INTRODUCTION

On the basis of sustained long-term results, sacral neuromodulation (SNM) has become a widely adopted and established treatment modality for overactive bladder, non-obstructive urinary retention and faecal incontinence [1–6]. Since its approval for clinical use in 1994 more than 325 000 patients have been treated worldwide with several further potential indications under investigation [7].

In the majority (about 80%) of patients undergoing implantation, SNM leads to a clinically significant reduction in symptoms [1,8–10]. However, it is recognized that, even within this group, stimulation parameters (such as amplitude, electrode configuration, frequency and pulse width) may vary at both initial device programming and at reprogramming, the latter often being required to optimize effectiveness. Although some recommendations exist for SNM programming, the scientific data to support them are understood by few clinicians.

SYSTEMATIC REVIEW

The science behind programming algorithms for sacral neuromodulation

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ABSTRACT

Aim: Sacral neuromodulation (SNM) is a widely adopted treatment for overactive bladder, non-obstructive urinary retention and faecal incontinence. In the majority, it provides sustained clinical benefit. However, it is recognized that, even for these patients, stimulation parameters (such as amplitude, electrode configuration, frequency and pulse width) may vary at both initial device programming and at reprogramming, the latter often being required to optimize effectiveness. Although some recommendations exist for SNM programming, the scientific data to support them are understood by few clinicians.

Methods: This is a narrative review of the literature covering some of the science behind stimulating a mixed peripheral nerve and available preclinical data in the field of SNM. It covers electrode configuration, amplitude, frequency, pulse width and cycling considerations. The review is targeted at clinicians with an interest in the field and does not seek to provide exhaustive detail on basic neuroscience.

Results and conclusions: Knowledge of the science of neuromodulation provides some guiding principles for programming but these are broad. These principles are not refuted by preclinical data but specific parameters in clinical use are not strongly supported by animal data, even after the limitations of small and large animal models are considered. The review presents a shortlist of programming principles on a theoretical basis but acknowledges that current practice is as much derived from evolved experience as science.

KEYWORDS
incontinence, overactive bladder, Sacral nerve stimulation, sacral neuromodulation
The aim of this article is to summarize (in one place) the basic scientific rationale as it stands for SNM programming. The review is targeted at practising physicians rather than those wishing to have a deeper understanding of relevant neuroscience that can be obtained elsewhere [20]. Definitions used in the article are provided in Table 1. The content is presented in a way that the reader can omit some text, for example background science, but still read the article in continuity. Such content is included as Appendix S1.

2 | METHODS

An international multidisciplinary expert group of 13 urological and colorectal surgeons with long-term experience (cumulatively, 251 years of SNM practice) convened on four occasions over a 4-year period (2016–2019) to perform and observe live surgeries with subsequent round-table discussion. This process has already resulted in the publication of didactic guidance on implantation technique [18]. Building on this success, attention then moved to address the standardization of SNM programming and to provide practical recommendations for less experienced surgeons and healthcare professionals [19]. The content of the current review is derived from a subgroup of these experts and scientists in the field of neuromodulation. The review is narrative in approach. This process was financially supported by Medtronic Inc.

3 | SCOPE

The aim of this article is to summarize (in one place) the basic scientific rationale as it stands for SNM programming. The review is targeted at practising physicians rather than those wishing to have a deeper understanding of relevant neuroscience that can be obtained elsewhere [20]. Definitions used in the article are provided in Table 1. The content is presented in a way that the reader can omit some text, for example background science, but still read the article in continuity. Such content is included as Appendix S1.

4 | APPLIED ANATOMY

The targeted nervous tissue for SNM is the third sacral spinal nerve (Figure 1). This nerve forms part of the cauda equina and is therefore far distant from its roots of origin which lie above L2 where the spinal cord terminates at the conus medullaris but...
the spinal canal continues. Two important points derive from this observation: first, that use of the term S3 nerve ‘root’ is confusing (and should be avoided); and secondly that the target is a mixed spinal nerve containing components of both dorsal and ventral roots, that is, lower motor neurons and sensory fibres. Anatomical studies of human sacral spinal nerves [21] reveal a mix of myelinated and unmyelinated axons, the former of different diameters. This mix of variably sized axons is the target of SNM. At lower spinal levels, for example S3, there is a strong predominance of B (preganglionic autonomic) over A fibres and of smaller diameter A fibres, for example, Aγ (sensory) and Aδ (pain, pressure and stretch), over large diameter motor Aα fibres [21]. The S4
spinal nerve may occasionally be targeted in the eventuality that bilateral approaches to S3 have failed to produce low amplitude stimulation. This is now uncommon with standardized electrode lead placement [18] but remains a valid option.

