The assessment of a novel Transdermal Amplitude Modulated Signal recently introduced for the treatment of Overactive Bladder symptoms

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ABSTRACT

Transdermal Amplitude Modulated Signal (TAMS) is a novel electrical stimulus which has been recently introduced for the treatment of Overactive Bladder (OAB) syndrome. It has been suggested that it has advantages over conventional waveforms by providing more effective penetration of the skin to enhance the efficacy of therapy. As there is no literature which supports this, we performed this study to evaluate potential advantages of the TAMS signal for electrical stimulation of subcutaneous nerves as compared to conventional stimuli. The stimuli were applied on forearms of 10 healthy volunteers and electrical parameters of stimuli and sensation measurements were recorded. None of the recorded electrical parameters showed significant differences (paired t-test $p>=0.250$) between the TAMS and conventional waveforms. Similarly, the mean sensation recorded at motor threshold level and at 50% of supra-maximal level showed no differences (paired t-test $p = 0.242$ and $p = 0.687$ respectively). It is unlikely based on the results of this study that TAMS provides any enhancement of the efficacy of conventional stimuli. We would recommend that further studies are carried out to clearly demonstrate in man what if any advantages the TAMS waveform has over conventional stimulation before it is widely deployed into clinical practice.

Keywords: Electrical stimulation, Overactive Bladder, Transdermal Amplitude Modulated Signal, TAMS

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1. Introduction

Overactive Bladder (OAB) syndrome is a set of symptoms which patients experienced during the storage phase of a micturition cycle. Urgency is the pivotal symptom of OAB and in all patients is accompanying by increased frequency and usually by nocturia (Abrams et al., 2003, Chapple et al., 2005), with one third of patients being severely bothered by urinary incontinence (Chapple et al., 2005).

Electrical stimulation in the management of OAB has been used for over 30 years. Whilst different methods have been investigated, implanted sacral neuromodulation has been widely used (Wollner et al., 2012); but is associated with surgical intervention, high cost and there is some debate

over the appropriate selection of patients. These factors therefore tend to limit its clinical use for the broader population suffering with OAB. Percutaneous tibial nerve stimulation was subsequently introduced as a minimally invasive alternative, but requires clinical intervention with regular patient visits to clinic (Peters et al., 2010).

Other sites of stimulation have been investigated and a significant body of literature has evaluated transcutaneous stimulation techniques. Several studies showed an effect by stimulating sacral dermatomes (Walsh et al., 2001, Yokozuka et al., 2004, Barroso et al., 2006, Fjorback et al., 2007, Hagstroem et al., 2009) and a study by De Seze et al., using transcutaneous stimulation of the posterior tibial nerve, reported significant efficacy (de Seze et al., 2011).

Recently, a novel stimulation technique using a 'Transdermal Amplitude Modulated Signal' (TAMS) has been introduced. This TAMS waveform has been described by Shen et al. 2011 (Shen et al., 2011); as "a high frequency sinusoidal carrier waveform (210KHz) amplitude-modulated by low frequency, monophasic rectangular pulses (1-ms pulse width)". Preclinical studies have evaluated the effect of TAMS stimuli of the pudendal nerve on the bladder in cat animal models (Shen et al., 2011, Tai et al., 2011, Tai et al., 2012). Tai et al. 2012 (Tai et al., 2012) reported that "TAMS uses a 210 kHz sinusoidal carrier waveform that has a minimal skin impedance and is optimal for stimulating nerves under skin and muscle". However there is no literature, to support this statement, based on comparative human studies. Low skin impedance would be an important advantage in all electrical stimulation techniques, because it will result in less electrical energy being required to deliver the charge for stimulation.

The TAMS waveform has been used in a novel neuromodulation system, which has been introduced into clinical practice as the VERV^{TM} Patient-Managed Neuromodulation System (PMNS, Ethicon Endosurgery Inc.). This system transmits the TAMS waveform through two hydrogel electrodes applied to the skin in the sacral region (Monga A, 2011). The results of an initial open study have been presented by Monga et al. 2011 (Monga A, 2011) showing beneficial effects.

There is no literature describing the specific physiological effects of stimulation using the TAMS waveform in humans. The main aim of this study was to compare the TAMS waveform with a conventional electrical stimulation waveform at different intensity levels of stimulation, both in terms of electrical parameters and acute physiological effects.

