but necessarily required a value judgement on inclusion of some techniques where the criterion for chronic stimulation for a minimum of 4 weeks was difficult to apply. The earlier (2005) randomised crossover study of Peters strictly had a 2-week experimental phase from which some data have been presented however the overall therapy duration and follow up was longer than 4 weeks. These studies all fall in a grey area of inclusion. We elected also to exclude far more numerous studies in which the dorsal genital nerve had been stimulated. The DGN is a branch of the pudendal nerve, and the effects of afferent stimulation are undoubtedly mediated by the pudendal nerve. However, most of these studies use surface or acute needle stimulation paradigms and did not fall under the broad aims of the review.

The quality of included studies was poor, being over-reliant on low quality observational studies and a few randomised studies with high levels of potential bias. All results, particularly in a field (functional

urology) that is dogged by placebo responses must be interpreted with caution. Finally, a further limitation was the dominance of certain centres in providing data for the review. In fact, the 15 papers were contributed by only 8 investigative groups. There is no doubt that some data are duplicate from Peters [20,45] and the Vaizey group at St Marks Hospital, UK [29,30]. The generalisability of technical experience and outcomes must therefore be questioned.

5. Conclusions

On the basis of systematic review of available data, and with the caveat of generally poor study quality, PNS appears to be a safe and technically feasible. Clinical outcome data suggest beneficial effects in various urinary disease populations including urinary incontinence. Where studied, some of these effects may be superior to SNM and possible even when SNM has failed.

Ethics approval

The authors declare that this study did not involve Humans or Animals

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Knowles CH, Kerrigan-Smith J, Noone T, Denison T, De Wachter S reports a relationship with Amber Therapeutics LTD that includes: consulting or advisory, employment, and equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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