Physiological data obtained in five patients with bladder conditions during early evaluation of SNM [22] suggest that, in addition to textbook contributions to the pudendal nerve and sciatic nerve, S3 provides small direct motor branches to the levator ani. The innervation of the levator ani has since been studied in 100 cadavers [23]. Fifteen subjects had direct contributions from S3 with the remainder having direct contributions from S4 and/or S5 branches. This explains at least in part the anatomic rationale for seeking to observe an upward movement of the pelvic floor termed 'bellows response', sphincter (pudendal) and toe responses acutely during optimized lead placement [18].

5 | CHOICE OF ELECTRODE CONFIGURATION

5.1 | Basics of engineering

The most commonly used implantable pulse generator (IPG) to date (InterStim™II) (Medtronic) produces a pulsed electric field via a programmable interface to a lead with four electrodes. Quadrupolar tined leads (Medtronic models 3889, 978B1 and 978A1, the last two being compatible with full body MRI) have electrodes of identical length and surface area and even spacing. Each electrode can be programmed as either off or on, the latter being programmable as (+) pole (anode) or (−) pole (cathode) alone or in combination (Figure 2A). The accompanying IPG can be programmed as (+) pole (anode) or not used as an electrode. If the IPG is set as anode (+), the electrode configuration is considered to be monopolar. If both the anode and the cathode are contact points (electrodes) of the tined lead, the configuration is termed bipolar (Figure 2B). To date, there are no recommendations about whether monopolar or bipolar is associated with a longer battery life. It has recently been reported that the battery life of the InterStim™ II device is about 5–7 years [24–26].

By convention, the electrodes on the quadrupolar lead are numbered between 0 and 3 starting with the most distal electrode (Figure 2A). To achieve current discharge and spread during stimulation at least one anode (+) and one cathode (−) must be defined to create an electrical circuit. This results in 59 theoretical electrode configurations. However, for initial programming this number can be reduced to four electrode settings/configurations for each of the monopolar and bipolar configurations (therefore eight in total) (Figure 3). These starting configurations are ‘recommended’ on the basis of the cathode being the dominant active electrode [13]. Our recent review of programming in practice [19] recommends that a cathode be chosen for therapeutic stimulation to produce a midline sensation at the lowest sensory threshold. Further, it has been suggested that monopolar stimulation is selected for this cathode at first programming following IPG implantation (testing is restricted to bipolar because there is no IPG to serve as the anode). How are these recommendations supported by scientific evidence?
5.2 | Basic scientific principles

An axon of peripheral nerve is a living tissue whose specific cellular properties, notably in relation to ion conduction, enable its specific functions. As noted in Table 1, the generation of an action potential requires depolarization of the nerve membrane. This can occur when an extracellular negatively charged electron field leads to changes in the transmembrane potential (by effects on a variety of membrane bound ion channels) making it less negative (inside relative to outside the membrane). This in turn leads to an influx of sodium ($Na^+$) ions through voltage-gated sodium channels ($Na_v$). At a critical point of influx, this ‘generator’ potential is sufficient for the membrane to depolarize leading to an action potential. This is the action potential threshold.

The probability of axonal depolarization depends on electrode proximity, myelination and axon diameter. The first point is simple, namely that, the closer the electrode is to the target nerve tissue, the greater the charge field at this point. Since charge falls away with the square of the distance from the electrode (Coulomb’s law), it is evident that electrode placement is absolutely key to achieve the desired effect at low stimulation amplitude. This was the subject of our previous paper on standardized lead placement [18] and is well established by surgeons as key to effectiveness of the therapy. Indeed, most implanters now aim for intra-operative stimulation amplitudes of $<1.0$ V (or $1$ mA for newer systems) to induce motor responses; a mean of 0.95 V was achieved by the expert group in a series of 90 patients in 2017 [19]. A corollary of this is that if the electrode is poorly placed then further programming will be required to broaden the charge field or increase the charge supplied (see below).