2. Materials and methods

We recruited ten subjects (5 male + 5 female) of age range (23-62). The study was reviewed by the Clinical Research Office of Sheffield Teaching Hospitals NHS Foundation Trust and an ethic waiver was obtained.

A purpose designed constant current stimulator, able to deliver both the TAMS and conventional stimuli was developed in accordance with IEC 60601-2-10 for medical electrical devices (nerve and muscle stimulators). A function generator (Textronix AFG 3102) was used to generate the two waveforms under test and drive the stimulator. The system was designed to deliver charge-balanced pulses to avoid electrochemical reactions. Figure 1 shows schematically the two waveforms used.

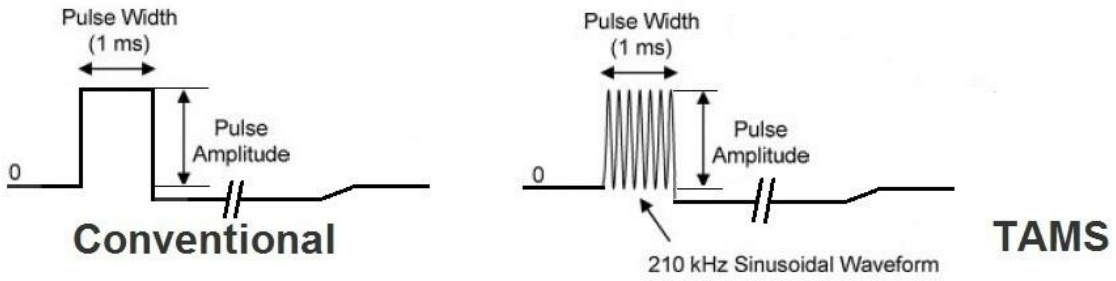

Figure 1. A sketch a of the conventional stimuli and the TAMS waveform (redrawn from (Shen et al., 2011)). Both of the pulses contain the charge balanced phase, which length was dependent on the applied current (typically 60-90ms).

Subjects underwent stimulation at four intensity levels (sensation threshold, strong sensation, motor threshold and 50% of supra maximal motor response) as describe below. Stimulation electrodes (Carefusion Disposable Disk electrodes type 019-415000) were placed over the ulnar nerve in one of two positions. For the sensation tests electrodes they were placed near the wrist, 3 cm apart. For the motor tests, electrode were placed just above the elbow sulcus 3 cm apart. 10Hz stimulation was used for the sensation tests, and 1Hz was used for the motor tests (the latter to avoid tetanic contraction). Stimulation electrodes were placed on the subject for at least 10 min before the measurements to allow the electrode-tissue interface to stabilise.

EMG signals were recorded using an XLTEK Neuromax 1004. A Medelec recording electrode (SE20 intra-electrode distance 20mm) were placed over the Abductor Digiti Minimi muscle (ADM). A ground electrode (CareFusion 2"x4" ground electrode type 019-422200) was placed between the stimulation site and the recording electrodes. Subjects were instructed to relax, with their arm resting on a soft foam support.

2.1. Experimental protocol

To determine the sensation threshold level, the stimulation current was gradually increased by the experimenter until the subject first reported sensation. The strong but comfortable sensation level was chosen by subjects for the TAMS waveform, and the intensity of the conventional stimuli were adjusted until subjects reported the same sensation when the stimuli were switched between conventional and TAMS. Motor threshold levels were defined as an EMG response of 200μV pk-pk, if noise levels were high then 300μV was used instead for both of the waveforms. The amplitude of the supra-maximal response was generated and measured using the inbuilt conventional stimulator of the XLTEK. Measurements were then made at 50% of this amplitude for both waveforms.

2.2. Data collection

After the stimulation intensity was set to the appropriate level for the measurement being made, the voltage across the stimulation electrodes (V), current through the electrodes (I), delivered power (P) and delivered charge (Q) waveforms were recorded using a battery operated oscilloscope (Tektronix THS 720) connected to the relevant points in the stimulator circuit. Electrode-skin impedance was calculated retrospectively as instantaneous voltage across the electrodes divided by current through the electrodes (bulk body impedance is assumed to be negligible for this purpose). The delivered charge was measured as the voltage (V_C) on a 1 μF capacitor (C) connected in series with the subject and then calculated as $Q[\mu C] = C[\mu F]*V_C[V]$. The recorded waveforms were then processed offline to give mean values for each pulse. In addition, dynamic impedances were compared by calculating V/I at five time points during a representative pulse for each subjects.

