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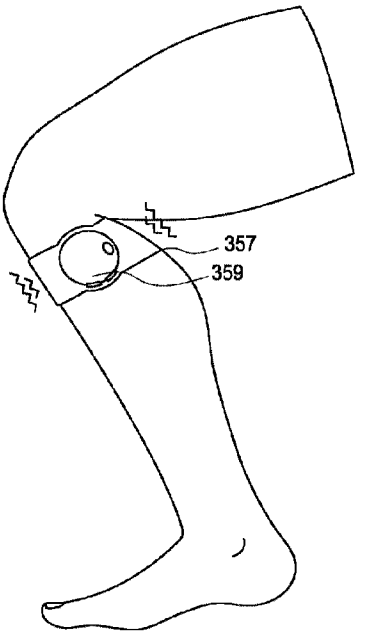
(54) Title: SYSTEMS, METHODS AND DEVICES FOR PERIPHERAL NEUROMODULATION FOR TREATING DISEASES RELATED TO OVERACTIVE BLADDER



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In some embodiments, systems and methods can include a wearable device with an electrically conductive skin interface that excites the underlying nerves from a transcutaneous surface stimulator. The device may be sized for a range of user sizes with stimulation electrodes positioned to target the appropriate nerves, such as the saphenous and/or posterior tibial nerves. Transcutaneous afferent stimulation of one, two, or more peripheral nerves can modulate a brain or spinal pathway associated with bladder function.

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(57) Abstract: In some embodiments, systems and methods can include a wearable device with an electrically conductive skin interface that excites the underlying nerves from a transcutaneous surface stimulator. The device may be sized for a range of user sizes with stimulation electrodes positioned to target the appropriate nerves, such as the saphenous and/or posterior tibial nerves. Transcutaneous afferent stimulation of one, two, or more peripheral nerves can modulate a brain or spinal pathway associated with bladder function.

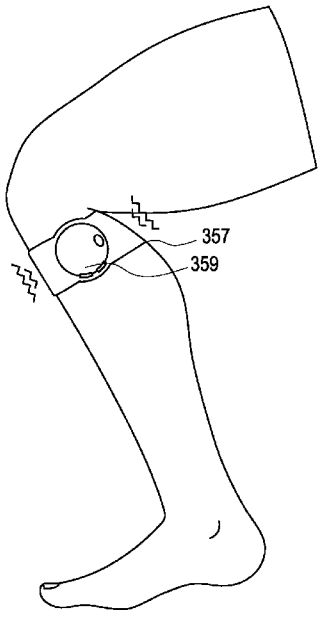

FIG. 3

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[Continued on next page]

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SYSTEMS, METHODS AND DEVICES FOR PERIPHERAL NEUROMODULATION FOR TREATING DISEASES RELATED TO OVERACTIVE BLADDER

BACKGROUND

Field of the Invention

[0001] The invention relates in some aspects to systems and methods for treating overactive bladder and related conditions.

Description of the Related Art

[0002] Overactive bladder (OAB) is a common condition affecting men and women with an estimated prevalence at 16% of the population affecting up to an estimated 500 million people by 2018. The total annual cost burden of OAB is projected to be US$3.9 billion across six countries (Canada, Germany, Italy, Spain, Sweden and the UK). Symptoms of overactive bladder include the uncontrollable desire to urinate immediately, known as urgency, which may or may not be followed by the loss of urine (incontinence), increased frequency of urination, and/or nocturia. Nocturia is a medical condition that results in the need to wake up one, two, three, or more times during the night to urinate. Lower urinary tract (LUT) dysfunction may be secondary to a variety of non-neurologic or neurologic causes, including stroke, spinal cord injury, multiple sclerosis or neurodegenerative conditions such as Parkinson's disease. Standard medical treatment options for overactive bladder include behavioral strategies such as timed voiding or pelvic muscle exercises, or pharmacologic therapies such as antimuscarinic medications or botulinum toxin injections into the bladder. However, oral medications can be incompletely effective and carry a high risk of adverse side effects leading to intolerance and frequent discontinuation. Efficacious therapies with reduced side effects are needed.

SUMMARY

[0003] Accordingly, there is described a non-implantable wearable device for dual transcutaneous stimulation of the saphenous nerve and posterior tibial nerve and for treating urinary symptoms in a patient, the device comprising: a controller; a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the saphenous nerve; a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the posterior tibial nerve; and at least one biomedical sensor or data input source configured to provide feedback information; wherein the controller comprises a processor and a memory for receiving the feedback information from the sensor that, when executed by the processor, cause the device to: adjust one or more parameters of a first electrical stimulus and a second electrical stimulus based at least in part on the feedback information; and deliver the first electrical stimulus to the saphenous nerve through the first peripheral nerve effector and deliver the second electrical stimulus to the posterior tibial nerve through the second peripheral nerve effector to reduce urinary symptoms, wherein the device is not configured for implantation within the patient.

[0004] There is also described a wearable device for treating urinary symptoms in a patient, the device comprising: a controller; a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a first afferent nerve pathway associated with bladder function; and a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a second afferent nerve pathway associated with bladder function; at least one input source configured to provide feedback information; wherein the controller comprises a processor and a memory for receiving the real-time feedback information from the at least one input source that, when executed by the processor, cause the device to: adjust one or more parameters of a first electrical stimulus based at least in part on the feedback information; adjust one or more parameters of a second electrical stimulus based at least in part on the feedback information independent from the first electrical stimulus; deliver the first electrical stimulus to the first afferent nerve pathway through the first peripheral nerve effector to reduce urinary symptoms; and deliver the second electrical stimulus to the second

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afferent nerve pathway through the second peripheral nerve effector to reduce urinary symptoms, wherein adjusting the one or more parameters of the first electrical stimulus and the second electrical stimulus modulates stimulation to improve efficacy, wherein the device is not configured for implantation within the patient.

[0005] There is also described a wearable device for dual transcutaneous stimulation of the saphenous nerve and posterior tibial nerve, the device comprising: a controller; a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the saphenous nerve; a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the posterior tibial nerve; and at least one biomedical sensor or data input source configured to provide feedback information; wherein the controller comprises a processor and a memory for receiving the feedback information from the sensor that, when executed by the processor, cause the device to: adjust one or more parameters of a first electrical stimulus and a second electrical stimulus based at least in part on the feedback information; and deliver the first electrical stimulus to the saphenous nerve through the first peripheral nerve effector and deliver the second electrical stimulus to the posterior tibial nerve through the second peripheral nerve effector to reduce urinary symptoms, wherein the device is not configured for implantation within the patient.

[0006] There is also described a wearable device for dual transcutaneous stimulation of two nerves for treating urinary symptoms, the device comprising: a controller; a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a first nerve, wherein the first nerve comprises the saphenous or tibial nerve; a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a second nerve; at least one biomedical sensor or data input source configured to provide feedback information; wherein the controller comprises a processor and a memory for receiving the feedback information from the sensor that, when executed by the processor, cause the device to: adjust one or more parameters of a first electrical stimulus and a second electrical stimulus based at least in part on the feedback information; and deliver the first electrical stimulus to the first nerve through the first peripheral nerve effector and deliver the second

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electrical stimulus to the second nerve through the second peripheral nerve effector to reduce urinary symptoms, wherein the device is not configured for implantation within the patient.

[0007] There is also described a non-implantable wearable device for treating urinary symptoms in a patient, the device comprising: a controller; a first non-implantable peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a first afferent nerve pathway associated with bladder function; a second non-implantable peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a second afferent nerve pathway associated with bladder function; and at least one biomedical sensor or data input source configured to provide information relating to autonomic nervous system activity of the patient; wherein the controller comprises a processor and a memory and is arranged to cause the device to: adjust one or more parameters of a first electrical stimulus and a second electrical stimulation based at least in part on the information received from the at least one biomedical sensor or data input source; and deliver the first electrical stimulus to the first afferent nerve pathway through the first non-implantable peripheral nerve effector and deliver the second electrical stimulus to the second afferent nerve pathway through the second non-implantable peripheral nerve effector to reduce urinary symptoms, wherein adjusting the one or more parameters of the first electrical stimulus and the second electrical stimulus modulates stimulation to improve efficacy.

[0008] There is also described a wearable device for treating urinary symptoms in a patient, the device comprising: a controller; a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a first afferent nerve pathway associated with bladder function; and a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a second afferent nerve pathway associated with bladder function; at least one input source configured to provide feedback information; wherein the controller comprises a processor and a memory for receiving the real-time feedback information from the input source that, when executed by the processor, cause the device to: adjust one or more parameters of a first electrical stimulus based at least in part on the feedback information; adjust one or more parameters of a second electrical stimulus based at least in part on the

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feedback information independent from the first electrical stimulus; deliver the first electrical stimulus to the first afferent nerve pathway through the first peripheral nerve effector to reduce urinary symptoms by affecting a first brain or spinal cord autonomic feedback loop relating to bladder function; and deliver the second electrical stimulus to the second afferent nerve pathway through the second peripheral nerve effector to reduce urinary symptoms by affecting a second brain or spinal cord autonomic feedback loop relating to bladder function, wherein adjusting the one or more parameters of the first electrical stimulus and the second electrical stimulus contributes to balancing sympathetic and parasympathetic nervous system activity.

[0009] There is also described a system of treating urinary symptoms in a patient, comprising: a wearable housing configured to be positioned on a patient's calf proximate the knee of the patient; a first electrode configured to be positioned at a first location on a skin surface relative to a first afferent peripheral nerve; a second electrode configured to be positioned at a second location on the skin surface relative to a second afferent peripheral nerve; a third electrode configured to be positioned at a third location on the skin surface spaced apart from the first electrode and the second electrode; a controller configured to deliver a first stimulus to the first peripheral nerve through the first electrode; and a second stimulus to the second peripheral nerve through the second electrode to affect at least one brain or spinal cord autonomic feedback loop relating to bladder function; wherein the third electrode is a single common return electrode to the first electrode and the second electrode, and wherein the first electrode, second electrode, and third electrode are configured to be positioned such that electric fields between the first electrode and the third electrode pass through the first afferent peripheral nerve, and electric fields between the second electrode and the third electrode pass through the second afferent peripheral nerve, wherein the wearable housing is attached to each of the first electrode, the second electrode, and the third electrode.

[0010] There is also described a system of treating urinary symptoms in a patient, comprising: a first pair of electrodes comprising an anode and a cathode and configured to be positioned at a first location on a skin surface relative to a first afferent peripheral nerve; a second pair of electrodes comprising an anode and a cathode and configured to be positioned

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at a second location on the skin surface relative to a second afferent peripheral nerve; a controller configured to deliver a first stimulus to the first peripheral nerve through the first pair of electrodes, and a second stimulus to the second peripheral nerve through the pair of second electrodes; wherein the first pair of electrodes and second pair of electrodes are configured to be positioned such that electric fields between the first pair of electrodes pass through the first peripheral nerve, and electric fields between the second pair of electrodes pass through the second peripheral nerve.

[0011] There is also described a device for stimulating a first nerve and a second nerve to treat overactive bladder in a patient, comprising: a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the first nerve; a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the second nerve; a control; and one or more sensors configured to sense biological measures about the patient; wherein the control is configured to receive the biological measures from the one or more sensors and adapt one or more parameters of a first stimulation waveform and of a second stimulation waveform based at least in part on the biological measures to reduce urinary symptoms.

[0012] In some embodiments, systems and methods can include a wearable device with an electrically conductive skin interface that excite the underlying nerves from a transcutaneous surface stimulator. The device may be sized for a range of user sizes with stimulation electrodes positioned to target the appropriate nerves, as in the device described in, for example, U.S. Pat. No. 9,452,287 to Rosenbluth et al., PCT Pub. No. WO 2015/187712 to Wong et al., and PCT App. No. PCT/US2016/037080.

[0013] This invention describes, in some embodiments, a wearable system that uses transcutaneous sensory stimulation in order to improve symptoms of overactive bladder and urinary incontinence. In some embodiments, key factors of this system enable chronic,

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home-use to improve the efficacy of peripheral nerve stimulation by avoiding the inconvenience of frequent office visits and invasive aspects of using percutaneous tibial neuromodulation or sacral nerve stimulation. Some embodiments can advantageously utilize transcutaneous neuromodulation of peripheral afferent nerve pathways to non-invasively affect brain or spinal cord pathways associated with physiologic, such as bladder function.

[0014] Chronic peripheral nerve stimulation in a wearable form that can be integrated easily into an individual's life, allowing full mobility and ease of use, can improve the efficacy of urinary neuromodulation. However, home use of a percutaneous system can be inconvenient and technically difficult for the patient. Transcutaneous neuromodulation is a more suitable modality for home use but is currently limited by the form factor depending on the needs for chronic daily use. Furthermore, adding aspects of responsiveness and more frequent use could greatly improve the effectiveness and comfort of such a chronic use device.

[0015] The effects of peripheral nerve stimulation on bladder function may occur only during the period of active stimulation or may outlast the stimulation period after stimulation has ceased. Different mechanisms such as the modulation of urinary reflexes or induction of brain or spinal plasticity can be responsible for these experimental and clinical observations. Furthermore, the onset of the effects of stimulation may occur acutely (e.g., during or immediately following therapy) or only after several stimulation sessions in a chronic manner. For example, the effect of transcutaneous tibial and/or saphenous nerve stimulation on patient related outcomes is estimated at 4-6 weeks after the initiation of weekly stimulation sessions. Depending on the underlying mechanisms and the time course of beneficial effects, stimulation may require delivery in a continuous fashion such as in sacral nerve stimulation, in discrete scheduled sessions or in an on-demand, conditional manner. Conditional stimulation may either rely on patient control to identify the sense of urinary urge or automated detection of an involuntary detrusor contraction (IDC) which is responsible for urgency symptoms or evolution to frank incontinence.

[0016] Several peripheral nerves can be selected as targets for urinary neuromodulation, including the tibial, pudendal, and dorsal genital nerve, with demonstrated acute and chronic effects on bladder function in animal and human experimental studies. The saphenous nerve can acutely reduce bladder hyperexcitability. The saphenous nerve is a

purely sensory nerve that innervates the skin on the medial lower leg. Its proximity to the skin surface makes it an advantageous target for transcutaneous stimulation. Selective stimulation of the tibial and saphenous nerve can reduce symptoms of overactive bladder.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Figure 1 illustrates non-limiting structures and pathways associated with bladder function.

[0018] Figures 1A and 1B illustrate examples of stimulation waveforms, according to some embodiments of the invention.

[0019] Figure 2 schematically illustrates a flow chart incorporating a stimulation protocol, according to some embodiments of the invention.

[0020] Figure 3 illustrates a calf band stimulator configured to be positioned proximate the knee, according to some embodiments of the invention.

[0021] Figures 4A-4B illustrate ankle stimulators, according to some embodiments of the invention.

[0022] Figures 5A-5C illustrate non-limiting embodiments of potential electrode placement locations for nerve stimulation.

[0023] Figures 6-7 illustrate views of stimulation devices with sticky electrodes, according to some embodiments of the invention.

[0024] Figure 8 illustrates a thin, bandage-like electrode that can be attached to the patient, according to some embodiments of the invention.

[0025] Figure 9 illustrates an embodiment of a distal saphenous nerve sensing and/or stimulation technique.

[0026] Figure 10 illustrates a stimulation device including a housing, according to some embodiments of the invention.

[0027] Figure 10A illustrates an embodiment of an electrode array with elements that can be individually addressable.

[0028] Figure 10B illustrates an embodiment of a stimulation system including a wearable device on the ankle or other desired anatomical location, as well as an implanted stimulation electrode around a target nerve.

[0029] Figures 11A-11E and 12 illustrate that systems and methods of peripheral nerve stimulation can be provided that target one, two, or more individual nerves.

[0030] Figures 12 and 13 show that the electrodes can be disposed on a wearable band (or sleeve) that can be circumferential or non-circumferential, and worn around the ankle, knee, leg, or other body part according to some embodiments of the invention.

[0031] Figures 14 and 15 illustrate embodiments of stimulation systems with at least three electrodes that can be configured to independently stimulate a plurality of nerves.

[0032] Figures 16A-16C illustrate clinical data relating to saphenous nerve stimulation, according to some embodiments of the invention.

[0033] Figures 17A-17F illustrate clinical data relating to tibial nerve stimulation, according to some embodiments of the invention.

DETAILED DESCRIPTION

[0034] As used herein, the terms "stimulating" and "stimulator" generally refer to delivery of a signal, stimulus, or impulse to neural tissue of the targeted region. The effect of such stimulation on neuronal activity is termed "modulation;" however, for simplicity, the terms "stimulating" and "modulating," and variants thereof, are sometimes used interchangeably herein. The effect of delivery of the signal to the neural tissue may be excitatory or inhibitory and may potentiate acute and/or long-term changes in neuronal activity. For example, the effect of "stimulating" or "modulating" a neural tissue may comprise one or more of the following effects: (a) depolarizing the neurons such that the neurons fire action potentials, (b) hyperpolarizing the neurons to inhibit action potentials, (c) depleting neurons ion stores to inhibit firing action potentials (d) altering with proprioceptive input, (e) influencing muscle contractions, (f) affecting changes in neurotransmitter release or uptake, or (g) inhibiting firing. "Proprioception" refers to one's sensation of the relative position of one's own body parts or the effort being employed to move one's body part. Proprioception may otherwise be referred to as somatosensory, kinesthetic or haptic sensation. A "proprioceptor" is a receptor providing proprioceptive information to the nervous system and includes stretch receptors in muscles, joints, ligaments, and tendons as well as receptors for pressure, temperature, light and sound. An "effector" is the mechanism by which the device modulates the target nerve. For example, the "effector" may be electrical stimulation of the nerve or mechanical stimulation of proprioceptors.