Perhaps less well understood by clinicians is the effect of axon diameter. In the anatomy section it was noted that the S3 mixed spinal nerve contains axons of different diameter, some of which are myelinated (Figure 4). The key point is that such nerves have a high concentration of $Na_v$ channels at the nodes of Ranvier (~2000 channels/μm$^2$). Nodes of Ranvier represent a focal point for sodium influx leading to a generator potential and thence an action potential by membrane depolarization. Thus, myelinated nerves are stimulated before (i.e. with a lower amplitude electric field) unmyelinated nerves. It can also be shown that large myelinated nerves (where intranodal distance is greater) are easier to depolarize than smaller myelinated nerves (due in simple terms to greater charge separation). Finally, a greater understanding of the physics of changes in transmembrane potential resulting from an applied stimulus also explains why the threshold for generating a propagated action potential is lower for a cathodic pulse than for an anodic pulse [27,28] (Appendix S1, Supplementary material I). All these remarks are made accepting the caveat that actual electrical field properties are almost certainly influenced by non-homogeneous tissue properties in relation to distance between nerve and electrode.

From the above discourse on activation functions, a charge field should stimulate the nearest axons first, myelinated before unmyelinated axons and larger before smaller axons. With the exception of a subpopulation of large diameter myelinated afferents from muscle spindles that may, at least peripherally, be larger in diameter and have greater intranodal distances (hence higher conduction velocities) than their motor counterparts [29,30], this would imply that motor responses should occur before sensory responses during incrementally increased stimulation. At first sight this appears to counter the clinical observation that, during SNM testing, ramped stimulation usually results in sensory responses before evident muscle contraction [31]. It also runs contrary to Fowler et al.’s widely cited experimental data [32] from nine women in whom motor

**Figure 4** Myelinated nerve showing concentration of sodium channels at the nodes of Ranvier. Myelination leads to charge separation between nodes and thus myelinated nerves are more readily depolarized than unmyelinated nerves.
responses were only measured between 52 and 140 ms after stimulation. Based on earlier studies of nerve conduction in which direct motor activity occurred at 3–5 ms, these late responses were deemed to represent a reflex activity, that is, that sensory fibres were stimulated before motor fibres [33,34].

This conundrum, however, has been laid to rest by two recent key papers. The first [35] studied 14 female patients using intravaginal and concentric anal sphincter electromyography (EMG) after tined leads had been optimally placed by the new technique [18]. The study showed that clinically observed inward movement of the pelvic floor was related to a direct efferent (motor) activation and that this occurred with latencies of around 3–4 ms at low stimulation amplitudes such as those used in clinical practice, for example 1 mA [35]. Further increases in stimulation amplitude correlated with EMG responses but reflex activity was only observed at stimulation amplitudes of >5 mA. The second [36] showed that, in the majority of 29 women, pelvic floor motor activity could be recorded below the sensory threshold, and that again these responses were the result of direct efferent motor response based on electrical latency. It is likely on reflection that the failure of Fowler et al. [32] to detect direct efferent motor activity was that their observations were based on using a train of five pulses which hide any direct activation and with an EMG needle on the contralateral side [37]. It is still worthy of comment that the gradient of afferent and efferent nerve activation may be heterogeneous between patients and this accords with the general acceptance that both sensory and motor responses can be helpful in placing electrodes and predicting efficacy [38].

Having selected a cathode that provides for the lowest sensory threshold, the selection of anode in bipolar stimulation (as required during the test phase when using the tined lead) may be varied in respect of adjacency to the cathode. In theory, this widens the electrical field although the field characteristics in a real inhomogeneous tissue environment are unknown. Simulations based on computer-generated models do not support a widening of the field nor do they support the use of a larger number or size (as in old 3093 lead) of cathodes or anodes [17]. It was noted that, for chronic stimulation post-implantation, both bipolar and monopolar configurations are possible. The electrical fields differ between a monopolar and a bipolar configuration. With monopolar stimulation, the anode is considered to be at an infinite distance away from the cathode [28]. Monopolar stimulation causes a larger, more homogeneous current spread [39]. It is associated with a more radial electrical field, whereas bipolar stimulation produces a narrower electrical field like a dipole (Figure 5). Whether this is important to basic programming is uncertain and may well depend on quality (proximity to the target nerve) of electrode placement. Theoretically, changes in charge field characteristics and distribution might be important in maximizing stimulation when electrode proximity is an issue, for example in less than optimal lead placement (increased field distribution) and also when adjacency of other neural structures appears to be manifest as unwanted stimulation events such as pain (tighten/reduce stimulation field).