Additionally, sensation obtained during the motor threshold and 50% of supra-maximal response tests were recorded by the subjects on a Visual Analog Scale (VAS). The VAS was 100mm long, with the left end of the VAS representing no sensation and the right side end representing very uncomfortable or painful sensation. The sensation score was defined as the distance in mm of the position marked by the subject from the left end.

Subjects were blinded as to which waveform was being applied and the order of stimulus waveform was randomized. The paired Student's t-test was used in the resultant statistical analysis, and no correction was made for multiple testing in order to maximise the likelihood of the study to detect differences between the two waveforms.

3. Results

Figure 2 shows representative recordings of current, voltage and power for the TAMS and conventional stimuli for a single subject. Four out of 80 power waveforms were not recorded due to technical problems. Where these waveforms were not obtained, the equivalent paired recording from the other stimulation type was excluded from the analysis. Mean values ± SEM of recorded parameters, and p-values of each paired t-test, are summarised in table 1 for all of the stimulus levels. None of the electrical parameters showed significant differences between the two waveforms.

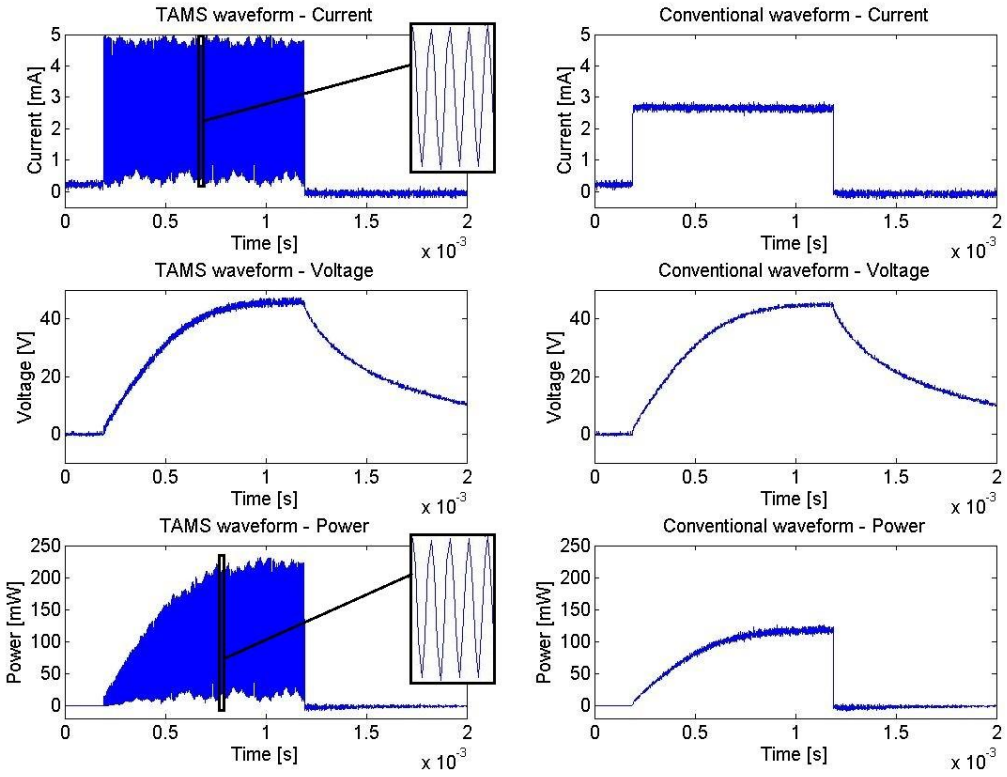

Figure 2. Representative recordings of stimulus waveforms. On the left side are TAMS waveforms for current, voltage and power. On the right side are conventional stimuli.

Table 1. Mean values ± SEM of recorded electrical parameters for different levels of stimulation (n=10 subjects) and P values of paired Student's t-test