[0035] "Electrical stimulation" refers to the application of electrical signals to the soft-tissue and nerves of the targeted area. The "cloud" refers to a network of computers communication using real-time protocols such as the internet to analyze, display and interact with data across distributed devices.

[0036] Some forms of therapy for control of urinary symptoms include electrical neuromodulation, including transcutaneous and/or percutaneous peripheral nerve stimulation and/or implantable pudendal or sacral nerve stimulation. Neuromodulation of the urinary system can be highly effective in the control of lower urinary tract symptoms. Modulation of urinary reflexes can be accomplished in some embodiments by stimulation of lumbosacral afferent pathways. Sacral neuromodulation can include surgical placement of an implant at the level of the S3 sacral foramina and can be highly effective and durable but requires an invasive procedure. The stimulation can be performed continuously and in an open-loop. Sacral stimulation can lead to modulation of the micturition reflex at the spinal or supraspinal level. Although sacral nerve stimulation is considered relatively long-lasting, it is invasive and side effects include buttock, lower extremity or pelvic pain, lead site infection, and negative changes in urinary, bowel or sexual function. Device related complications include battery failure, lead migration, or loss of efficacy necessitating revision or explantation of the device.

[0037] Modulation of bladder dysfunction can also be achieved in some cases using intermittent tibial nerve stimulation. The acute effects of stimulation can include improvements in cystometry measures, including bladder capacity. Stimulation can be performed, for example, weekly with a percutaneous needle electrode in 30 minute sessions. As the stimulation is not continuous, there can be a carry-over effect. The effects of percutaneous tibial nerve stimulation can be maintained after, for example, 12 weeks, but a continued schedule of sessions can be required thereafter every month to maintain efficacy. Stimulation of the posterior tibial nerve can lead to spinal root L4-S3 stimulation inhibiting bladder activity although it is unclear whether spinal reflex or brain networks are responsible for the effects. The presence of a carry-over effect after the period of stimulation suggests a plasticity mechanism either at the level of the spine or brain.

[0038] Transcutaneous stimulation of one, two, or more target nerves of interest, e.g., the saphenous nerve, and/or or tibial nerve stimulation can control urinary incontinence

symptoms with varying levels of success. However, in some embodiments, transcutaneous stimulation can be preferred. The feasibility of home-based stimulation has been limited by device form factor and limited programming flexibility of current devices.

[0039] In some embodiments, more continuous stimulation at the level of the tibial and/or saphenous nerve can potentially improve the efficacy of peripheral nerve stimulation for conditions such as, for example, urinary incontinence. An implanted percutaneous tibial nerve stimulator can be efficacious and safe. Some embodiments can use frequencies of, for example, between about 1 kHz and about 100 kHz, 1 Hz and about 100 Hz, between about 1 Hz and about 50 Hz, between about 5 Hz and about 30 Hz, or between about 10 Hz and about 20 Hz stimulation for a specified period of time, such as about, at least about, or no more than about 20, 30, 40, 50 or 60 minutes at a sensory or sub-sensory threshold or below motor contraction threshold that is tolerable to the patient. Varying the regularity of stimulation and the frequency of the stimulation waveform may improve tolerance or efficacy in some cases. An increased frequency of stimulation may be more effective but could require a more chronic at-home portable system to provide continuous transcutaneous stimulation throughout the day.

[0040] Stimulating at intensities below the sensory threshold or with high frequencies (e.g., between about 1 kHz to about 100 kHz) can avoid the discomfort (tingling, numbness, pain) that can be associated with peripheral nerve stimulation. Because the exact electrode position, size and surface contact have a large effect on the stimulation level and the anatomical structures that receive the stimulation, the sensory threshold may need to be calibrated for each patient and even for each session. This calibration may be done by the user manually setting the stimulation parameters or otherwise indicating their sensory threshold. Another possible embodiment is for the device to automatically sweep through a range of stimulation parameters and the patient chooses the most comfortable set of parameter values. Another possible embodiment is for the patient to choose from among a set of previously chosen parameter values that provided effective and comfortable stimulation.

[0041] In some embodiments, disclosed herein are peripheral nerve stimulators to improve conditions including but not limited to urinary dysfunction. The stimulation can target one, two, three, or more nerves associated with bladder function. The nerves can include, for example, the tibial nerve or posterior tibial nerve, which can branch into the

medial and lateral plantar nerve branches, and the calcaneal nerves. The saphenous nerve is the cutaneous branch of the femoral nerve. Other nerves include, for example, the pudendal nerve, pelvic nerve, dorsal genital nerve, external anal sphincter nerve, and the dorsal genital nerve, for example. In some embodiments, the posterior tibial nerve can be stimulated transcutaneously in a manner similar to percutaneous tibial nerve stimulation but noninvasively and in a more prolonged manner. In some embodiments, systems and methods include only transcutaneous elements without any implanted and/or percutaneous components.

[0042] Not to be limited by theory, voluntary control of the bladder can be mediated in large part by the autonomic nervous system (ANS). The ANS maintains a balance which can be important to the normal functioning of the body's organs. For instance, the hypogastric nerve (sympathetic) and pelvic nerve (parasympathetic) both carry information about bladder fullness to the brain, and also work together to enable the relaxation-contraction mechanism that controls micturition. Figure 1 illustrates non-limiting structures and pathways associated with bladder function.

[0043] Activation of the pontine micturition center (PMC) results in parasympathetic activation of the bladder. This in turn contracts muscles in the bladder and relaxes muscles in the urethra. Micturition commands cease when CNS structures including the periaqueductal gray (PAG) receive signals that the bladder is no longer full.

[0044] Inappropriate activation and inhibition of the parasympathetic and sympathetic systems can result in a sense of bladder fullness, urgency, sensory discomfort, and/or involuntary voiding. Peripheral stimulation that affects the activity of autonomic nerves can be used to modulate or interrupt micturition reflex circuits to correct abnormal bladder functioning. This modulation can be achieved by, for example, stimulation of the saphenous nerve, tibial nerve, or a combination of the two. In some embodiments, systems and methods use stimulation schemes designed to dephase, override or obscure the abnormal networks. In some embodiments, systems and methods use stimulation schemes designed to restore balance of sympathetic and parasympathetic activity of the micturition reflex loop. Advantageously, certain embodiments utilize transcutaneous afferent stimulation of one, two, or more peripheral nerves to modulate a brain or spinal pathway associated with bladder function, and/or an organ or target remote from the site(s) of stimulation.

[0045] Generally, sympathetic fibers originate in the T11 to L2 segments of the spinal cord, while parasympathetic fibers originate in the S2 to S4 spinal segments. The sympathetic fibers travel through the hypogastric nerve and inferior mesenteric ganglia, while the parasympathetic fibers travel in the pelvic nerves and plexus. In some cases, effective frequency band for this parasympathetic modulation can be, for example, around the frequency band of 10 to 20 Hz, while the frequency band sympathetic modulation can be, in some cases, as high as 30 Hz or as low as 5 Hz. Not to be limited by theory, in some cases the higher frequencies may offer benefit in comfort while the lower frequencies may offer benefit in better preservation.

[0046] In some embodiments, systems and methods involve stimulation parameters including frequency and spatial selectivity on the surface of the distal limb to selectively modulate and balance the sympathetic and parasympathetic system.

[0047] Not to be limited by theory, stimulation of a first target nerve, such as the saphenous nerve can provide sympathetic modulation of the bladder circuit. Specifically, electrical stimulation tuned to excite large myelinated fibers in a target nerve, e.g., the saphenous nerve can provide somatic afferent input to the lumbar plexus, mediating the sympathetic input to the bladder circuitry via the hypogastric nerve. Sympathetic nerves relax the detrusor muscle of the bladder by releasing norepinephrine, activating the β adrenergic receptors, and contract the intrinsic urethral sphincter, by activating the α-adrenergic receptors. Relaxing the bladder and contracting the intrinsic sphincters can give comfort during the filling and storage phases of the bladder cycle. Stimulation of a second target nerve, e.g., the tibial nerve can provide parasympathetic modulation of the bladder circuit. Specifically, electrical stimulation tuned to excite large myelinated fibers in the tibial nerve provides somatic afferent input to sacral plexus, the sacral micturition center, mediating parasympathetic input to the bladder circuitry via the pelvic nerves via release of cholinergic transmitters. There may also be input from the somatic efferents of the pelvic floor to the external urethral sphincter and modulates the afferent sensation of bladder fullness. Due to widely connected and circuit-based mechanisms of these circuits, all mechanisms described above can in some embodiments modulate the central cortical and pontine micturition centers which coordinate and time signals.

[0048] The system may run on a selection of pre-specified programs that vary stimulation parameters and target one or more nerves individually or in combination to improve symptoms of overactive bladder in a specific patient, e.g. whether their challenge is primarily daytime urinary urgency, nighttime waking (nocturia), or incontinence. Alternatively, the system may be closed loop on a number of parameters including: the subject's symptomatic history, including night waking events, or manually entered urination indicated on board the device or a secondary device; direct detection of sympathetic and parasympathetic tone in the bladder or general circuitry, including HRV and galvanic skin response; and/or closed-loop based on previous usage of device, e.g., purely sympathetic excitation may be enhanced by brief periods of parasympathetic balance.

[0049] In some embodiments, nerve stimulation can be synergistically combined with one, two, or more pharmacologic therapies for overactive bladder, including but not limited to an anti-cholinergic (e.g., oxybutynin, tolterodine, trospium, darifenacin, solifenancin, and/or fesoterodine), a beta-3 adrenergic (e.g., mirabegron), an anti-spasmodic (e.g., flavoxate), and/or an anti-depressant (e.g., a tricyclic antidepressant such as desipramine or imipramine), a hormone (such as an estrogen and/or progesterone), or botulinum toxin.

[0050] Use of chronic, noninvasive stimulation can involve certain waveform characteristics to excite sensory neurons in a comfortable manner. The frequency of stimulation used can be, for example, within the between about 1 Hz and about 500 Hz range (such as, for example, between about 5 Hz and about 30 Hz, such as between about 10 Hz and about 20 Hz) or between about 1 kHz and about 100 kHz to preferentially affect the proper targets. In some embodiments, the waveforms can be biphasic rectangular or balanced in charge in order to minimize irritation to the skin, such as illustrated schematically in Figure 1A. In some embodiments, waveforms could also be asymmetric, especially in the case to stimulate one, two, three, or more nerves as described in, for example, WO 2018/009680. In some embodiments, waveform shapes and rising edges can be altered in order to increase patient comfort and tolerability to the treatment. In some embodiments, the waveforms can include higher frequency sine waves carried inside the rectangular signal as illustrated in Figure 1B. An interval between the opposite-going waveforms can be adjusted to a value that

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allows for charge balance, while allowing the first waveform's excitatory effects to not be immediately negated by the second waveform, but balancing the charge at the interface to reduce skin irritation and improve comfort. In some cases, spacing between 0 microseconds to 300 microseconds has been effective. The waveform amplitude can be adjusted so that it is perceptible, above a minimum sensation threshold, but not intolerable to the patient.

[0051] In some embodiments, the effector can be excitatory to the nerve. In other embodiments, the effector can be inhibitory to the nerve. In some embodiments, the system can be used to excite the nerve during some portions of the treatment and inhibit the nerve during other portions of the treatment.

[0052] In some embodiments, waveforms including those described herein can be modified over time in order to minimize certain effects, such as habituation. One way of decreasing habituation is to modify the frequency, pulse width, or amplitude of the stimulation. For instance, randomizing or pseudo-randomizing parameters such as, for example, the frequency or pulse width can reduce habituation. Using a Gaussian distribution for randomization can be effective in some cases, and used in such waveforms as stochastic waveforms. Another way of reducing habituation is to the lower the frequency below a certain threshold, such as, for example, no more than about 60Hz, 55Hz, 50 Hz, 45Hz, or 40Hz, in which humans tend not to habituate.

[0053] Varying other parameters such as amplitude can be a way to improve waveform comfort. For example, the amplitude of the stimulation can be adjusted based on the threshold necessary to produce strong sensory perception and paresthesia without eliciting motor contraction. Excitation of muscles can lead to unpleasant cramping sensations in some embodiments. This amplitude could also be modulated throughout a session to be the appropriate, comfortable value depending a person's position or motion.

[0054] The stimulation waveforms described herein can be applied continuously to target nerves such as the tibial and/or saphenous nerves, for example, or can be provided in a manner that is adaptive in applying stimulation of various durations or by adjusting properties of the stimulation waveform, including but not limited to amplitude, frequency, and pulse width, in response to different inputs in the system. In some embodiments, the system could include closed loop control, using one or more signals measured by the device or feedback input into the device by the patient or physician to modulate the stimulation to

improve efficacy. The signals or input could include, for example, any number of the following: sensors on-board the device or connected in the digital ecosystem; evaluation of autonomic function, reflex loop integrity, or excitability using heart rate variability, measuring muscle sympathetic nerve activity (MSNA), and/or measuring h-reflex by sending a stimulation signal and measure response with EMG. In some embodiments, the signals or input can also include sleep sensor sets, including but not limited to accelerometers, gyroscopes, infrared based motion sensors, and/or pressure sensors under a mattress, to measure night time motion as a measure of nocturia events. For example, patients may wear a stimulator while sleeping and therapy can be triggered by night time restlessness, which is an indicator of an upcoming nocturia event. A motion sensor set (e.g., accelerometer, IR based motion sensor, etc.) can measure rapid back and forth movement of legs typically seen when someone has a sense of urgency. An EEG headband could be used to measure different sleep states. Patient and/or physician input can provide feedback on the effectiveness of and/or satisfaction with the therapy into the device or into another connected device. Also, usage of the stimulation device can be tracked; and specific stimulation programs (e.g., a specified set of stimulation parameters) can be changed based on symptoms presented by the patient or outcomes of the therapy.

[0055] In some embodiments, a stimulator can be part of a system with sensors to assess the state of sleep and modulate stimulation based on the wearer's sleep state. Sensors could include motion sensors (e.g., body worn accelerometers and gyroscopes, or wireless motion tracking via video or infrared), temperature sensors to measure body temperature, pressure sensor under the mattress to measure movement, heart rate sensors to measure HRV, other sensors to measure sympathetic and parasympathetic activity, and/or EEG sensors to measure brain activity to assess the wearer's sleep state. For example, if nocturia events occur during slow wave sleep when parasympathetic activity can be elevated, stimulation parameters are modulated to affect parasympathetic activity, and vice-versa for sympathetic activity.

[0056] In some embodiments, a first stimulation frequency can be provided for short term benefit, and a second stimulation frequency different (e.g., higher or lower) from the first stimulation frequency can be provided for long-term benefit. For example, 10Hz stimulation can provide a short term benefit and 20 Hz stimulation can provide a long term

benefit in some cases. As one example, 10 Hz stimulation can be provided in an initial period with the therapy (e.g., 3 weeks) for acute therapy, then 20 Hz stimulation can be provided for long term maintenance or condition therapy, or vice versa depending on the desired clinical result. In some embodiments, particular sympathetic and/or parasympathetic nervous system targets and circuits can be specifically targeted to modulate upward or downward sympathetic and/or parasympathetic nervous system activity depending on the patient's underlying autonomic nervous system activity. Utilization of data and/or sensors directly or indirectly measuring sympathetic and/or parasympathetic nervous system activity as disclosed, for example, elsewhere herein can be utilized as closed loop feedback inputs into a hardware and/or software controller to modify stimulation parameters, including on a real-time basis.

[0057] In some embodiments, the therapy (e.g., stimulation) can be applied for about, at least about, or no more than about 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, or more a day. In some embodiments, the patient is treated nocturnally, such as during sleep, and/or during waking hours. The treatment can be repeated 1, 2, 3, 4, 5, or more times daily or weekly, every other day, every third day, weekly, or other interval depending on the desired clinical result.

[0058] In some embodiments, the responsiveness could be dependent on different times of day. For instance, the patient or physician (or algorithm) could pre-schedule different episodic treatment sessions throughout the day and the device could provide treatment stimulation at those different times of day. In one example, treatments are applied at regular or irregular intervals during the day at a frequency related to the typical amount of voiding. In the treatment of nocturia, stimulation could be timed to periodic intervals during a person's sleep. In some embodiments, stimulation schemes are applied to restore autonomic dysregulation based on natural diurnal patterns of sympathetic or parasympathetic activity. Treatment could also occur at irregular intervals that are human-entered or predicted by machine learning from previous days' voiding incidents. In some embodiments, a first frequency (e.g., 10Hz or 20Hz) therapy can be applied in the morning for acute day time relief, and a second different higher or lower frequency (e.g., 20Hz or 10Hz) therapy can be provided before bed for longer night time relief.

[0059] In some embodiments, the responsiveness could be dependent on activity. For instance in nocturia, a motion sensor such as an accelerometer or gyroscope could sense if a person is stirring, which could indicate a desired potential voiding. During that time, the device could turn on to provide appropriate stimulation. In some embodiments, the device could turn off once voiding is complete.