5.3 | Preclinical data

Few animal studies have used multi-electrode leads to derive data pertinent to human anatomy. In an ovine model, it was demonstrated that the poles of the tined lead most proximal to the foramen were the optimal electrodes to induce an ‘on-target’ motor response (movement of the perineum, tail or bellows) with low intensity stimulation [40] in both anaesthetized and conscious sheep. Specifically, 3–/0+ and 3–/2+ were the electrode configurations with the lowest stimulation thresholds, whereas the stimulation of the electrode configuration 0–/1+ delivered the highest response threshold among the tested electrode configurations.

6 | STIMULATION AMPLITUDE AND PULSE WIDTH

6.1 | Basic scientific principles

Amplitude of stimulation determines the energy delivered to the sacral spinal nerve and the probability of axonal depolarization. Precise lead placement allows for lower amplitude stimulation and thence low energy consumption to produce the desired effect. It has already been noted that modern IPGs produce a pulsed waveform for which pulse duration (as well as amplitude and frequency) can be varied. A function of neurostimulation is that as pulse duration is shortened then stimulation amplitude must be increased to maintain the same level of nerve depolarization. This strength–duration relationship is relevant to all forms of electrical stimulation; further detail is provided in Appendix S1 (Supplementary material II). In essence, the decision-making around pulse duration is a trade-off between having the potential disadvantages of a long pulse duration versus those of having a high amplitude. The default setting of the InterStim™ device for pulse duration is 210 μs which meets the requirements of this trade-off although a range of 60–450 μs is possible.
A further consideration of stimulus current pulse width relates to the effect on nerve fibre size recruitment patterns. Based on these theoretical predictions, it has been suggested that the stimulus pulse width parameter may be used to selectively recruit fibres of different sizes and that this selectivity should increase with increasing distance from the stimulus electrode. Szlak and de Bruin provide experimental data based on histologically defined motor fibres using surface electrical stimulation of the median nerve in five healthy men [41]. These showed that at pulse durations in the range 100–1000 μs there was no difference in the fibre diameters recruited.

6.2 | Preclinical data

6.2.1 | Large animal models

Before the first human could be treated with sacral nerve stimulation in 1981, extensive experiments were conducted in animals [42–44]. Tanagho and colleagues developed a paraplegic dog model for acute and chronic stimulation of the sacral nerves (since the gross anatomy of the human sacral nerves is quite similar to that of the dog) by transecting the spinal cord. With this model it was possible to investigate both detrusor inhibition and micturition [45,46]. During chronic stimulation over a period of up to 12 months, urodynamic studies with recordings of the bladder and urethral sphincter pressure were performed at least twice per month. Some animals had a total stimulation time of up to 150 h. In addition, the stimulated voiding pattern was observed radiographically.

At the time of these experiments, pulse widths of 1000 μs were established as the norm for the treatment of incontinence [47]. However, Tanagho and colleagues used much shorter pulse widths of 200 μs in these and subsequent clinical studies in order to reduce the risk of sacral spinal nerve damage [45]. This decision was based on the observation that good sphincteric responses were still maintained with 200 μs pulses. In dogs, postmortem histological and electron microscope examinations demonstrated complete preservation of the stimulated sacral spinal nerves without axonal damage or evidence of nerve degeneration despite chronic (6–12 month) stimulation at a variety of frequencies of 7–100 Hz [42,45,48].