		Sensation threshold	**Strong sensation**	**Motor threshold**	**50% of supra-maximal EMG**
Mean current [mA]	TAMS	1.11±0.12	1.92±0.28	3.81±0.77	6.32±0.98
	Conv.	1.10±0.12	1.93±0.28	3.84±0.68	6.26±0.92
	P value	0.769	0.539	0.793	0.710
Mean voltage [V]	TAMS	25.92±3.66	36.68±5.19	42.51±4.80	58.12±4.53
	Conv.	26.12±4.02	36.92±5.07	42.45±4.57	58.19±4.74
	P value	0.721	0.275	0.942	0.936
Mean charge [μC]	TAMS	1.14±0.13	1.98±0.28	3.83±0.84	6.62±1.04
	Conv.	1.13±0.13	1.98±0.28	3.84±0.77	6.45±0.93
	P value	0.732	0.725	0.883	0.430
Mean electrode-skin impedance [kΩ]	TAMS	22.98±1.19	19.66±1.23	12.54±1.19	10.91±1.61
	Conv.	23.02±1.27	19.76±1.24	12.33±1.30	10.80±1.51
	P value	0.896	0.368	0.503	0.642
Mean power [mW]	TAMS	33.69±9.75	76.28±23.82	198.8±69.07	405.9±91.84
	Conv.	33.30±9.80	76.08±22.51	187.6±60.51	386.6±87.48
	P value	0.770	0.907	0.250	0.277

The mean sensation recorded at motor threshold level in all of the participants was 34.9 ± 6.6mm for the TAMS stimuli and 39.2 ± 7.1mm for the conventional stimuli (paired t-test $p = 0.242$) and, for the 50% of supra-maximal level, 49.2 ± 5.0mm for the TAMS and 50.3 ± 5.2mm for the conventional stimuli (paired t-test $p = 0.687$).

As examples of the data sets, electrode impedance and sensation levels are shown graphically in figures 3 and 4. Electrode-skin impedance did not show significant differences, either in magnitude (figure 3) or in the dynamic impedance (data not shown for brevity), between TAMS and conventional stimuli. The decrease in electrode-skin impedance at higher levels of stimulation is consistent with established tissue non-linearity as a function of current (Dorgan and Reilly, 1999).

Similarly, figure 4 shows the lack of difference between the TAMS and conventional datasets for sensation measurements.

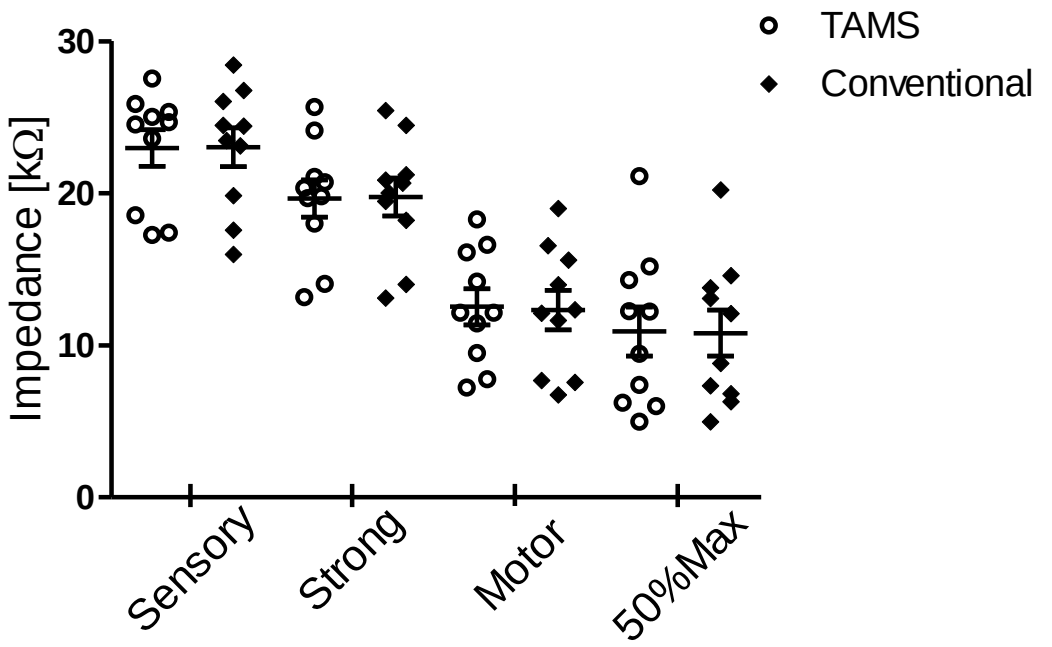

Figure 3. Mean electrode-skin impedances ± SEM for different levels of stimulation (n=10 subjects).