[0060] In some embodiments, the responsiveness of stimulation could be dependent on one, two, or more sensors housed in the device to collect, store, and analyze biological measures about the wearer including, but not limited to, motion (e.g., accelerometers, gyroscopes, magnetometer, bend sensors), ground reaction force or foot pressure (e.g., force sensors or pressure insoles), muscle activity (e.g., EMG), cardiovascular measures (e.g., heart rate, heart rate variability (HRV)), skin conductance (e.g., skin conductance response, galvanic skin response), respiratory rate, skin temperature, and sleep state (e.g., awake, light sleep, deep sleep, REM). Using standard statistical analysis techniques, such as a logistical regression or a Naïve Bayes classifier, these biological measures can be analyzed to assess the wearer's activity state, such as sedentary versus active, level of stress and/or bladder fluid volume, and the like, which in turn, can serve as a predictor for increases in urinary urgency.

[0061] Sympathetic and parasympathetic activity can be measured through several methods, including microneurography (MSNA), catecholamine tests, heart rate, HRV, or galvanic skin response. HRV can provide a quick and effective approximation of autonomic activity in the body. HRV can be determined by analyzing the time intervals between heartbeats, also known as RR intervals. Heart rate can be accurately captured, for example, through recording devices such as chest straps or finger sensors. The differences between successive RR intervals can provide a picture of one's heart health and autonomic activity. Generally speaking, healthier hearts have more variability between successive RR-intervals. This interbeat data can also be used to denote an individual's sympathetic and parasympathetic activity levels. Through frequency-domain analysis, heartbeat frequencies can be separated into distinct bands. High-frequency signals (~0.15-0.4 Hz) almost exclusively reflect parasympathetic activity, and low-frequency signals (~0.04-0.15 Hz) represents a mixture of sympathetic and parasympathetic activity. Therefore, taking the ratio of high frequency (HF) to low frequency (LF) signals yields an approximation of one's

sympathetic tone. In some embodiments, HRV can be analyzed, for example, under time-domain, geometric domain methods in addition to frequency domain methods. In some embodiments, increased heart rate variability can signify increased parasympathetic response and/or decreased sympathetic response. Decreased heart rate variability can signify decreased parasympathetic response and/or increased sympathetic response. In some embodiments, a system can sense an increase or decrease in HRV of about or more than about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 75%, 100%, or more over a baseline value (or target desired HRV value) and institute a change in one, two, or more stimulation modality parameters accordingly. In some embodiments, the one, two, or more stimulation modalities can be configured to modulate, such as increase or decrease stimulation to one or more nerves (e.g., peripheral nerves) associated with the sympathetic and/or parasympathetic nervous system, and a response to therapy can be confirmed by sensing an increase or decrease in parasympathetic or sympathetic tone, including but not limited to increase or decrease in HRV, changes in high frequency content of HRV, and changes in the ratio of high frequency and low frequency content of HRV.

[0062] In some embodiments, balance of parasympathetic and sympathetic activity of the bladder reflex loop can be assessed with frequency analysis of heart rate variability measured with pulsed plethysmography with an LED light source and optical sensor disposed in the device that measures fluctuations in light level due to blood flow that target one of the major blood vessels around the knee, which could include one or more of the following, femoral, popliteal, posterior tibial, anterior tibial, and/or descending genicular arteries or veins.

[0063] A large source of error in optical measurements of heart rate is motion artifacts due to relative motion between the optical sensor and the blood vessel being measures. In some embodiments, the optical heart rate sensor has an adhesive on the side of housing that contacts the wearer's skin to reduce relative motion between the sensor and the target blood vessel.

[0064] In some embodiments, one, two, or more additional sensors are disposed in the device, including electrical sensors in contact with the wearer's skin to measure cardiac activity or pressure sensors to measure changes in blood vessels, to be used in combination with an optical sensor to improve the fidelity of heart rate measurement.

[0065] In some embodiments, the system and device have memory and a processor to extract RR intervals from sensor data, calculate variability of RR intervals, transform data into frequency domain, and calculate high frequency signals, low frequency signals, and the ration of the high frequency and low frequency signals.

[0066] In some embodiments, the heart rate sensor store collected data for specified time period to gather adequate date for heart rate variability calculation. Specified time period can range in some cases from 1 – 60 seconds, and may extend to 10 minutes.

[0067] In some embodiments, electrodermal activity, also known as galvanic skin response or skin conductance response, for example, can be measured using sensors, such as electrodes. Galvanic skin response is the change of the electrical resistance of the skin caused by emotional stress, and measurable with, e.g., a sensitive galvanometer. Not to be limited by theory, skin resistance varies with the state of sweat glands in the skin. Sweating is controlled by the sympathetic nervous system, and skin conductance can be an indication of psychological or physiological arousal. If the sympathetic nervous system is highly aroused, then sweat gland activity also increases, which in turn increases skin conductance. In this way, skin conductance can be a measure of emotional and sympathetic responses, which can be measured, and the feedback data can be sent to the controller, which will in turn modulate stimulation to, for example, decrease sympathetic nervous system activity. Other non-limiting parameters associated with sympathetic and/or parasympathetic nervous system activity that can be sensed include, for example, sweating during particular times of the day and/or night, sleep states as detected, for example, by an EEG headband (to determine when sympathetic and/or parasympathetic activity is particularly high or low, and potentially correlating a sleep state such as stage 1, 2, 3, 4, or REM with nocturia), and/or motion.

[0068] The device could also be responsive to number of episodes of symptoms, including overactive bladder. If more episodes occur in one day, treatment can be increased by increasing the amplitude of the stimulation, duration of the stimulation, or number of treatment sessions, for example.

[0069] The number of episodes of symptoms such as overactive bladder could be detected in various ways to control the stimulation applied by system and devices. In some embodiments, the patient can enter events related to symptoms of overactive bladder, including but not limited to bladder voiding events, urgency event, or incontinence events on

a mobile device. In some embodiments, location services on the device, such as GPS, can detect when the person has entered a building or bathroom..

[0070] Information regarding bladder voiding can be combined in some embodiments with an understanding of the amount of fluid a person has consumed in order to better apply a desired amount of treatment. For example, in days where more beverages were consumed by an individual, more bladder voiding would be expected. Figure 2 schematically illustrates a flow chart incorporating a stimulation protocol, according to some embodiments of the invention. The times, amounts, and types of beverages ingested by a patient over the day can be recorded manually or electronically, such as in a software application, as shown in box 200. Knowing when and what was consumed can be used to predict when and how much a person's bladder should be emptied and the amount of treatment can be applied accordingly. The information regarding the processing time of a certain amount of liquid in the human body could be used to anticipate through literature studies with additional information from the patient (such as gender, weight, and height, and potentially measuring bladder size using an initial pelvic ultrasound procedure). This processing and consolidation of data (shown in box 202) to anticipate the amount and timing of treatment necessary can be done within a single device or utilizing another separate device, for instance a mobile phone. In this manner, stimulation 204 can be applied accordingly based on the number of episodes a person experiences.

[0071] One method of recording the times and types of beverages consumed is through a journal or diary, for example on a smartphone, tablet, or other device. Another method of achieving this is to use a device such as a smart cup that identifies the types and amounts of beverages consumed through the day and syncs this information to the system or device. This information can advantageously be an automatic journal of the amount of liquids consumed through the day.

[0072] Bladder control and comfort require a delicate balance of sympathetic, parasympathetic, somatic efferent and afferent innervation of the bladder reflex circuits. In some embodiments, a variable frequency stimulator in electrical connection with three or more electrodes to target at least two nerves that provide sympathetic, parasympathetic and somatic input into the bladder reflex circuits. In some embodiments, the device is disposed in a knee strap fitted just below the knee with a fastening mechanism to hold the device

securely on the body. In some embodiments, the electrodes, constructed from an adhesive hydrogel, are disposed in the housing of the device allowing the device to adhere to the wearer's skin.

[0073] In some embodiments, as shown schematically in Figure 3, the nerve stimulator can be designed like a calf band 357 having a stimulator housing 359 attached thereto and configured to be positioned just distal to the knee for stimulating the posterior tibial nerve and the saphenous nerve transcutaneously. As illustrated in Figures 4A-4B, the nerve stimulator can include an ankle brace or anklet 400 with a stimulator box 402 (shown in Figure 4A) or an ankle brace (shown in Figure 4B). This form factor could also be extended to a sock, shoe, boot, or stocking for example. These form factors can be advantageous in some cases, as they are compact and do not necessarily interfere with gait. The electrodes can be integrated into a garment in the form of conductive polymers or silver fabrics, for example. In some embodiments, dry electrodes can be utilized, such as dry electrodes that include a conductive backing layer (e.g., a metal foil material, such as disposed on a flexible polymer substrate) and a skin contact layer disposed on the conductive backing layer, that can include for example a polymer, plastic, or rubber material, and a conductive filler material (e.g., powder, fine particulate material, metal, carbon, mixtures thereof, or porous material treated with a conductive coating) dispersed substantially evenly throughout the silicone, plastic, or rubber material. In some embodiments, the skin contact layer has a skin facing surface that is not coated with a hydrogel or liquid.

[0074] In some embodiments, the weave of the brace or sock could be designed to provide tight pressure at the knee, calf, ankle, or other desired region of the device, similar to the weave of commonly found anklet socks. Electrodes can also be made from, for example, conventional hydrogels. In some cases, a clasp or fastening element such as Velcro may be needed because with sticky electrodes, the device cannot be easily slid on the foot. In some embodiments, the, e.g., knee, calf, ankle brace or anklet embodiments can be extended to electrode positions that are on the top (dorsal) or bottom (ventral) surfaces of the foot. In some cases, a sock with electrodes on the sole of the foot can be used with connectivity through the sock to an electronics module located near the ankle.

[0075] Figures 5A-5C illustrate non-limiting embodiments of potential electrode placement locations for nerve stimulation. The sensor systems, including those disclosed

herein can communicate via wires or wirelessly to the stimulator 502. Placement of the electrodes of the tibial stimulator could vary with electrodes 500 placed along the tibial nerve (Figure 5A), at the bottom of the foot (Figure 5C), or on either side of the ankle or attached to a stimulator (Figure 5B).

[0076] In some embodiments if the electrodes 606 are sticky, as shown in the embodiment of Figures 6-7, a device 600 in the form of a bandage can be made, which circumferentially or non-circumferentially envelop a portion of a body part, such as an extremity. The strip can be any shape, including an annular, square, rectangular, triangular, or other shape. In some cases, the electronics can be located inside a removable housing 602 that can be removably attached at site 604 from the entire device 600 when the disposable is thrown away. Figure 6 is a bottom view, while Figure 7 is a top view of the device 600.

[0077] In another embodiment, as illustrated in Figure 8, a thin, bandage-like electrode 802 can be attached to the patient. Power can be coupled from a battery source that is loosely wrapped around the target body region, such as the knee or ankle for example, like a knee band, thigh band, calf band, an anklet 800 or sock, or located on the side of the shoe in the general vicinity of the electrode. In some embodiments, power can be delivered wirelessly to the electrode 802, such as via inductive charging. This configuration can be advantageous, in some embodiments, in that the disposable can be made very thin, increasing the comfort of the skin interface even if the disposable is very sticky (this is analogous to an adhesive bandage). This embodiment can also be adapted for use if the electrode bandages are placed on the bottom of the foot. In some cases, the electronics could be located/clipped on the top of a shoe or in the sole of the shoe.

[0078] Several peripheral nerves in addition to, or instead of the tibial nerve can serve as targets for urinary neuromodulation, including the pudendal and dorsal genital nerve, with acute and/or chronic effects on bladder function in animal and human experimental studies. Saphenous nerve stimulation can acutely or chronically reduce bladder hyperexcitability. The saphenous nerve is a purely sensory nerve that innervates the skin on the medial lower leg. Its proximity to the skin surface makes it an advantageous target in some embodiments for transcutaneous stimulation. Selective stimulation of the saphenous nerve can in some embodiments advantageously reduce overactive bladder symptoms. In some embodiments, peripheral nerves can be independently targeted with specific same or

differing frequencies to prove acute or chronic relief of symptoms of overactive bladder, and/or to alter sympathetic and/or parasympathetic activity.

[0079] The effects of peripheral nerve stimulation on bladder function may occur only during the period of active stimulation in some embodiments, or may outlast the stimulation period after stimulation has ceased. Different mechanisms such as the modulation of urinary reflexes or induction of brain and/or spinal plasticity can be triggered using systems and methods as disclosed herein. Furthermore, in some cases the onset of the effects of stimulation may occur acutely or only after several stimulation sessions in a chronic manner. For example, the effect of transcutaneous or percutaneous tibial nerve stimulation on patient related outcomes is estimated in some embodiments at 4-6 weeks after the initiation of weekly stimulation sessions. Depending on the underlying mechanisms and the time course of beneficial effects, stimulation may require delivery in a continuous fashion such as in sacral nerve stimulation, in discrete scheduled sessions or in an on-demand, conditional manner. Conditional stimulation may either rely on patient control to identify the sense of urinary urge or automated detection of an involuntary detrusor contraction (IDC) which is responsible for urgency symptoms or evolution to frank incontinence.

[0080] Conditional stimulation of the dorsal genital nerve and/or pudendal nerve can be advantageous in some embodiments. Alternatively or in addition, continuous stimulation can be utilized to control bladder symptoms. The advantages of conditional stimulation in some embodiments can include customization of symptom control, improved battery life, and reduction of the risk of habituation with continuous stimulation. A patient controlled conditional stimulation device for overactive bladder may be effective for suppressing urge symptoms prior to the progression to incontinence.

[0081] The stimulation frequency can be varied depending on the desired clinical result. In some embodiments, a relatively higher frequency, such as between about 10 Hz and about 33 Hz, between about 10 Hz and about 30 Hz, between about 10 Hz and about 20 Hz, or between about 20 Hz and about 33 Hz, or about or at least about 10 Hz, 15 Hz, 20 Hz, 25 Hz, 30 Hz, 33 Hz, 35Hz, or more can be used. The stimulation frequency can also be tailored to the specific nerve targeted. In some embodiments, lower stimulation rates such as 2 Hz can have an excitatory effect on bladder function and worsen incontinence. However, in some embodiments, a frequency of about or no more than about 10 Hz, 9 Hz, 8 Hz, 7 Hz, 6

Hz, 5 Hz, 4 Hz, 3 Hz, 2 Hz, or 1 Hz can be utilized. In some embodiments, the stimulation frequency could be in the kHz range, such as, for example, between about 1 kHz and about 100 kHz, such as between about 10 kHz and about 50 kHz. The stimulation could be regular, irregular, or random in some embodiments. In some embodiments, a frequency or a plurality of frequencies for one, two, or more nerves could be selected from, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50 Hz. In some embodiments, two or more of the same or different frequencies or frequency ranges can be applied to the same or different target nerves.

[0082] The exact location of stimulation in the lower leg can vary depending on the desired target. For example, the tibial nerve may be stimulated at the level of the ankle or behind the knee,. As the saphenous nerve territory is over the medial lower leg, stimulation of the nerve may be achieved at the ankle or closer to the knee in some cases.

[0083] In some embodiments, stimulation of the saphenous nerve can be used instead of or in conjunction with tibial nerve stimulation to treat overactive bladder and/or urinary incontinence. The saphenous nerve runs through the upper leg, descends along the medial side of the knee, descends along the tibial side of the lower leg and divides into two branches, a branch that continues to descend along the tibia that extends to the ankle and a branch that passes in front of the ankle and extends along the medial side of the foot.

[0084] In some embodiments, a stimulator worn around the ankle or lower leg or knee or upper leg can be used to stimulate the saphenous nerve and, optionally, also the tibial nerve. In other embodiments, the stimulator can be worn around any other part of the leg or foot in order to stimulate the saphenous nerve at other locations. The electrode(s) of the stimulator can be placed proximate or over the saphenous nerve.

[0085] In some embodiments, the stimulation can be electrical and be provided transcutaneously using an electrode placed on the patient's skin. In some embodiments, the stimulation of the saphenous nerve can be patient activated. In some embodiments, the stimulation of the saphenous nerve can be automated and/or patient activated. In some embodiments, the stimulation of the saphenous nerve can be solely patient activated, meaning the stimulation is only provided while the patient is awake. If stimulation while the patient is asleep is desired, an automated stimulation regimen can be provided.

[0086] Figure 9 illustrates an embodiment of a distal saphenous nerve sensing and/or stimulation technique. In some embodiments, the therapy can be performed in a supine, upright, or sitting position. In some embodiments, a bar electrode (e.g., 3cm) can be used. A reference electrode (R) can be positioned slightly anterior to the highest prominence of the medial malleolus, between the malleolus and the tendon of the tibialis anterior. The active electrode (A) can be positioned proximal and slightly medial to the tibialis anterior tendon. A return, e.g., ground electrode (G) can be placed, for example, between the recording electrodes and the cathode. With regard to the stimulation point (S), the cathode (C) can be placed, for example, 14 cm proximal to the active electrode deep to the medial border of the tibia. The anode (A) can be, for example, proximal. In some embodiments, the device settings could include any of the following: Sensitivity—2–5 μV/division, Low frequency filter—20 Hz, High frequency filter—2 kHz, Sweep speed—1 msec/division. In some embodiments, the L3 and L4 nerve roots, through the posterior division of the lumbosacral plexus, can be tested. In some embodiments, sensing and its associated components such as the reference electrode (R) may not be required.