In order to further assess bladder responses and to optimize stimulation patterns, Brink et al. (2015) described the establishment of a large animal, preclinical, quantitative model in fully conscious sheep for permanently implanted, commercial SNM systems [49]. Using quantitative urodynamic measurements, bladder capacity was increased by almost 60% during acute sacral nerve stimulation at 10 Hz and 210 μs pulse widths. Other pulse widths were also investigated with this model [50] and the strength–duration curves indicated a chronaxie of about 40–50 μs. Similarly, the effect of different pulse widths on acetic-acid-induced bladder overactivity has been examined in pigs by cystometric bladder capacity measurements during acute sacral nerve stimulation [51]. With frequency fixed at 14 Hz there were no significant differences in bladder capacity between pulse widths of 64, 204 and 624 μs. However, the stimulation threshold to obtain a motor response at a pulse width of 64 μs was significantly (P < 0.05) higher than those for pulse widths of 204 μs and 624 μs (5.64 V vs. 3.11 V and 2.52 V, respectively).

6.2.2 | Small experimental animals

A rodent model of acute spinal nerve stimulation at motor threshold tested a number of pulse widths at a fixed frequency of 10 Hz on attenuation of frequency of bladder contractions in 35 rats [52]. There were no significant differences in attenuation of bladder contractions between 30, 90 or 210 μs stimulation.

7 | PULSE FREQUENCY

7.1 | Basic scientific principles

A biphasic wave oscillates equally between cathodic and anodic pulses. In this way, the charge is roughly balanced (although actually it is not completely balanced without modifying the relative phases slightly). A monophasic waveform produces a charge that is imbalanced. A full understanding of imbalanced charge relates to ensuring reversibility of electrochemical reactions at the electrode–tissue interface and its general significance lies in the fact that long-term monophasic stimulation may be injurious to neural tissue [53] and also lead to accelerated electrode corrosion (which, aside from reducing stimulator life, might be injurious with certain electrode compositions [54]). This potential risk is mitigated with the InterStim™ device by the use of charge-balanced pulses. Further, tissue injury relates to a charge density, which is a function also of amplitude, pulse width and area of electrode contact. This may be an issue if very high frequencies, amplitudes or unbalanced pulses are used [55], but these are well outside the limits of any IPG used in practice. Low frequencies in the perceptible range, however, may suffer from producing unwanted side effects (the frequency is slow enough to be perceived as a pulsation). Nevertheless, the IPG can vary frequency from 2.1 to 130 Hz and there are proponents of changing frequency in both directions with the aim of improving clinical efficacy.

7.2 | Preclinical data

7.2.1 | Large animal models

Tanagho and colleagues’ experiments in dogs showed that the quality of urethral sphincter contraction was highly dependent on frequency of stimulation: on the one hand, force of contraction increased with the frequency of stimulation, but, on the other, fatigue set in above 50 Hz and was the dominant effect at high frequencies [45]. Consequently, for continuous stimulation, a frequency of 10 Hz was suggested as a trade-off in order to avoid fatigue of the urethral sphincter. It is noteworthy that due to anatomical differences the
optimal stimulation parameters were not the same in all dogs. In a neurogenic dog model, micturition could be induced by applying a 200 Hz stimulation above the first bladder response threshold (3 V) [46]; however, such high frequencies have never been introduced into clinical practice.

In pigs, frequencies of stimulation between 5 and 50 Hz (with constant pulse width of 210 μs) have been tested for their effects on bladder capacity. No significant differences were found in bladder capacity at 15, 30 and 50 Hz (but 5 Hz was not associated with any improvement) [56]. These data contrast with those from a chlortalose-anaesthetized cat model using cystometry [57]. In cats, a wide range of S1 or S2 dorsal root stimulation frequencies (1–30 Hz) could inhibit isovolumetric rhythmic bladder contractions but the effect on bladder capacity had a more striking frequency dependence with no significant increase in bladder capacity achieved by 15 or 30 Hz. In contrast, a 5 Hz stimulation was optimal leading to a marked improvement in bladder capacity. In another experiment using the same animal model with 14 cats, both stimulation of the pudendal nerve and S1 demonstrated a significant frequency dependency between 2 Hz and 33 Hz with an optimum at 7.5–10 Hz, when examining isovolumetric bladder contractions [58].