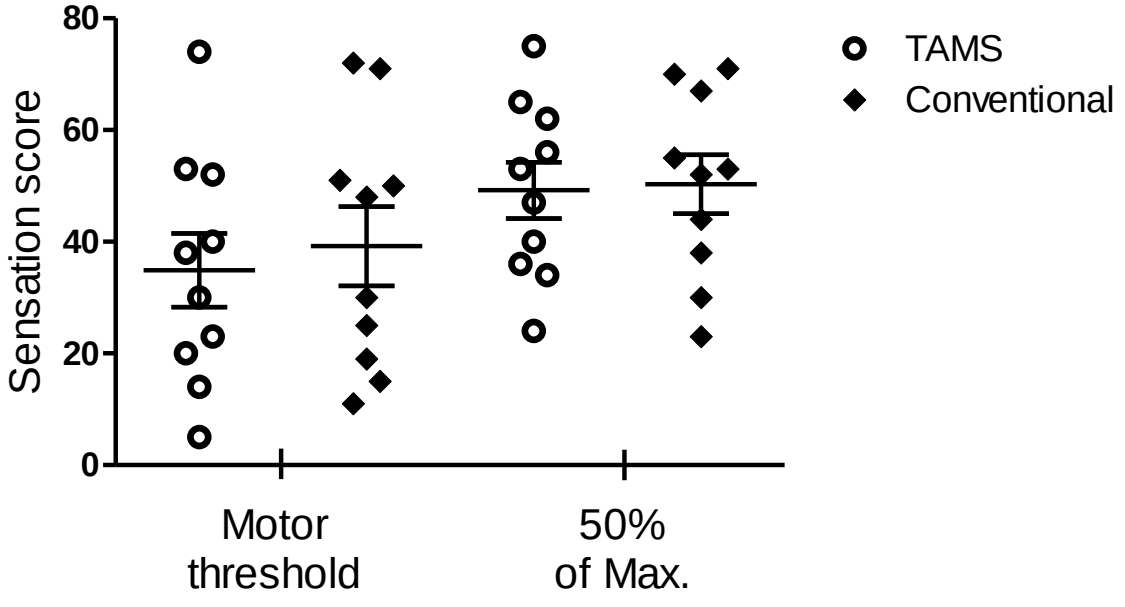

Figure 4. Mean sensation measurement ± SEM recorded by VAS during stimulation at the motor threshold and at the 50% of maximum level (n=10 subjects)

4. Discussion

TAMS has been recently introduced as a novel stimulation waveform for the treatment of OAB, however there is no background literature on the physiological effect of this stimulation waveform in man.

In this study we have shown that the TAMS waveform is able to stimulate nerves. Shen et al. (Shen et al., 2011) suggests that the well-known decrease in skin impedance with frequency (Rosell et al., 1988), when measured with sinusoidal signals, can also be obtained using the TAMS waveform. However, we have shown no difference in impedance when stimulating with TAMS as compared to conventional waveforms. High frequency sinusoidal signals penetrate skin more easily due to tissue capacitance, mainly but not exclusively within the stratum corneum. The TAMS waveform, in contrast to sinusoidal signals, is offset relative to zero and hence has a net unidirectional component (see figure 1). As a result, charge build up in tissue capacitance occurs in the same way as with conventional unidirectional stimuli and the frequency dependent impedance changes associated with non-offset sinusoidal signals are not seen.

Nerve membranes have an electrical time constant, typically of order 150 μs (Barker et al., 1991, Reilly, 2011), caused by their capacitance and the relatively high internal resistance of the cell body and this acts as a low pass filter to incoming stimuli. Because the TAMS waveform high frequency component is well above this filter frequency it is integrated at the nerve membrane in the same way as is the conventional stimulus waveform. This results in the mean current required to achieve stimulation being the same for both signals. It should be noted that the peak current delivered by the TAMS waveform needs to be twice that of the conventional waveform in order to deliver the same mean current.

5. Conclusions

We found no significant differences in sensation levels between the two stimuli tested when adjusted to give a standardised motor response. This suggests that the same nerve structures were being targeted by both waveforms.

We have shown no significant differences in either electrical, or physiological ,metrics between TAMS and conventional stimuli waveforms. Hence it is unclear what advantages TAMS may have over conventional stimuli.

We would recommend that further studies are carried out to clearly demonstrate any advantages that the TAMS waveform may have over conventional stimulation before it is widely deployed into clinical practice.

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References

Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U., Van Kerrebroeck, P., Victor, A. and Wein, A. 2003. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology,* 61**,** 37-49.