[0087] In some embodiments, a device for stimulating one, two, or more nerves is illustrated schematically in Figure 10. The device 10 can include a housing 20 and one, two or more effectors 30, power sources 50, and/or controls 40. In some embodiments, the device further includes one or more sensors 70. The effectors can include a pulse generator and electrodes for delivering electrical stimulation, and/or can be a mechanical stimulator for delivering mechanical stimulation, such as vibratory stimulation, for example. The sensors can include, for example, accelerometers, gyroscopes, and electrodes to measure electrical activity including nerve activity and muscle activity.

[0088] In some embodiments, as illustrated in Figure 10A, the device can include a 2D or 3D array of electrodes 1000 such that the stimulation may be targeted. The elements 1002 may be individually addressable such that the location of stimulation can be adjusted on-the-fly or for each session, such as electronic referencing. Alternatively, the elements may be configured for an individual user, such as a mechanical configuration in which the electrode connections are cut or spliced to customize the device.

[0089] Figure 10B illustrates an embodiment of a stimulation system 1001 including a wearable device 1010 on the ankle or other desired anatomical location, as well

as an implanted stimulation electrode 1020 around a target nerve 1030, such as the tibial nerve for example. In another embodiment, the wearable device may be a component of a stimulation system including subcutaneous, transcutaneous, and/or percutaneous components. For example, the wearable device may communicate with an implanted stimulation device to power and control the device. Additionally, the implantable electrode can be powered by a rechargeable battery housed within the implant and recharged wirelessly from an external power source or the wearable device. Alternatively, the wearable may contain a guiding array used to direct the location of percutaneous needles either in a patient-directed or healthcare setting.

[0090] In some embodiments, an implanted electrode that stimulates the nerve can be powered by an external stimulation unit, and the stimulation pulse is directly coupled to the electrode and nerve using capacitive or inductive coupling. In some embodiments, the wearable device can communicate with an external computer or device (e.g., tablet, smartphone, smartwatch, or custom base station) to store data. Communication between the wearable device and external device can be a direct, physical connection, or with a wireless communication connection such as Bluetooth, Wi-Fi, Zigbee, GSM, or cellular for example. In some embodiments, the system communicates with an external, portable computational device, such as a smartphone via an app, or other mobile digital interaction. The device may be used to track information of relevant events either user-entered or automatically captured from biological sensors, such as the time since the last urination and fluid intake, or biometric data predicting upcoming episodes of urinary incontinence or urinary urgency. This information may be used to close the loop to adjust stimulation parameters (waveforms, amplitude, on/off) or suggest user behaviors.

[0091] In some embodiments, the wearable device can have a GPS or similar device to track the location and assess activity of the wearer. GPS measures can be combined with mapping or location systems to determine context of the wearer's activity (e.g., gym versus office) or determine changes in elevation during specific activities, such as running or cycling.

[0092] In some embodiments, the wearable device can track parameters about stimulation provided by the stimulation unit, including time of stimulation, duration of the stimulation session, and power used by the stimulation unit. This data can be stored on

memory in the wearable device, processed by the wearable device, and/or transmitted to an external computing device.

[0093] The stimulation unit can use switches or electrical sensor to detect connection of electrodes: (1) to ensure proper and unique electrodes are being installed (e.g., not using a different or incorrect type of electrode) communicating a unique code, for example via RFID, (2) to regulate the number of uses for each electrode to prevent over use, and/or (3) to prevent the usage of the device without an electrode to prevent small shock.

[0094] In some embodiments, a system may include features to increase skin comfort. One solution is to use a high frequency carrier (e.g., kHz such as 1 kHz or greater) wave over the low frequency beats (10 to 200 Hz), or to position electrodes such that the interaction of two waveforms combines to produce a low frequency beat.

[0095] In some embodiments, systems and methods of peripheral nerve stimulation can be provided that target one, two, or more individual nerves as illustrated in Figures 11A-11E. In some embodiments, the system 10 can that allows customization and optimization of transcutaneous electrical treatment to an individual. In particular, the device 10 described is for electrical stimulation of one, two, or more nerves. For example, a two electrode embodiment can be used to stimulate the tibial and/or saphenous nerve. Targeting these specific nerves and utilizing appropriately customized stimulation can in some embodiments result in more effective therapy. In some embodiments, the target nerves can include nerves in the leg, e.g., the tibial and/or saphenous nerve, that can be used to treat overactive bladder. In some embodiments, the device 10 can be configured to be worn on the leg, knee, or ankle and can be formed from a housing 12 and a band 14 or sleeve. In some embodiments, electronics and sensors located in a housing 12 can measure indications of bladder fullness or other symptoms of overactive bladder, as described herein. The electronics can include, for example, a pulse generator, a controller, and one, two, or more sensors such as an accelerometer and/or gyroscope and/or electrodes for measuring nerve activity. Electrical contacts and/or traces in the band 14 and/or housing 12 transmit the stimulation waveform from the pulse generator to the electrodes 16, which can be disposable. The location of the contacts in the band 12 can be arranged such that specific nerves are targeted, such as the tibial and/or saphenous nerve, or others including those disclosed herein.

The housing 12 also can have a digital display screen to provide feedback about the stimulation and sensor data to the wearer of the device.

[0096] In some embodiments, disclosed herein is a dual nerve stimulator with the entire device or a portion thereof configured to be positioned just below the knee to target the saphenous and posterior tibial nerves, including sensors for measuring slow changes in heart rate variability to assess autonomic dysregulation (e.g., to balance sympathetic and parasympathetic activity), and/or accelerometry for measuring overall activity, where the nerve targeted and the frequency of stimulation are controlled based on sensor data. Stimulation of each of the target nerves can be turned on or off independently, and the stimulation frequency can be adjusted independently to provide acute or chronic relief of symptoms due to a condition such as overactive bladder, as needed.

[0097] In some embodiments, the treatment device 10 can be a wearable device including an electronics box or housing 12 containing the stimulator or pulse generator 18, sensors 20, and other associated electronics such as a controller or processor 22 for executing instructions, memory 24 for storing instructions, a user interface 26 which can include a display and buttons, a communications module 28, a battery 30 that can be rechargeable, and optionally an inductive coil 32 for charging the battery 30, and the like. The device 10 can also include, for example, a band or sleeve to hold all the components together and securely fasten the device around the leg, knee, foot, or ankle of an individual. The device can also include, for example, a pair of electrodes on the band or sleeve.

[0098] Additional system and device embodiments are shown in Figures 12 and 13, which show that the electrodes can be disposed on a wearable band (or sleeve) that can be circumferential or non-circumferential, and worn around the ankle, knee, leg, or other body part. The wearable band may include a removable/detachable controller as further described in International Application No. PCT/US2016/37080, titled SYSTEMS AND METHOD FOR PERIPHERAL NERVE STIMULATION TO TREAT TREMOR WITH DETACHABLE TERHAPY AND MONITORING UNITS. As shown, the wearable bands have two electrodes which can be used to stimulate up to two nerves. However, other embodiments can have N electrodes to stimulate up to N nerves, or N+1 electrodes to stimulate N nerves (e.g., 2

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electrodes to stimulate up to 1 nerve; 3 electrodes to stimulate 2 nerves; or 4 electrodes to stimulate 3 nerves).

[0099] Figure 12 illustrates a wearable band 800 with disposable electrodes 802, 804. The disposable electrodes 802, 804 can be coated or covered with an electrically conductive hydrogel and may be disposed on a strip 806 that can be removably attached to the wearable band 800, which may have a receptacle 808 for receiving the strip 806. The strip 806 and the band 800 can have electrical contacts and a flexible circuit so that the electrodes are electrically connected to the controller 810. To accommodate various body part sizes, the disposable strip 806 can be provided with a variety of electrode spacings. This allows one band size to accommodate users with different body part sizes. Since hydrogels can dry out, hydrogel coated electrodes may be more suitable for use with removable electrodes, as shown in Figure 12, that can be disposed and replaced on a regular basis, such as every 1, 2, 3, 4, 5, 6, or 7 days.

[0100] In some embodiments, stimulating three or more electrodes can be used to stimulate two or more nerves. In some embodiments as shown in Figure 12A, the electronics and electrical circuit 1200 used to drive the array can include an adaptable switch that allows each individual electrode 1202 to be connected to either one of the two contacts 1204, 1206 of the stimulator 1208 at a given time by opening or closing switches 1210 in each channel. Each channel can include a DC blocking circuit 1212, as charge balance can be important to prevent skin irritation and bums, and also be individually current limited by current IO limiters 1214 in order to prevent current surges that could cause injury or discomfort. This current limitation can be set to a predetermined tolerability threshold for a particular patient or group of patients.

[0101] There are many transistor circuits or components like polyfuses to limit or shutdown the current to a particular node. These circuits and its components, such as the stimulator, switches, and current limiters, can be controlled and/or be programmable by a microprocessor 1216 in real-time. The 15 switch matrix allows multiple electrodes to be connected to the same stimulator contacts at a given time for maximum flexibility. In addition, electrodes can be switched between the positive and negative contacts of the stimulator to produce a bipolar pulse.

[0102] Figure 13 shows an embodiment of a wearable band 900 with integrated electrodes 902, 904. The integrated electrodes 902, 904 can be dry electrodes in electrical communication with a detachable controller 910 through a flexible circuit embedded in the band. In some cases, dry electrodes may be more suitable for longer term use electrodes that can be used for months, such as at least 1, 2, or 3 months, before the band needs to be replaced. In some embodiments, the band may be a single use band that can be used for a relatively long period of time before replacement.

[0103] In some embodiments, disclosed herein are systems and methods for stimulating a plurality of nerves for the treatment of conditions including but not limited to overactive bladder. Stimulation of 2, 3, or more nerves, such as the saphenous and tibial nerve could be used for the treatment of conditions such as overactive bladder. Dual nerve stimulation can in some cases synergistically increase the effectiveness of therapy by combining synergistically the effects of, for example, saphenous and tibial nerve stimulation. In some embodiments, including those disclosed in connection with Figures 14 and 15 below, the system can be configured to independently control stimulation of a first target nerve (including stimulation parameters such as frequency and others listed herein) and a second target nerve respectively. In other words, the first target nerve and the second target nerve can be stimulated with either the same or different parameters, and can be stimulated simultaneously or in alternating or other fashion. In some embodiments, the stimulation systems can include a plurality of independent stimulation circuits, or a common circuit with a controller configured to switch stimulation parameters for one, two, or more nerves.

[0104] In some embodiments, as illustrated schematically in Figure 14, a system 1400 can utilize three electrodes: a first electrode 1404 positioned over a first nerve, e.g., the tibial nerve 1402, a second electrode 1406 positioned over a second nerve, e.g., the saphenous nerve 1408, and a third electrode 1410 positioned, for example, on the outer side of the leg, opposite to the first two electrodes 1404, 1406. This third electrode 1410 would serve as a common cathode for the other two electrodes 1404, 1406. The three electrodes 1404, 1406, 1410 can be oriented in such a way that the electric fields between each of the

first two electrodes 1404, 1406 and the common cathode 1410 pass through the tibial nerve 1402 and saphenous nerve 1408, respectively.

[0105] Another possible configuration shown in Figure 15 utilizes four electrodes. Similar to the embodiment illustrated in Figure 14, three channels are used: a first targeting the tibial nerve 1402, a second targeting the saphenous nerve 1408, and one acting as a common cathode 1410. However, the cathode in the electronics is split between two common electrodes 1411, 1413, each serving as a cathode electrode for the other two electrodes 1404, 1406. Thus, a first electrode 1404 is positioned over the tibial nerve 1402 with a first cathode electrode 1411 positioned directly below it and a second electrode 1406 is positioned over the saphenous nerve 1408 with a second common electrode 1413 positioned directly below it. Each electrode pair 1404, 1411 and 1406, 1413 can be oriented in such a way that the electric field between the two electrodes (the electrode over the nerve and its respective common electrode) passes through the intended nerve (e.g., tibial or saphenous).

[0106] A 4 week proof of concept (POC) study of transcutaneous saphenous nerve stimulation was performed, and 7 subjects were enrolled. Eligibility was confirmed using industry-standard OAB-V8 screen and a week of baseline data. The subjects were treated with 60 minutes of daily saphenous nerve stimulation. Data collected included a weekly 3-day voiding diary, and ICIQ-SF and OAB-Q patient assessments at a 4 week appointment. The study data is shown in Figures 16A-16C. Figure 16A illustrates bar graphs showing that patients responded after 1 week of daily therapy, faster than the 4 week response reported for percutaneous stimulation. All subjects improved, and 4 subjects with mild to moderate incontinence experienced near-complete alleviation of incontinence. Figure 16B illustrates that nocturia generally improved as well. Figure 16C shows results of the OAB-q scale, an established scale for quality of life in overactive bladder, and demonstrates clinically significant (e.g., 10 point or more) improvement in quality of life.

[0107] A 4 week proof of concept (POC) study of transcutaneous tibial nerve stimulation was performed, and 4 subjects were enrolled. Eligibility was confirmed using industry-standard OAB-V8 screen and a week of baseline data. The subjects were treated with 60 minutes of daily tibial nerve stimulation. Data collected included frequency, incontinence, and nocturia data. The study data is shown in Figures 17A-17F. Figure 17A

illustrates a table of subject baseline parameters, including OAB-V8 score, frequency, incontinence, and nocturia rates in 24 hours. Figure 17B illustrates a table of responder rates for nocturia, incontinence, and frequency. Figure 17C illustrates a table of improvement in urinary parameters, including frequency, incontinence, and nocturia. As illustrated in the graphs of Figures 17D, 17E, and 17F, urinary frequency episodes per 24 hours, incontinence episodes per 24 hours, and nocturia episodes per 24 hours generally improved with stimulation. When a feature or element is herein referred to as being "on" another feature or element, it can be directly on the other feature or element or intervening features and/or elements may also be present. In contrast, when a feature or element is referred to as being "directly on" another feature or element, there are no intervening features or elements present. It will also be understood that, when a feature or element is referred to as being "connected", "attached" or "coupled" to another feature or element, it can be directly connected, attached or coupled to the other feature or element or intervening features or elements may be present. In contrast, when a feature or element is referred to as being "directly connected", "directly attached" or "directly coupled" to another feature or element, there are no intervening features or elements present. Although described or shown with respect to one embodiment, the features and elements so described or shown can apply to other embodiments. It will also be appreciated by those of skill in the art that references to a structure or feature that is disposed "adjacent" another feature may have portions that overlap or underlie the adjacent feature.

[0108] Terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. For example, as used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms "comprises" and/or "comprising," when used in this specification, specify the presence of stated features, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, steps, operations, elements, components, and/or groups thereof. As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items and may be abbreviated as "/".

[0109] Spatially relative terms, such as "under", "below", "lower", "over", "upper" and the like, may be used herein for ease of description to describe one element or

feature's relationship to another element(s) or feature(s) as illustrated in the figures. It will be understood that the spatially relative terms are intended to encompass different orientations of the device in use or operation in addition to the orientation depicted in the figures. For example, if a device in the figures is inverted, elements described as "under" or "beneath" other elements or features would then be oriented "over" the other elements or features. Thus, the exemplary term "under" can encompass both an orientation of over and under. The device may be otherwise oriented (rotated 90 degrees or at other orientations) and the spatially relative descriptors used herein interpreted accordingly. Similarly, the terms "upwardly", "downwardly", "vertical", "horizontal" and the like are used herein for the purpose of explanation only unless specifically indicated otherwise.

[0110] Although the terms "first" and "second" may be used herein to describe various features/elements (including steps), these features/elements should not be limited by these terms, unless the context indicates otherwise. These terms may be used to distinguish one feature/element from another feature/element. Thus, a first feature/element discussed below could be termed a second feature/element, and similarly, a second feature/element discussed below could be termed a first feature/element without departing from the teachings of the present invention.

[0111] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising" means various components can be co-jointly employed in the methods and articles (e.g., compositions and apparatuses including device and methods). For example, the term "comprising" will be understood to imply the inclusion of any stated elements or steps but not the exclusion of any other elements or steps.

[0112] As used herein in the specification and claims, including as used in the examples and unless otherwise expressly specified, all numbers may be read as if prefaced by the word "about" or "approximately," even if the term does not expressly appear. The phrase "about" or "approximately" may be used when describing magnitude and/or position to indicate that the value and/or position described is within a reasonable expected range of values and/or positions. For example, a numeric value may have a value that is +/- 0.1% of the stated value (or range of values), +/- 1% of the stated value (or range of values), +/- 2% of the stated value (or range of values), +/- 5% of the stated value (or range of values), +/-

10% of the stated value (or range of values), etc. Any numerical values given herein should also be understood to include about or approximately that value, unless the context indicates otherwise. For example, if the value "10" is disclosed, then "about 10" is also disclosed. Any numerical range recited herein is intended to include all sub-ranges subsumed therein. It is also understood that when a value is disclosed that "less than or equal to" the value, "greater than or equal to the value" and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value "X" is disclosed the "less than or equal to X" as well as "greater than or equal to X" (e.g., where X is a numerical value) is also disclosed. It is also understood that the throughout the application, data is provided in a number of different formats, and that this data, represents endpoints and starting points, and ranges for any combination of the data points. For example, if a particular data point "10" and a particular data point "15" are disclosed, it is understood that greater than, greater than or equal to, less than, less than or equal to, and equal to 10 and 15 are considered disclosed as well as between 10 and 15. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0113] Although various illustrative embodiments are described above, any of a number of changes may be made to various embodiments without departing from the scope of the invention as described by the claims. For example, the order in which various described method steps are performed may often be changed in alternative embodiments, and in other alternative embodiments one or more method steps may be skipped altogether. The methods disclosed herein include certain actions taken by a practitioner; however, they can also include any third-party instruction of those actions, either expressly or by implication. For example, actions such as "stimulating a peripheral nerve" includes "instructing the stimulating of a peripheral nerve." Optional features of various device and system embodiments may be included in some embodiments and not in others. Therefore, the foregoing description is provided primarily for exemplary purposes and should not be interpreted to limit the scope of the invention as it is set forth in the claims.