7.2.2 Small experimental animals

In rodents, a clear frequency dependency has been observed for physiological parameters relevant to faecal continence. In 72 female anaesthetized rats, the magnitude of potentiation of anal canal evoked potentials (recorded over the primary somatosensory cortex) with S1 sacral stimulation, the rodent homologue of human S2–S4 nerves, depended significantly on stimulation frequency. The calculated optimal stimulation frequency range was 1.7–2.1 Hz and corresponded to an increase of 120–140% of the amplitude of evoked activity. The theoretical increase for 14 Hz stimulation (used clinically), however, was still 89–104% [59]. A subsequent study in a rat obstetric injury model showed similar effects of 2 Hz and 14 Hz frequencies on the latency of evoked potential [60].

In an anaesthetized female rat model, a broad range of frequencies between 0.01 and 100 Hz (with a constant pulse width of 100 μs) was investigated for the effects of acute spinal nerve stimulation on bladder reflex contractions in an isovolumetric bladder induced by a saline infusion [61]. At motor threshold, a maximal inhibition of bladder reflex contractions could be achieved with 10 Hz at 10 min post-stimulation, but not at 1 Hz or 20 Hz.

Additionally, using the anaesthetized rat model, Crook and Lovick demonstrated that 1000–3000 Hz stimulation of the pelvic nerve could rapidly reversibly suppress a bladder voiding event. Applying this frequency of stimulation during the bladder filling phase resulted in a slight increase in bladder pressure, an increase in external urethral sphincter contraction and no urine output. While the mechanisms of void suppression by stimulating the pelvic nerve may differ slightly from sacral nerve stimulation, there is significant overlap of nerve pathways and it is interesting to note that these very high frequencies of stimulation-induced void inhibition were reversible [62].

8 CYCLING MODE

8.1 Basic scientific principles

Cyclic (intermittent) SNM is a less commonly used programming feature of currently used IPGs although it is possible; for example, the InterStim II IPG can vary cycle times from 0.1 s to 24 h. From a scientific perspective, if efficacy can be maintained with cycling then this results in reduced charge delivery and a theoretical (but unproven) reduction in nerve tissue damage (see above). Practically, it may result in a reduction of energy consumption and increased longevity of the IPG; however, this depends on cycle times (very frequent cycling drains the battery more than continuous stimulation [19]). Clinical data support the use of cycling in the treatment of overactive bladder [24,63] although current evidence (reviewed by Lehur et al. [19]) is insufficient to underpin any didactic guidance on the subject.

8.2 Preclinical data

Tanagho et al.’s early experiments on dogs were typically carried out with a phasic or cyclic stimulation pattern (e.g. 3 s on, 5 s off) [45]. Most animal studies use acute stimulation paradigms and provide little information since cycling is relevant only to the chronic effects of SNM. However, Potts et al. [64] demonstrated in anaesthetized rats that stimulation of the L6/S1 nerve trunks during the last half or last quartile of the bladder filling cycle increased bladder capacity to the same extent as continuous stimulation. Applying stimulation during the first half of the fill cycle had no effect on bladder capacity. Unpublished data on anaesthetized cats and fully conscious sheep are currently under review and point to a similar effect of sacral nerve stimulation delivered during the last 7–10% of the bladder fill cycle when specifically timed to the neural signal or bladder pressure, respectively, of the voiding event.

9 DISCUSSION

SNM has now been applied for over 25 years as a treatment for bladder conditions and faecal incontinence. Other indications are under investigation and new market entrants are now manufacturing IPGs. This review provides the reader with background information pertinent to understanding how we have come to be ‘where we are’ with commonly employed programming parameters (these being applicable to any currently available device). What is clear immediately is that the evolution of current programming parameters has not been based on a systematic or logical sequence of experiments from animals to man. Rather, parallel (in time) studies have selected and tested a variety of stimulation variables in a variety of available models and disease
contexts with the only common feature that the parameters of testing fell well within perceived limits of safety. In some instances it is not easy to see the mental leap that led from one experiment to another. For instance in Tanagho et al.'s original canine experiments (when continuous stimulation was used) it was concluded that stimulation frequencies of 20–30 Hz represented a trade-off between urethral sphincter muscle fatigue and force of contraction. It is thus unclear why his original collaborator (Schmidt) later used a continuous train of pulses with a frequency of 15 Hz to take forward into humans with paraplegia [65].