Barker, A. T., Garnham, C. W. and Freeston, I. L. 1991. Magnetic nerve stimulation: the effect of waveform on efficiency, determination of neural membrane time constants and the measurement of stimulator output. *Electroencephalogr Clin Neurophysiol Suppl,* 43**,** 227-37.

Barroso, U., Jr., Lordelo, P., Lopes, A. A., Andrade, J., Macedo, A., Jr. and Ortiz, V. 2006. Nonpharmacological treatment of lower urinary tract dysfunction using biofeedback and transcutaneous electrical stimulation: a pilot study. *BJU Int,* 98**,** 166-71.

Chapple, C. R., Artibani, W., Cardozo, L. D., Castro-Diaz, D., Craggs, M., Haab, F., Khullar, V. and Versi, E. 2005. The role of urinary urgency and its measurement in the overactive bladder symptom syndrome: current concepts and future prospects. *BJU Int,* 95**,** 335-40.

de Seze, M., Raibaut, P., Gallien, P., Even-Schneider, A., Denys, P., Bonniaud, V., Game, X. and Amarenco, G. 2011. Transcutaneous posterior tibial nerve stimulation for treatment of the overactive bladder syndrome in multiple sclerosis: Results of a multicenter prospective study. *Neurourol Urodyn*.

Dorgan, S. J. and Reilly, R. B. 1999. A model for human skin impedance during surface functional neuromuscular stimulation. *IEEE Trans Rehabil Eng,* 7**,** 341-8.

Fjorback, M. V., Van Rey, F. S., Rijkhoff, N. J., Nohr, M., Petersen, T. and Heesakkers, J. P. 2007. Electrical stimulation of sacral dermatomes in multiple sclerosis patients with neurogenic detrusor overactivity. *Neurourol Urodyn,* 26**,** 525-30.

Hagstroem, S., Mahler, B., Madsen, B., Djurhuus, J. C. and Rittig, S. 2009. Transcutaneous electrical nerve stimulation for refractory daytime urinary urge incontinence. *J Urol,* 182**,** 2072-8.

Monga A, D. R., Miller D 2011. Evaluation of a novel, non-inavise, Patient-Managed Neuromodulation System (PMNS) on urgency, urinary incontinence and patient-reported outcomes in subjects with Overative Bladder (OAB) syndrome who had previously failed therapy: a four week, multicenter, prospective randomized trial. *Abstract,* international continence asociation Glasgow August 2011.

Peters, K. M., Carrico, D. J., Perez-Marrero, R. A., Khan, A. U., Wooldridge, L. S., Davis, G. L. and Macdiarmid, S. A. 2010. Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial. *J Urol,* 183**,** 1438-43.

Reilly, J. P., A.M. Diamant 2011. *Electrostimulation,* Artech House.

Rosell, J., Colominas, J., Riu, P., Pallas-Areny, R. and Webster, J. G. 1988. Skin impedance from 1 Hz to 1 MHz. *IEEE Trans Biomed Eng,* 35**,** 649-51.

Shen, B., Roppolo, J. R., Subbaroyan, J., Diubaldi, A., Wahlgren, S., de Groat, W. C. and Tai, C. 2011. Neuromodulation of bladder activity by stimulation of feline pudendal nerve using a transdermal amplitude modulated signal (TAMS). *Neurourol Urodyn*.

Tai, C., Shen, B., Wang, J., Liu, H., Subbaroyan, J., Roppolo, J. R. and de Groat, W. C. 2011. Inhibition of bladder overactivity by stimulation of feline pudendal nerve using transdermal amplitude-modulated signal (TAMS). *BJU Int*.

Tai, C., Shen, B., Wang, J., Subbaroyan, J., Roppolo, J. R. and de Groat, W. C. 2012. Bladder inhibition by intermittent pudendal nerve stimulation in cat using transdermal amplitude-modulated signal (TAMS). *Neurourol Urodyn*.

Walsh, I. K., Thompson, T., Loughridge, W. G., Johnston, S. R., Keane, P. F. and Stone, A. R. 2001. Non-invasive antidromic neurostimulation: a simple effective method for improving bladder storage. *Neurourol Urodyn,* 20**,** 73-84.

Wollner, J., Hampel, C. and Kessler, T. M. 2012. Sacral neuromodulation. *BJU Int,* 110**,** 146-59.

Yokozuka, M., Namima, T., Nakagawa, H., Ichie, M. and Handa, Y. 2004. Effects and indications of sacral surface therapeutic electrical stimulation in refractory urinary incontinence. *Clin Rehabil,* 18**,** 899-907.