[0114] The examples and illustrations included herein show, by way of illustration and not of limitation, specific embodiments in which the subject matter may be practiced. As mentioned, other embodiments may be utilized and derived there from, such

that structural and logical substitutions and changes may be made without departing from the scope of this disclosure. Such embodiments of the inventive subject matter may be referred to herein individually or collectively by the term "invention" merely for convenience and without intending to voluntarily limit the scope of this application to any single invention or inventive concept, if more than one is, in fact, disclosed. Thus, although specific embodiments have been illustrated and described herein, any arrangement calculated to achieve the same purpose may be substituted for the specific embodiments shown. This disclosure is intended to cover any and all adaptations or variations of various embodiments. Combinations of the above embodiments, and other embodiments not specifically described herein, will be apparent to those of skill in the art upon reviewing the above description.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A non-implantable wearable device for dual transcutaneous stimulation of the saphenous nerve and posterior tibial nerve and for treating urinary symptoms in a patient, the device comprising:

a controller;

a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the saphenous nerve;

a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the posterior tibial nerve; and

at least one biomedical sensor or data input source configured to provide feedback information;

wherein the controller comprises a processor and a memory for receiving the feedback information from the sensor that, when executed by the processor, cause the device to:

adjust one or more parameters of a first electrical stimulus and a second electrical stimulus based at least in part on the feedback information; and

deliver the first electrical stimulus to the saphenous nerve through the first peripheral nerve effector and deliver the second electrical stimulus to the posterior tibial nerve through the second peripheral nerve effector to reduce urinary symptoms,

wherein the device is not configured for implantation within the patient.

2. The device of Claim 1, wherein the feedback information comprises real-time feedback information.

3. The device of Claim 1 or 2, wherein the first electrical stimulus has a frequency of between about 5 Hz and about 30 Hz.

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4. The device of any one of Claims 1 to 3, wherein the second electrical stimulus has a frequency of between about 10 Hz and about 20 Hz.

5. The device of any one of Claims 1 to 4, wherein the feedback information comprises autonomic nervous system activity of the patient.

6. The device of any one of Claims 1 to 4, wherein the feedback information comprises heart rate variability.

7. The device of any one of Claims 1 to 4, wherein the feedback information comprises information relating to at least one of nocturia events of the patient and patient sleep state.

8. The device of any one of Claims 1 to 7, wherein delivering the first electrical stimulus and delivering the second electrical stimulus contributes to balancing sympathetic and parasympathetic nervous system activity.

9. A wearable device for treating urinary symptoms in a patient, the device comprising:

a controller;

a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a first afferent nerve pathway associated with bladder function; and

a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a second afferent nerve pathway associated with bladder function;

at least one input source configured to provide feedback information;

wherein the controller comprises a processor and a memory for receiving the feedback information from the at least one input source that, when executed by the processor, cause the device to:

adjust one or more parameters of a first electrical stimulus based at least in part on the feedback information;

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adjust one or more parameters of a second electrical stimulus based at least in part on the feedback information independent from the first electrical stimulus;

deliver the first electrical stimulus to the first afferent nerve pathway through the first peripheral nerve effector to reduce urinary symptoms; and

deliver the second electrical stimulus to the second afferent nerve pathway through the second peripheral nerve effector to reduce urinary symptoms,

wherein adjusting the one or more parameters of the first electrical stimulus and the second electrical stimulus modulates stimulation to improve efficacy,

wherein the device is not configured for implantation within the patient.

10. The device of Claim 9, wherein the first peripheral nerve effector is configured to transcutaneously modulate the tibial nerve.

11. The device of Claim 9 or 10, wherein the second peripheral nerve effector is configured to transcutaneously modulate the saphenous nerve.

12. The device of any one of Claims 9 to 11, wherein the first peripheral nerve effector is configured to be positioned proximate the knee of the patient.

13. The device of any one of Claims 9 to 12, wherein the first electrical stimulus is different from the second electrical stimulus.

14. The device of any one of Claims 9 to 13, wherein a frequency of the first electrical stimulus is different from a frequency of the second electrical stimulus.

15. The device of any one of Claims 9 to 14, wherein the first electrical stimulus has a frequency of between about 10 Hz and about 20 Hz.

16. The device of any one of Claims 9 to 15, wherein the second electrical stimulus has a frequency of between about 5 Hz and about 30 Hz.

17. The device of any one of Claims 9 to 16, wherein the at least one input source is configured to provide real-time feedback information.

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18. The device of any one of Claims 9 to 17, wherein the at least one input source is configured to provide feedback information relating to nocturia events of the patient.

19. The device of any one of Claims 9 to 17, wherein the at least one input source comprises an EEG sensor configured to provide feedback information relating to patient sleep state.

20. The device of any one of Claims 9 to 17, wherein the at least one input source is configured to provide feedback information relating to autonomic nervous system activity of the patient.

21. The device of any one of Claims 9 to 17, wherein the at least one input source comprises a sensor configured to measure at least one of heart rate variability and galvanic skin response.

22. The device of any one of Claims 9 to 17, wherein adjusting the one or more parameters of the first electrical stimulus and the second electrical stimulus comprises modulating the first and/or second electrical stimulus to achieve a heart rate variability within a targeted desired range.

23. The device of any one of Claims 9 to 22, wherein the controller is configured to deliver the first electrical stimulus and the second electrical stimulus below a sensory threshold.

24. A wearable device for dual transcutaneous stimulation of the saphenous nerve and posterior tibial nerve, the device comprising:

a controller;

a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the saphenous nerve;

a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the posterior tibial nerve; and

at least one biomedical sensor or data input source configured to provide feedback information;

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wherein the controller comprises a processor and a memory for receiving the feedback information from the sensor that, when executed by the processor, cause the device to:

adjust one or more parameters of a first electrical stimulus and a second electrical stimulus based at least in part on the feedback information; and

deliver the first electrical stimulus to the saphenous nerve through the first peripheral nerve effector and deliver the second electrical stimulus to the posterior tibial nerve through the second peripheral nerve effector to reduce urinary symptoms,

wherein the device is not configured for implantation within a patient.

25. The device of Claim 24, wherein the feedback information comprises real-time feedback information.

26. The device of Claim 24 or 25, wherein the first electrical stimulus has a frequency of between about 5 Hz and about 30 Hz.

27. The device of any one of Claims 24 to 26, wherein the second electrical stimulus has a frequency of between about 10 Hz and about 20 Hz.

28. The device of any one of Claims 24 to 27, wherein the feedback information comprises autonomic nervous system activity of the patient.

29. The device of any one of Claims 24 to 28, wherein the feedback information comprises heart rate variability.

30. The device of any one of Claims 24 to 28, wherein the feedback information comprises information relating to nocturia events of the patient.

31. The device of any one of Claims 24 to 28, wherein the feedback information comprises information relating to patient sleep state.

32. A wearable device for dual transcutaneous stimulation of two nerves for treating urinary symptoms, the device comprising:

a controller;

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a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a first nerve,

wherein the first nerve comprises the saphenous or tibial nerve;

a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a second nerve;

at least one biomedical sensor or data input source configured to provide feedback information;

wherein the controller comprises a processor and a memory for receiving the feedback information from the sensor that, when executed by the processor, cause the device to:

adjust one or more parameters of a first electrical stimulus and a second electrical stimulus based at least in part on the feedback information; and

deliver the first electrical stimulus to the first nerve through the first peripheral nerve effector and deliver the second electrical stimulus to the second nerve through the second peripheral nerve effector to reduce urinary symptoms,

wherein the device is not configured for implantation within the patient.

33. The device of Claim 32, wherein the first nerve comprises the saphenous nerve and the second nerve comprises either the tibial nerve or the peroneal nerve.

34. The device of Claim 32 or 33, wherein the device further modulates the first and/or second electrical stimulus to achieve a heart rate variability within a targeted desired range.

35. The device of any one of Claims 32 to 34, wherein the feedback information comprises real-time feedback information.

36. The device of any one of Claims 32 to 35, wherein the first electrical stimulus has a frequency of between about 10 Hz and about 20 Hz.

37. The device of any one of Claims 32 to 36, wherein the second electrical stimulus has a frequency of between about 5 Hz and about 30 Hz.

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38. The device of any one of Claims 32 to 37, wherein the feedback information comprises autonomic nervous system activity of the patient.

39. The device of any one of Claims 32 to 38, wherein the feedback information comprises heart rate variability.

40. The device of any one of Claims 32 to 38, wherein the feedback information comprises information relating to at least one of nocturia events of the patient and patient sleep state.

41. A non-implantable wearable device for treating urinary symptoms in a patient, the device comprising:

a controller;

a first non-implantable peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a first afferent nerve pathway associated with bladder function;

a second non-implantable peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a second afferent nerve pathway associated with bladder function; and

at least one biomedical sensor or data input source configured to provide information relating to autonomic nervous system activity of the patient;

wherein the controller comprises a processor and a memory and is arranged to cause the device to:

adjust one or more parameters of a first electrical stimulus and a second electrical stimulation based at least in part on the information received from the at least one biomedical sensor or data input source; and

deliver the first electrical stimulus to the first afferent nerve pathway through the first non-implantable peripheral nerve effector and deliver the second electrical stimulus to the second afferent nerve pathway through the second non-implantable peripheral nerve effector to reduce urinary symptoms,

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wherein adjusting the one or more parameters of the first electrical stimulus and the second electrical stimulus modulates stimulation to improve efficacy.

42. The device of Claim 41, wherein the first electrical stimulus has a frequency of between about 5 Hz and about 30 Hz.

43. The device of Claim 41 or 42, wherein the second electrical stimulus has a frequency of between about 10 Hz and about 20 Hz.

44. A wearable device for treating urinary symptoms in a patient, the device comprising:

a controller;

a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a first afferent nerve pathway associated with bladder function; and

a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate a second afferent nerve pathway associated with bladder function;

at least one input source configured to provide feedback information;

wherein the controller comprises a processor and a memory for receiving the feedback information from the input source that, when executed by the processor, cause the device to:

adjust one or more parameters of a first electrical stimulus based at least in part on the feedback information;

adjust one or more parameters of a second electrical stimulus based at least in part on the feedback information independent from the first electrical stimulus;

deliver the first electrical stimulus to the first afferent nerve pathway through the first peripheral nerve effector to reduce urinary symptoms by affecting a first brain or spinal cord autonomic feedback loop relating to bladder function; and

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deliver the second electrical stimulus to the second afferent nerve pathway through the second peripheral nerve effector to reduce urinary symptoms by affecting a second brain or spinal cord autonomic feedback loop relating to bladder function,

wherein adjusting the one or more parameters of the first electrical stimulus and the second electrical stimulus contributes to balancing sympathetic and parasympathetic nervous system activity.

45. The device of Claim 44, wherein the first peripheral nerve effector is configured to transcutaneously modulate the tibial nerve.

46. The device of Claim 44 or 45, wherein the second peripheral nerve effector is configured to transcutaneously modulate the saphenous nerve.

47. The device of any one of Claims 44 to 46, wherein the first peripheral nerve effector is configured to be positioned proximate the knee of the patient.

48. The device of any one of Claims 44 to 47, wherein the first electrical stimulus is different from the second electrical stimulus.

49. The device of any one of Claims 44 to 48, wherein a frequency of the first electrical stimulus is different from a frequency of the second electrical stimulus.

50. The device of any one of Claims 44 to 49, wherein the first electrical stimulus has a frequency of between about 10 Hz and about 20 Hz.

51. The device of any one of Claims 44 to 50, wherein the second electrical stimulus has a frequency of between about 5 Hz and about 30 Hz.

52. The device of any one of Claims 44 to 51, wherein the input source is configured to provide real-time feedback information.

53. The device of any one of Claims 44 to 52, wherein the input source is configured to provide feedback information relating to nocturia events of the patient.

54. The device of any one of Claims 44 to 53, wherein the input source comprises an EEG sensor configured to provide feedback information relating to patient sleep state.

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55. The device of any one of Claims 44 to 54, wherein the input source is configured to provide feedback information relating to autonomic nervous system activity of the patient.

56. The device of Claim 55, wherein the input source comprises a sensor configured to measure heart rate variability.

57. The device of Claim 55, wherein the input source comprises a sensor configured to measure galvanic skin response.

58. The device of any one of Claims 44 to 57, wherein the controller is configured to deliver the first electrical stimulus and the second electrical stimulus below a sensory threshold.

59. A system of treating urinary symptoms in a patient, comprising:

a wearable housing configured to be positioned on a patient's calf proximate the knee of the patient;

a first electrode configured to be positioned at a first location on a skin surface relative to a first afferent peripheral nerve;

a second electrode configured to be positioned at a second location on the skin surface relative to a second afferent peripheral nerve;

a third electrode configured to be positioned at a third location on the skin surface spaced apart from the first electrode and the second electrode;

a controller configured to deliver a first stimulus to the first peripheral nerve through the first electrode; and a second stimulus to the second peripheral nerve through the second electrode to affect at least one brain or spinal cord autonomic feedback loop relating to bladder function;

wherein the third electrode is a single common return electrode to the first electrode and the second electrode, and

wherein the first electrode, second electrode, and third electrode are configured to be positioned such that electric fields between the first electrode and the third electrode pass through the first afferent peripheral nerve, and electric fields between the

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second electrode and the third electrode pass through the second afferent peripheral nerve,

wherein the wearable housing is attached to each of the first electrode, the second electrode, and the third electrode.

60. The system of Claim 59, wherein the first afferent peripheral nerve is the posterior tibial nerve.

61. The system of Claim 59 or 60, wherein the second afferent peripheral nerve is the saphenous nerve.

62. The system of any one of Claims 59 to 61, wherein the symptoms comprise overactive bladder.

63. The system of any one of Claims 59 to 61, wherein the symptoms comprise nocturia.

64. The system of any one of Claims 59 to 61, wherein the symptoms comprise urinary urgency.

65. The system of any one of Claims 59 to 61, wherein the symptoms comprise urinary frequency.

66. The system of any one of Claims 59 to 65, wherein the first electrode, second electrode, and third electrode are all connected on a wearable device and configured to be positioned on the calf proximate to, and distal to the patient's knee.

67. The system of any one of Claims 59 to 65, wherein the first electrode, second electrode, and third electrode are all connected on a wearable device and configured to be positioned proximate the patient's ankle.

68. The system of any one of Claims 59 to 65, wherein the first electrode, second electrode, and third electrode are all connected on a wearable device and configured to be positioned proximate the patient's foot.

69. A system of treating urinary symptoms in a patient, comprising:

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a first pair of electrodes comprising an anode and a cathode and configured to be positioned at a first location on a skin surface relative to a first afferent peripheral nerve;

a second pair of electrodes comprising an anode and a cathode and configured to be positioned at a second location on the skin surface relative to a second afferent peripheral nerve;

a controller configured to deliver a first stimulus to the first peripheral nerve through the first pair of electrodes, and a second stimulus to the second peripheral nerve through the pair of second electrodes;

wherein the first pair of electrodes and second pair of electrodes are configured to be positioned such that electric fields between the first pair of electrodes pass through the first peripheral nerve, and electric fields between the second pair of electrodes pass through the second peripheral nerve.

70. The system of Claim 69, wherein the first afferent peripheral nerve comprises the posterior tibial nerve.

71. The system of Claim 69 or 70, wherein the second afferent peripheral nerve comprises the saphenous nerve.

72. The system of any one of Claims 69 to 71, wherein the first and second pairs of electrodes are all connected on a wearable device that is configured to be positioned on the calf proximate to, and distal to the patient's knee.

73. The system of any one of Claims 69 to 71, wherein the first and second pairs of electrodes are all connected on a wearable device that is configured to be positioned proximate the patient's ankle.

74. The system of any one of Claims 69 to 71, wherein the first and second pairs of electrodes all connected on a wearable device that is configured to be positioned proximate the patient's foot.

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75. The system of any one of Claims 69 to 74, wherein the symptoms comprise overactive bladder.

76. The system of any one of Claims 69 to 74, wherein the symptoms comprise nocturia.

77. The system of any one of Claims 69 to 74, wherein the symptoms comprise urinary urgency.

78. The system of any one of Claims 69 to 74, wherein the symptoms comprise urinary frequency.

79. The system of any one of Claims 69 to 78, wherein the controller is configured to deliver the first electrical stimulus and the second electrical stimulus below a sensory threshold.

80. The system of any one of Claims 69 to 79, wherein the first electrical stimulus has a frequency of between about 5 Hz and about 30 Hz.

81. The system of any one of Claims 69 to 80, wherein the second electrical stimulus has a frequency of between about 10 Hz and about 20 Hz.

82. A device for stimulating a first nerve and a second nerve to treat overactive bladder in a patient, comprising:

a first peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the first nerve;

a second peripheral nerve effector comprising at least one stimulation electrode configured to be positioned to transcutaneously modulate the second nerve;

a control; and

one or more sensors configured to sense biological measures about the patient;

wherein the control is configured to receive the biological measures from the one or more sensors and adapt one or more parameters of a first stimulation waveform and of a second stimulation waveform based at least in part on the biological measures to reduce urinary symptoms.