Another issue is that the use of animal models necessitates certain caveats not least the fact that measurable physiological responses are all necessarily surrogates for effects on symptom reporting (therapeutic outcomes) in humans. It should be noted that the majority of these experiments were performed on normal animals in the absence of pathology, and bladder capacity as measured by urodynamics was the primary urological function quantified for comparison even though SNM is applied at the same parameters for other indications. This is aside from translational differences conferred by comparative anatomy and physiology. It is known for instance that different peripheral nerves may be associated with different optimal stimulation parameters even within one species [66]. Moreover, acute sacral nerve stimulation at or above motor thresholds (used in animals) may not reflect the effects of a chronic, often sub-sensory, electrical modulation used in humans. Finally, some preclinical studies revealed a huge variation in terms of physiological responses among the same species.

Accepting these significant limitations, preclinical data generally support the assertion that currently used frequencies (i.e. 14 Hz) and pulse widths (i.e. 210 μs) for SNM fall in relevant ranges to exert measurable surrogate responses in large and small animal models as well as meeting the fundamental principles of neuromodulation based on neurophysiological conservation across mammalian species. Further, small clinical studies and coalescence of expert opinion suggest no obvious dissent from their use in practice [19]. On this basis the textbook suggests the following principles of programming.

1. The electrode closest to the nerve will have the theoretically lowest stimulation threshold and should be selected.
2. This electrode should be set to be the cathode.
3. There is no strong theoretical basis to support use of unipolar or bipolar as a starting setting and choice may vary from patient to patient based on electrode positioning and therefore optimal charge field characteristics.
4. The amplitude should be set to just achieve the desired biomarker of stimulation (e.g., sensory threshold) and there is a theoretical basis (as well as clinical data) for using sub-sensory thresholds. This will extend battery life and reduce unwanted stimulation effects.
5. If amplitude is serially increased to achieve stimulation then the mixed composition of the S3 sacral spinal nerve needs to be considered and also its proximity to other neural tissue (other spinal and autonomic nerves). In a mixed nerve, the large diameter fibres closest to the cathode are depolarized by the least amount of current. That means more fibres are depolarized as the pulse amplitude is increased.
6. Both sensory and motor responses have relevance during electrode placement and in subsequent programming decisions.
7. The default setting of 210 μs pulse duration should be used unless specific scenarios suggest evidence to the contrary. Shorter or longer pulse durations should be compensated for by appropriate changes in stimulation amplitude.
8. The default frequency of 14 Hz is neither ‘low’ nor ‘high’. There is no compelling theoretical basis that small changes in frequency affect efficacy. Large animal data (albeit mostly at 10 Hz) suggest that this frequency results in measurable changes in bladder behaviour but does not result in motor fatigue.
9. The combination of 210 μs pulse duration and 14 Hz frequency results in a charge that does not induce nerve damage.
10. There is no current evidence to suggest that different parameters (pulse width, amplitude, frequency) are preferred for different clinical indications, for example urinary versus bowel.

10 | CONCLUSIONS

This review illustrates a general lack of specific scientific evidence to underpin current programming practice for SNM. Implanters are faced with basing their practice on a combination of starting parameters that mix fundamental principles with preclinical data (which themselves are subject to considerable translational limitations). Fortunately, programming recommendations covered by a recent review [19] seem to provide benefit to most patients. However, experts in the field should be obligated to try and narrow the evident gap between the ‘science and the art’. This will offer reassurance to patient and physician alike that future therapy is applied to its full potential.

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CONFLICT OF INTEREST

All the authors have attended meetings of a European standardization group (Medtronic, directly relating to this paper). Charles Knowles and Klaus E. Matzel have management/advisory affiliations with a global advisory panel regarding SNM for pelvic indications (directly relating to this paper) and also have paid consulting agreements with Medtronic (lectures). Charles Knowles also receives research support from Medtronic. Paul A. Lehur has consulting agreements with Medtronic and B. Braun. Stefan De Wachter
receives paid consulting fees from Medtronic as honoraria for invited speaker. Stefan Engelberg and Lance Zipfel are Medtronic employees.

**AUTHOR CONTRIBUTIONS**

All authors contributed to the content of the paper. All authors approved the final version of the paper.

**DATA AVAILABILITY STATEMENT**

Data sharing not applicable – no new data generated.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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