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83. The device of Claim 82, wherein at least the first nerve is a tibial nerve.

84. The device of Claims 82 or 83, wherein the at least one stimulation electrode is arranged in an array.

85. The device of any one of Claims 82 to 84, wherein the one or more sensors is configured to sense motion of the patient.

86. The device of any one of Claims 82 to 85, wherein the one or more sensors is configured to sense muscle activity.

87. The device of any one of Claims 82 to 86, wherein the one or more sensors is configured to sense cardiovascular measures.

88. The device of any one of Claims 82 to 87, wherein the one or more sensors is configured to sense skin conductance.

89. The device of any one of Claims 82 to 88, wherein the one or more sensors is configured to sense respiratory rate.

90. The device of any one of Claims 82 to 89, wherein the one or more sensors is configured to sense sleep state.

91. The device of any one of Claims 82 to 90, wherein the one or more sensors is configured to sense heart rate variability.

92. The device of any one of Claims 82 to 91, wherein the device is configured to communicate with a base station.

93. The device of any one of Claims 82 to 91, wherein the device is configured to communicate with a portable communicating device.

94. The device of any one of Claims 82 to 93, wherein the device comprises a cuing system configured to warn the patient of upcoming urinary events.

95. The device of any one of Claims 82 to 94, wherein the device is an ankle band.

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96. The device of any one of Claims 82 to 95, further comprising a processing device configured to analyze the biological measures.

97. The device of any one of Claims 82 to 96, further comprising a GPS configured to track the patient.

98. The device of any one of Claims 82 to 97, further comprising a memory configured to store the one or more parameters.

99. The device of any one of Claims 82 to 98, further comprising a vibratory motor configured to apply vibrational stimulation to the patient.

100. The device of any one of Claims 82 to 99, further comprising a power source configured to power the device.

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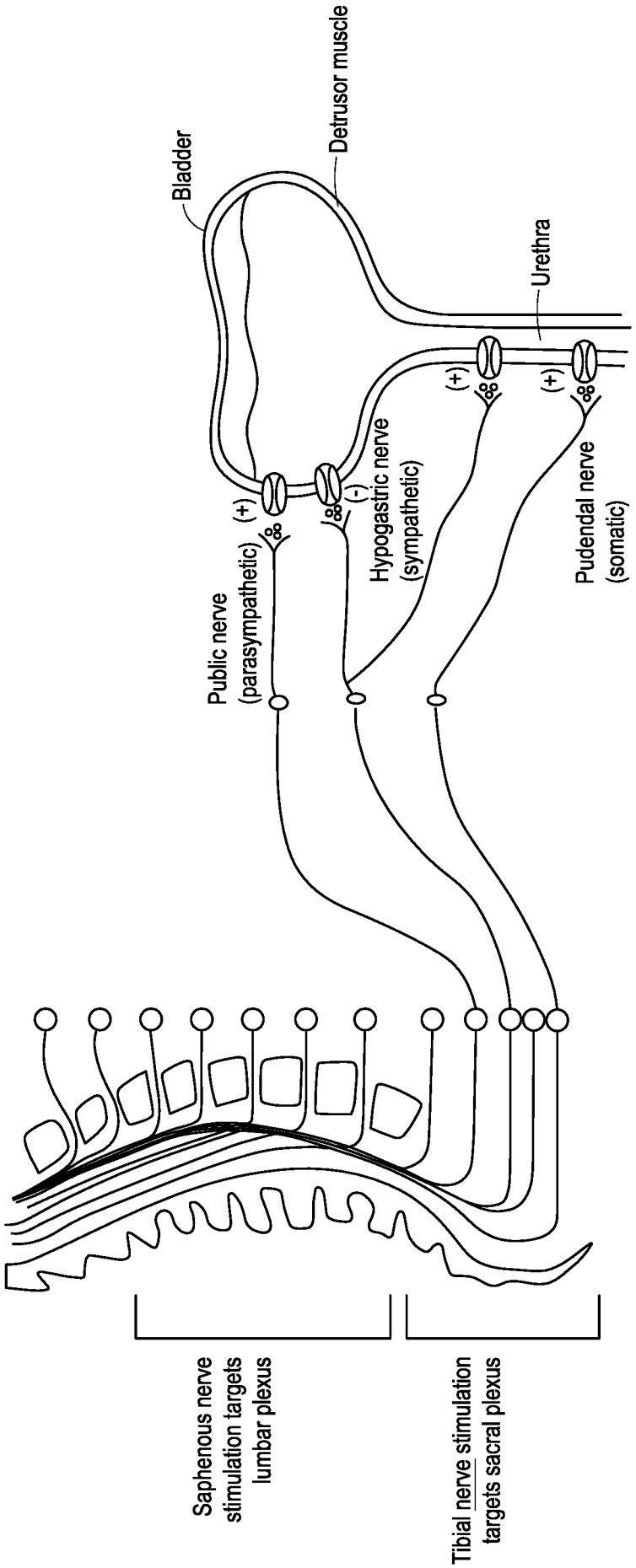

Bladder
Detrusor muscle
Urethra
(+)
(+)
(+)
(-)
Public nerve
(parasympathetic)
Hypogastric nerve
(sympathetic)
Pudendal nerve
(somatic)
Saphenous nerve
stimulation targets
lumbar plexus
Tibial nerve stimulation
targets sacral plexus

FIG. 1

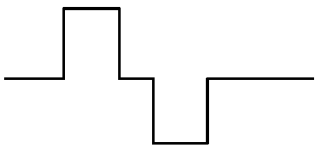


FIG. 1A

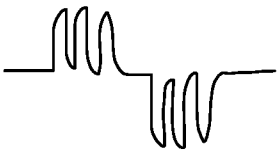


FIG. 1B

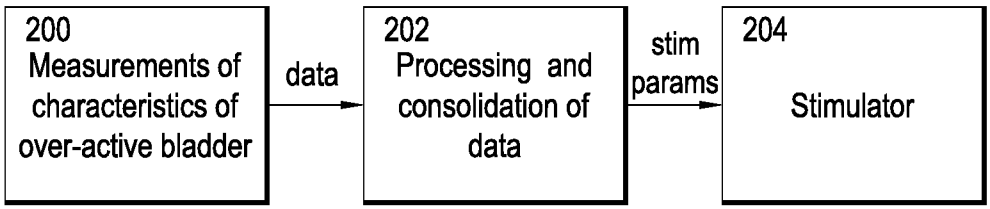


FIG. 2

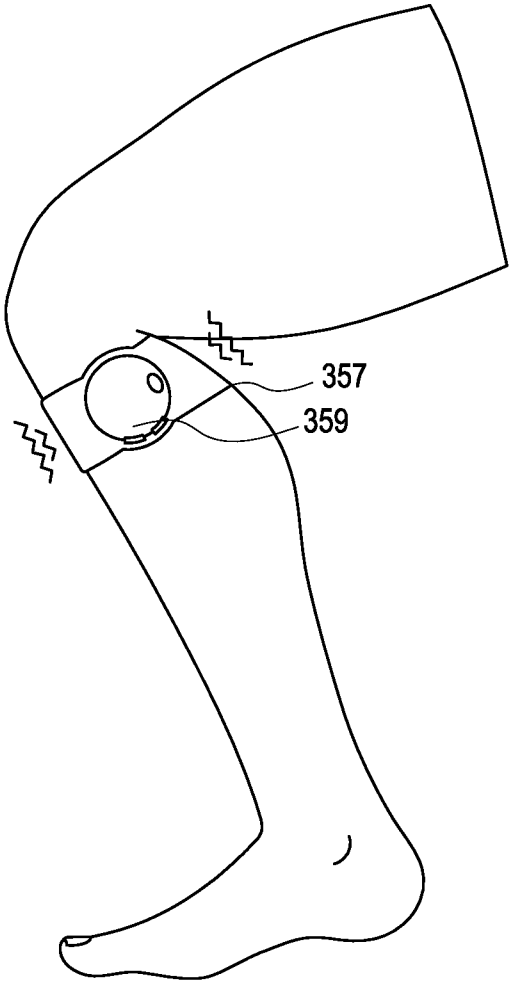


FIG. 3

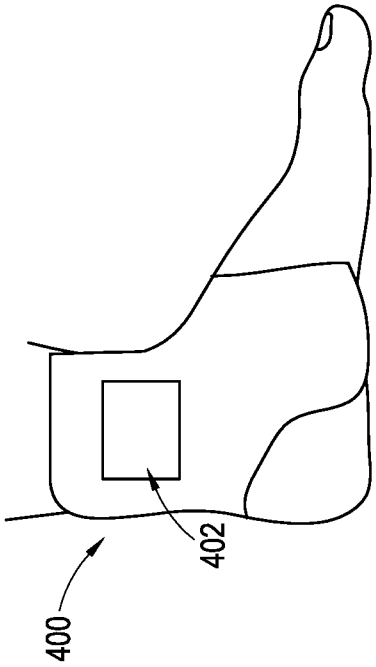


FIG. 4B

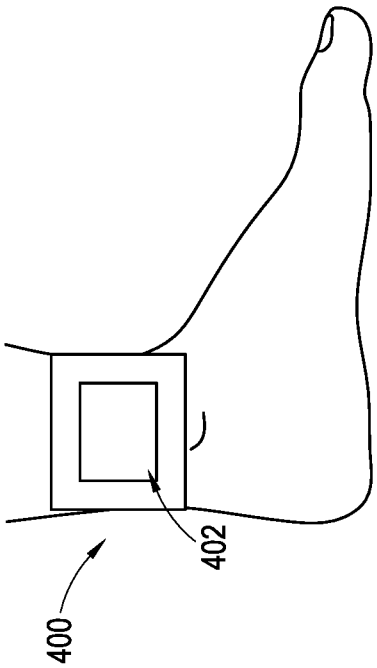


FIG. 4A

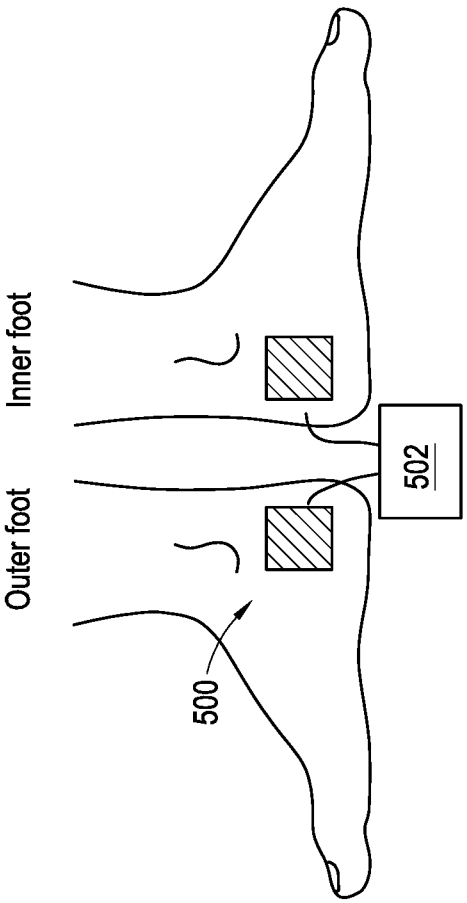


FIG. 5B

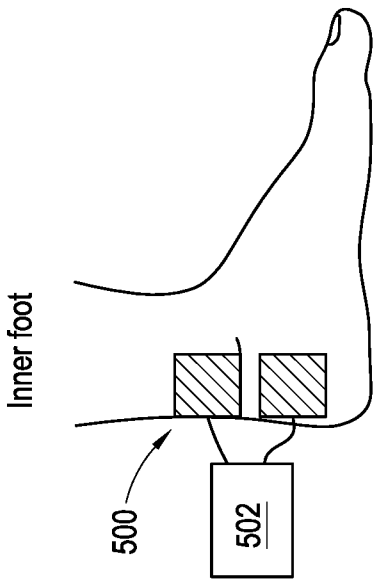


FIG. 5A

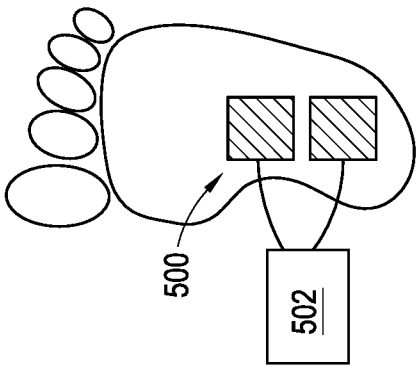


FIG. 5C

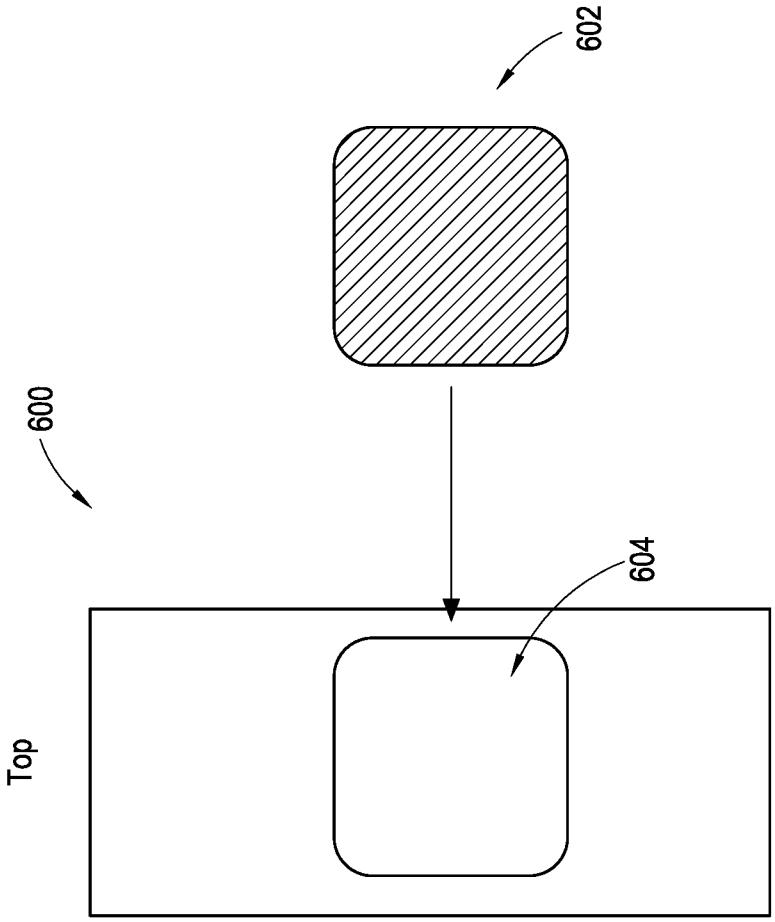


FIG. 7

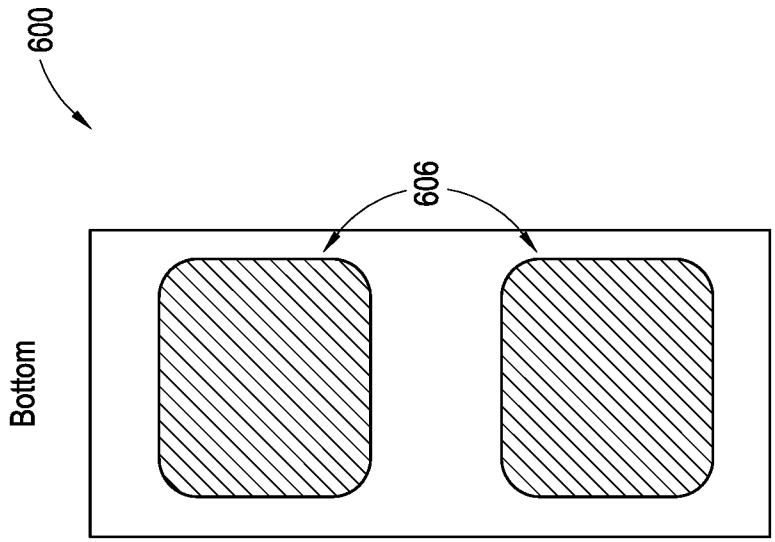


FIG. 6

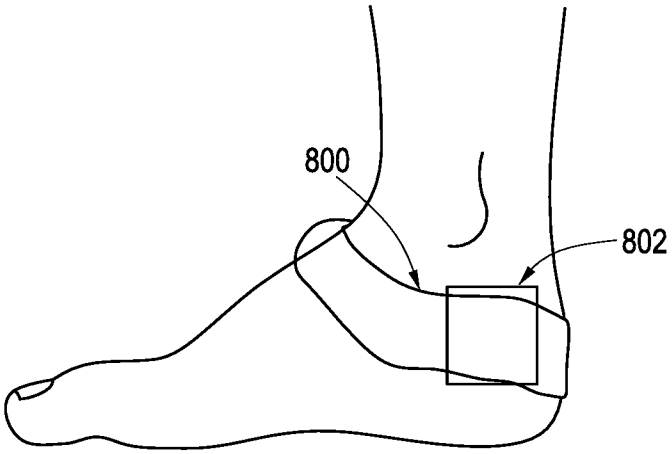


FIG. 8

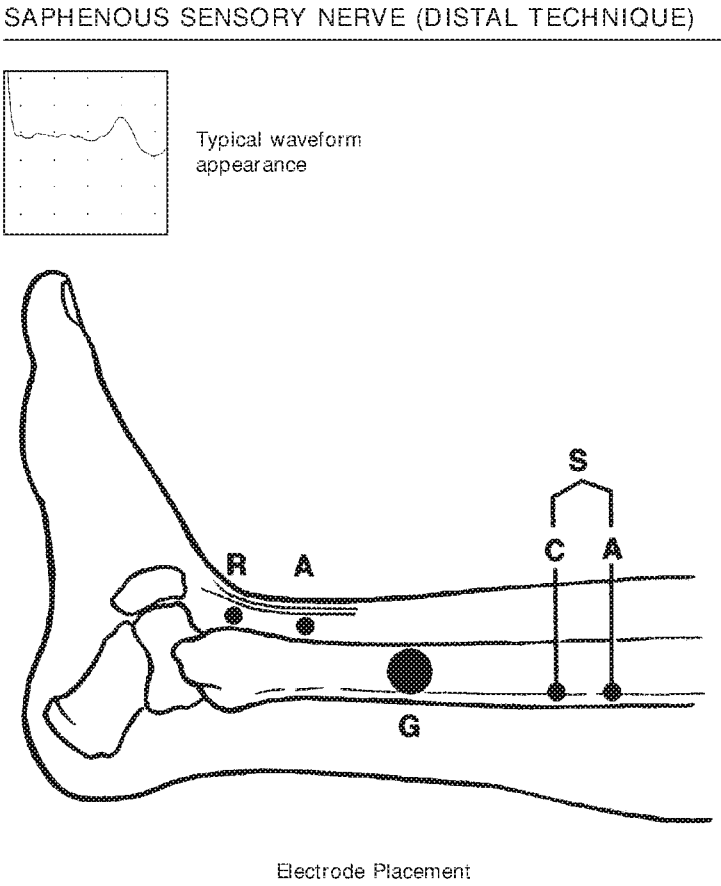

SAPHENOUS SENSORY NERVE (DISTAL TECHNIQUE)
Typical waveform appearance
S
R
A
C
A
G
Electrode Placement

FIG. 9

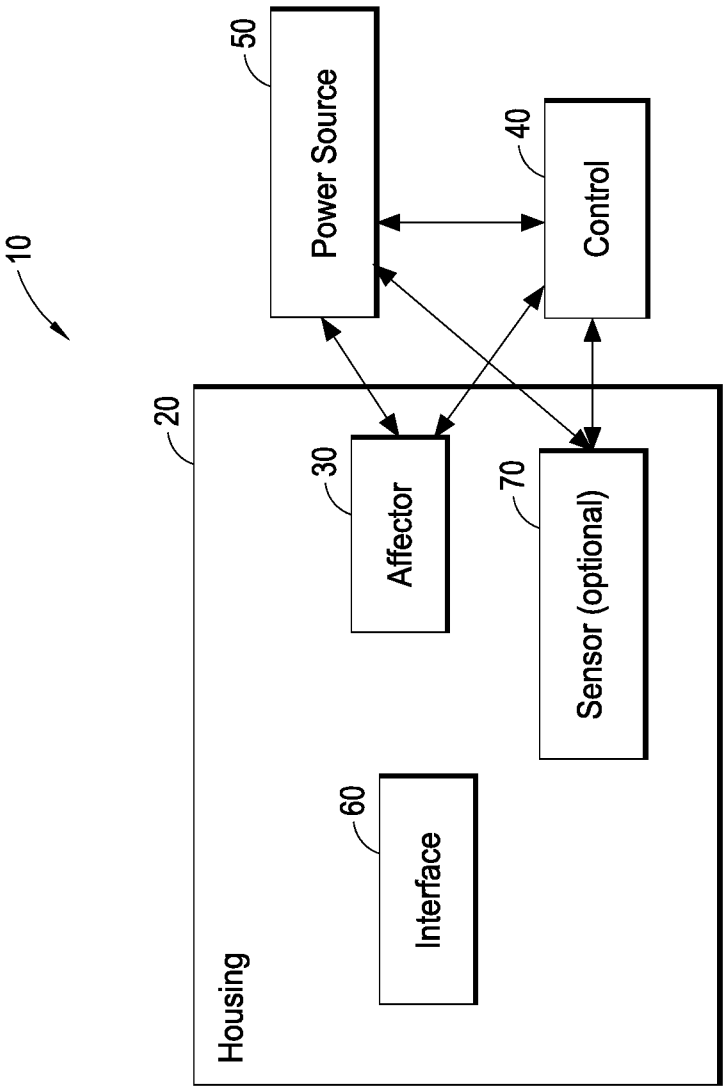

10
20
Housing
30
Affector
40
Control
50
Power Source
60
Interface
70
Sensor (optional)

FIG. 10

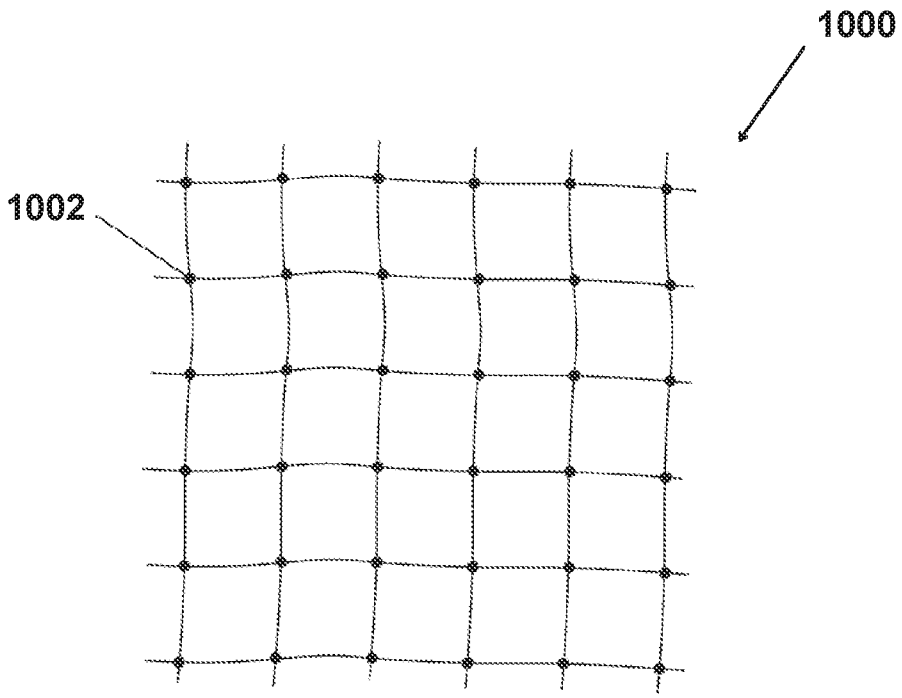


FIG. 10A

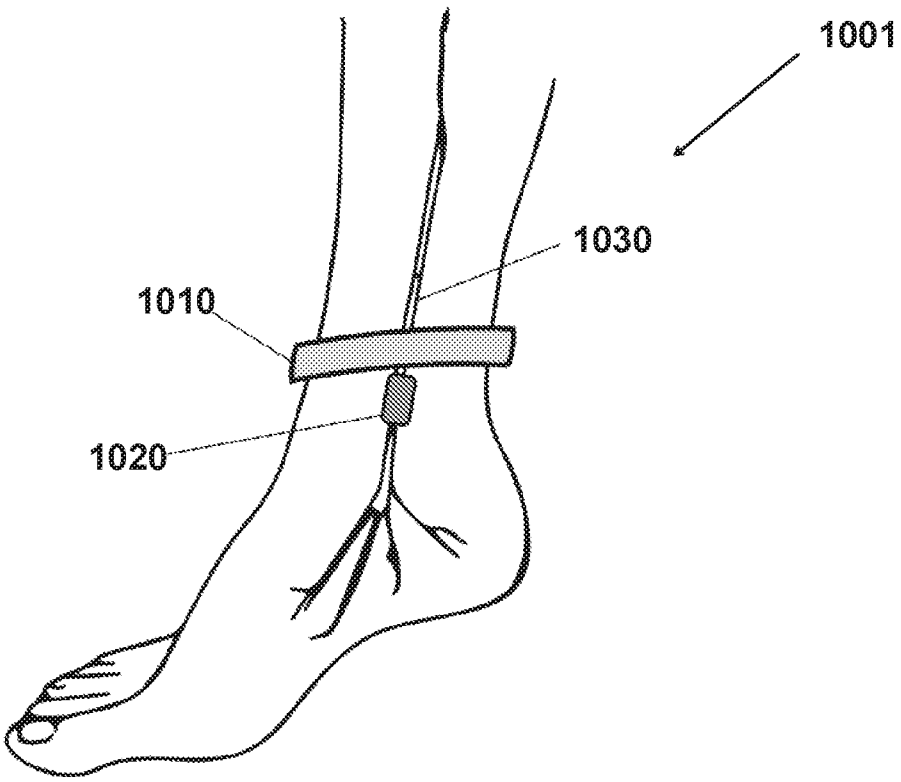


FIG. 10B

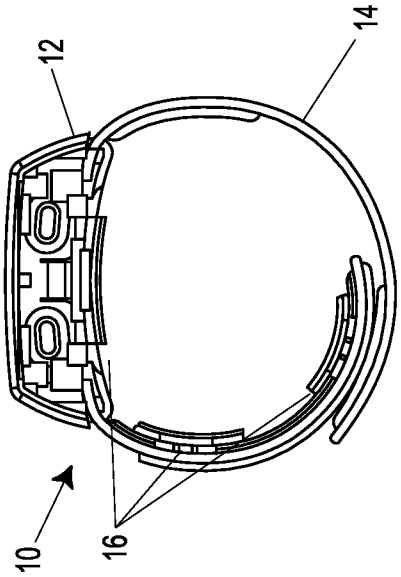


FIG. 11D

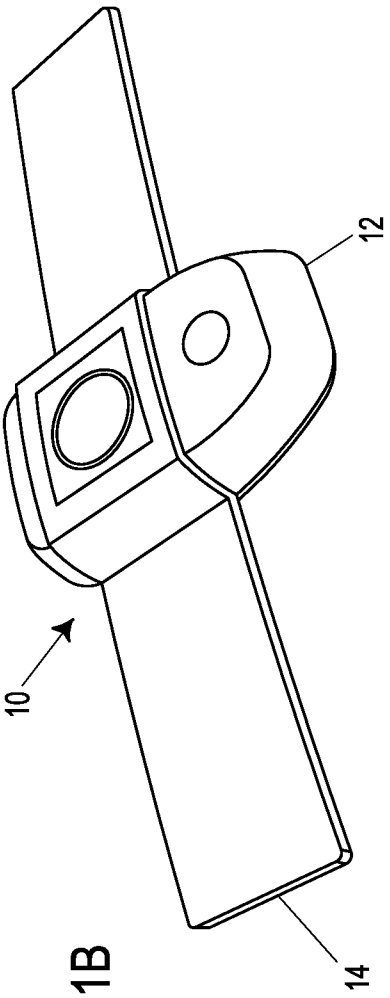


FIG. 11C

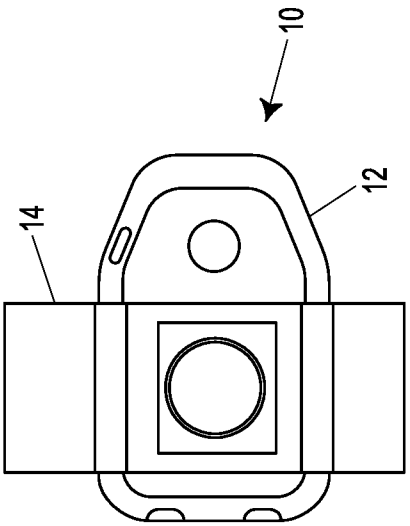


FIG. 11B

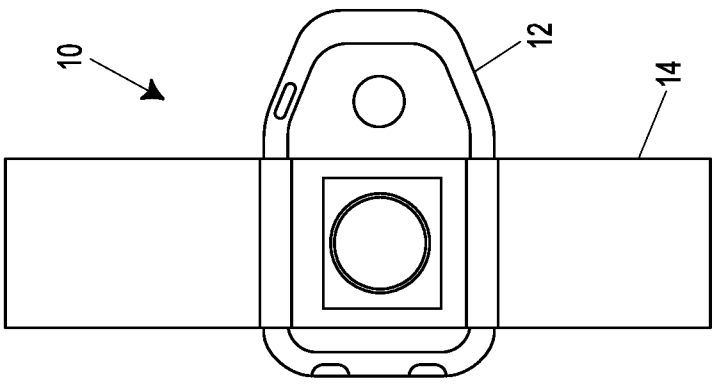


FIG. 11A

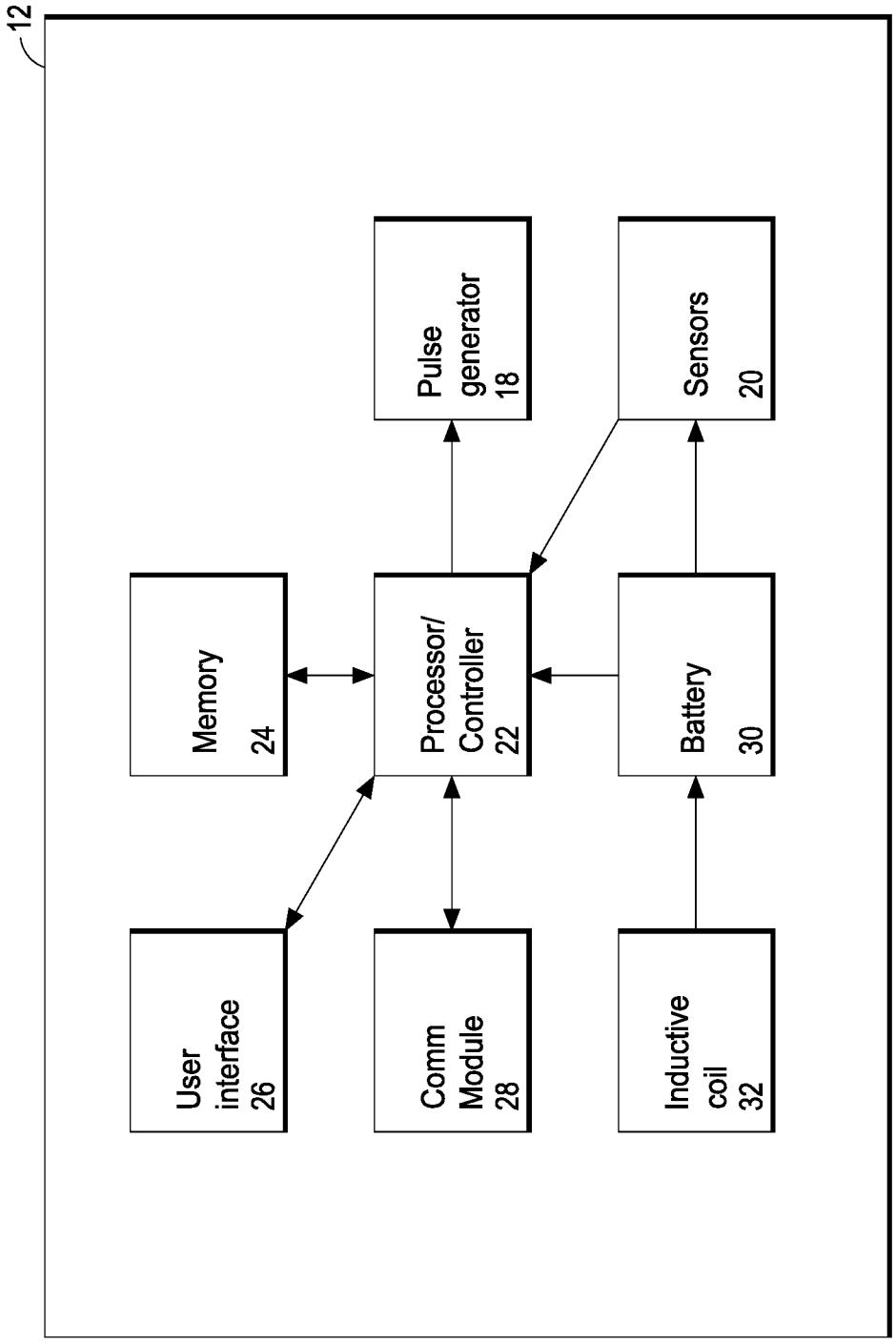

12
Pulse generator 18
Sensors 20
Memory 24
Processor/ Controller 22
Battery 30
User interface 26
Comm Module 28
Inductive coil 32

FIG. 11E

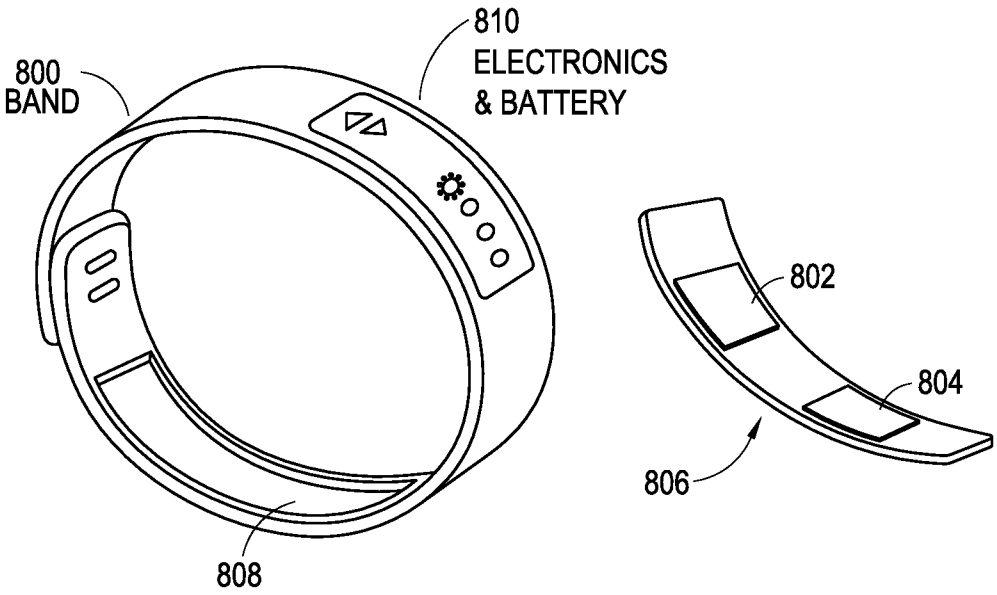

800
BAND
810
ELECTRONICS
& BATTERY
802
804
806
808

FIG. 12

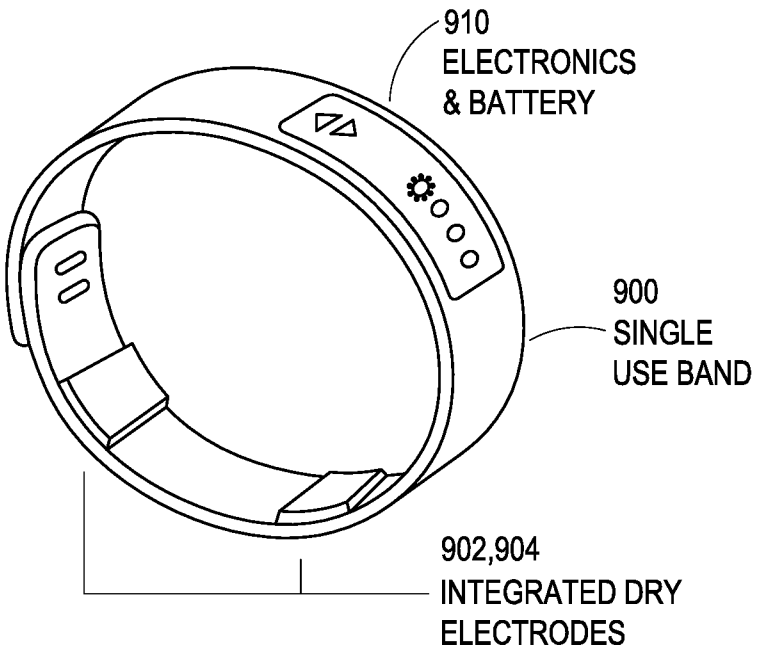

910
ELECTRONICS
& BATTERY
900
SINGLE
USE BAND
902,904
INTEGRATED DRY
ELECTRODES

FIG. 13

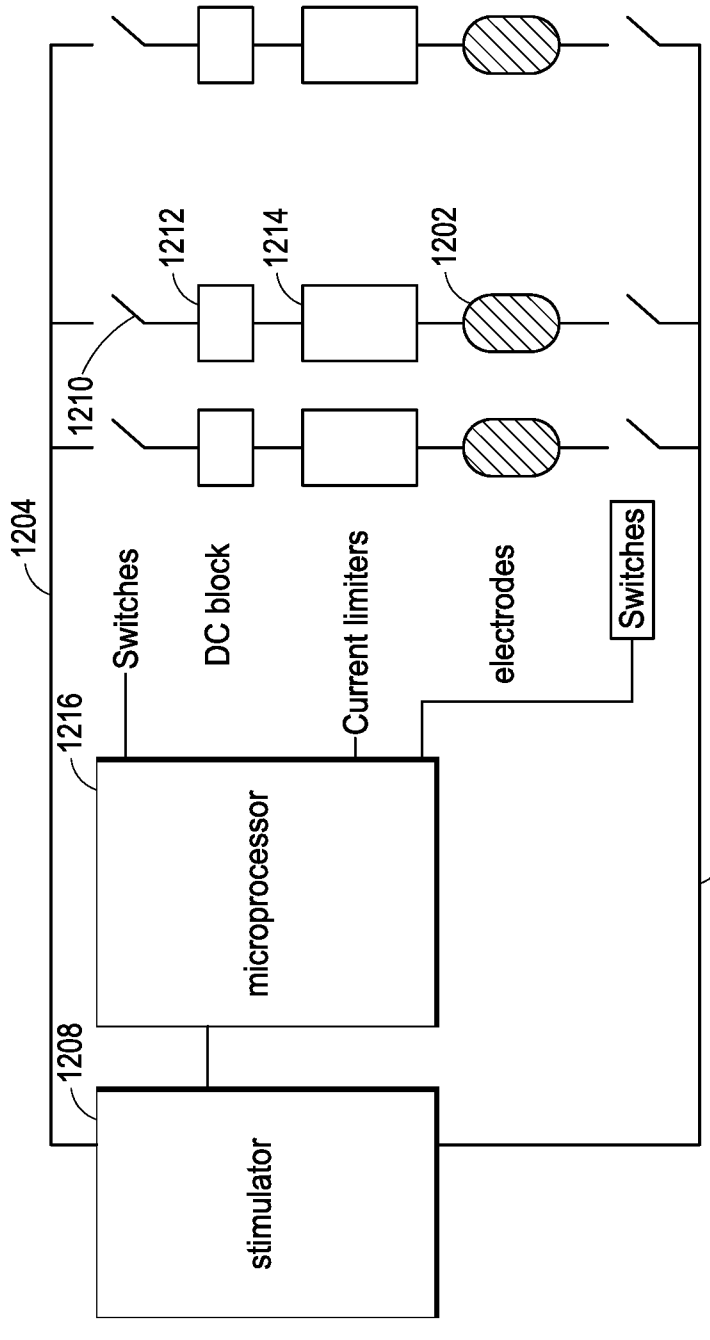

1212
1214
1202
1210
1204
Switches
DC block
Current limiters
electrodes
Switches
1216
microprocessor
1206
1208
stimulator
1200

FIG. 12A

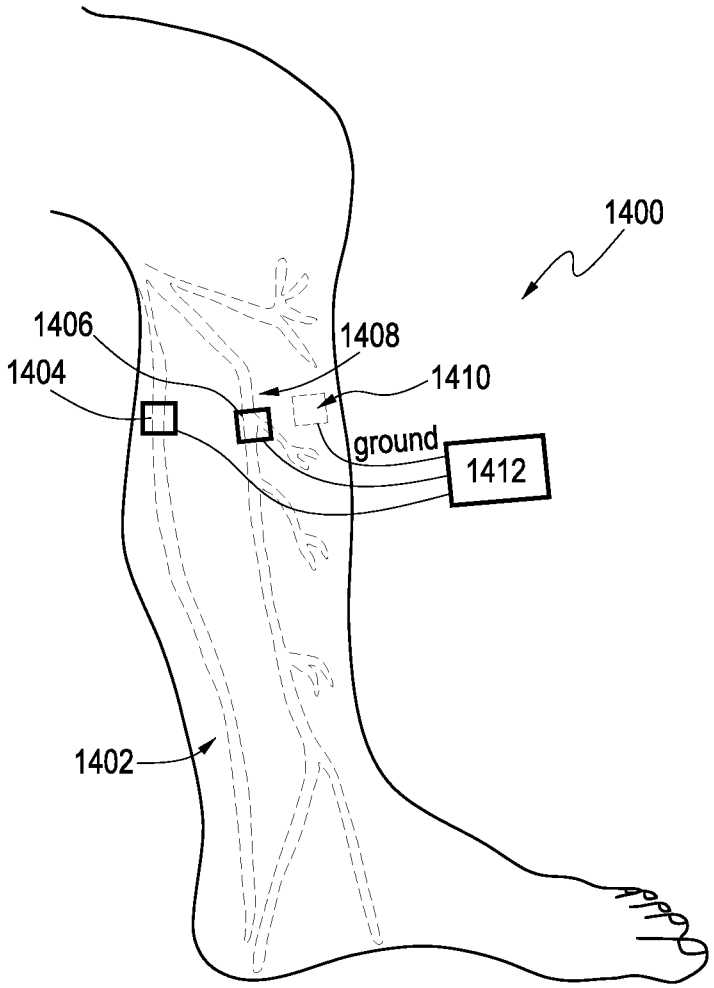


FIG. 14

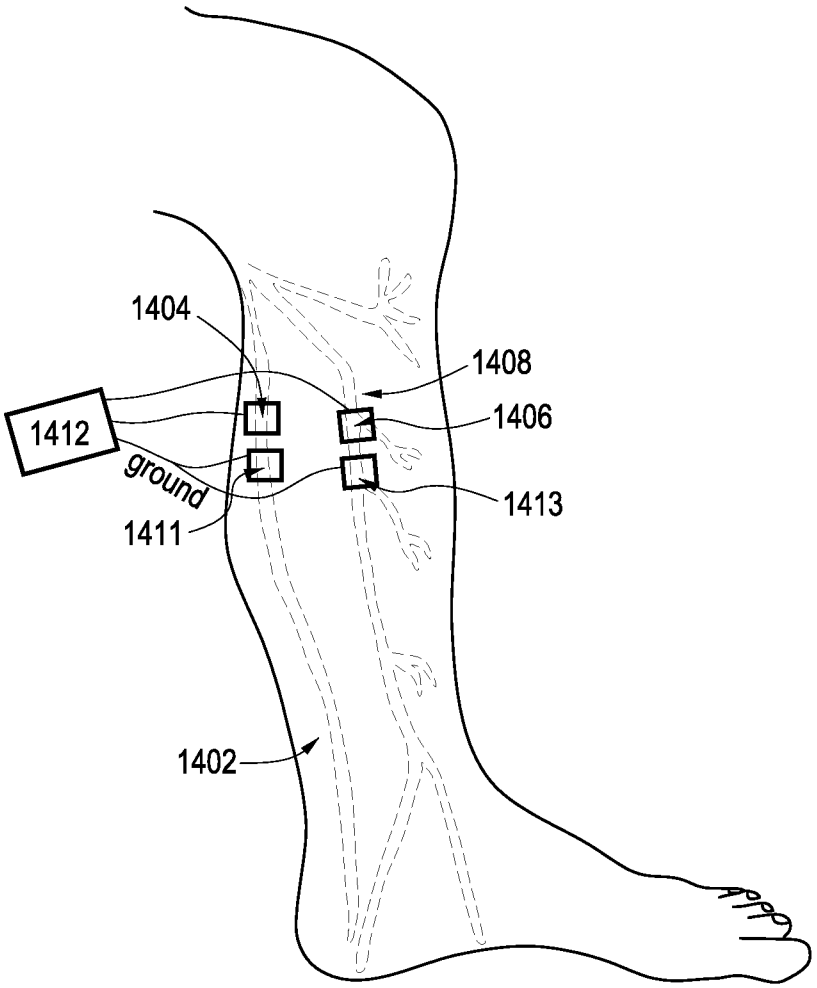


FIG. 15

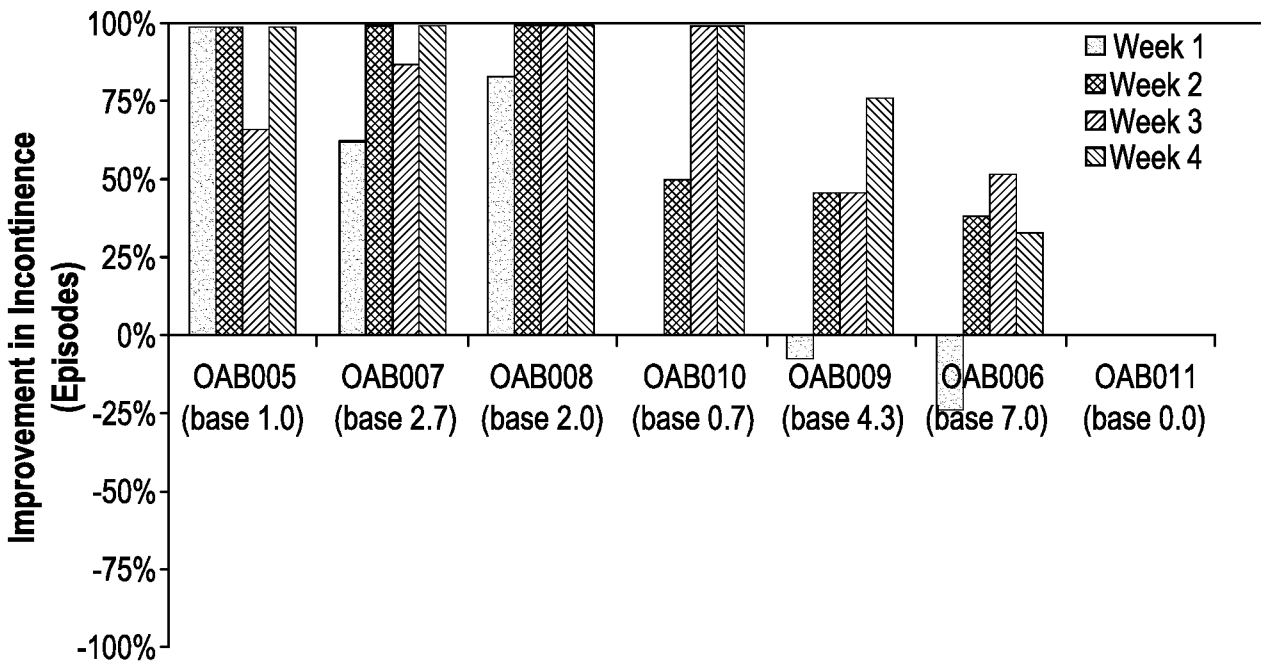

Improvement in Incontinence (Episodes)
100%
75%
50%
25%
0%
-25%
-50%
-75%
-100%
Week 1
Week 2
Week 3
Week 4
OAB005 (base 1.0)
OAB007 (base 2.7)
OAB008 (base 2.0)
OAB010 (base 0.7)
OAB009 (base 4.3)
OAB006 (base 7.0)
OAB011 (base 0.0)

FIG. 16A

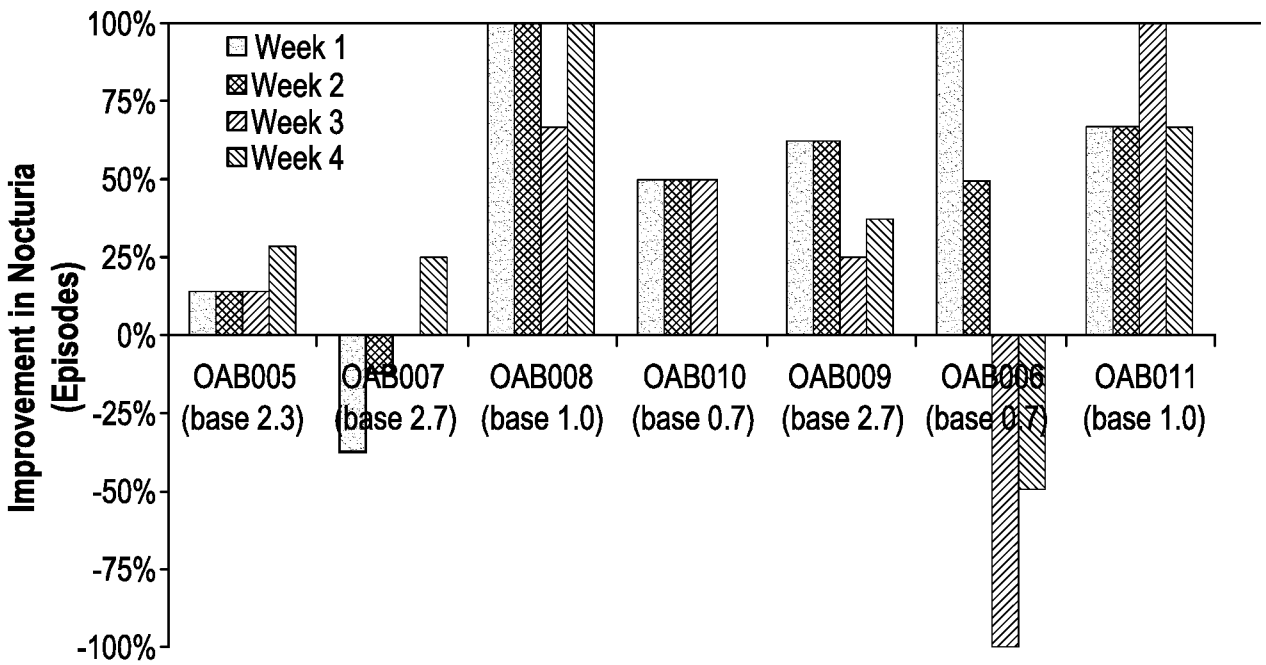

Improvement in Nocturia (Episodes)
100%
75%
50%
25%
0%
-25%
-50%
-75%
-100%
Week 1
Week 2
Week 3
Week 4
OAB005 (base 2.3)
OAB007 (base 2.7)
OAB008 (base 1.0)
OAB010 (base 0.7)
OAB009 (base 2.7)
OAB006 (base 0.7)
OAB011 (base 1.0)

FIG. 16B

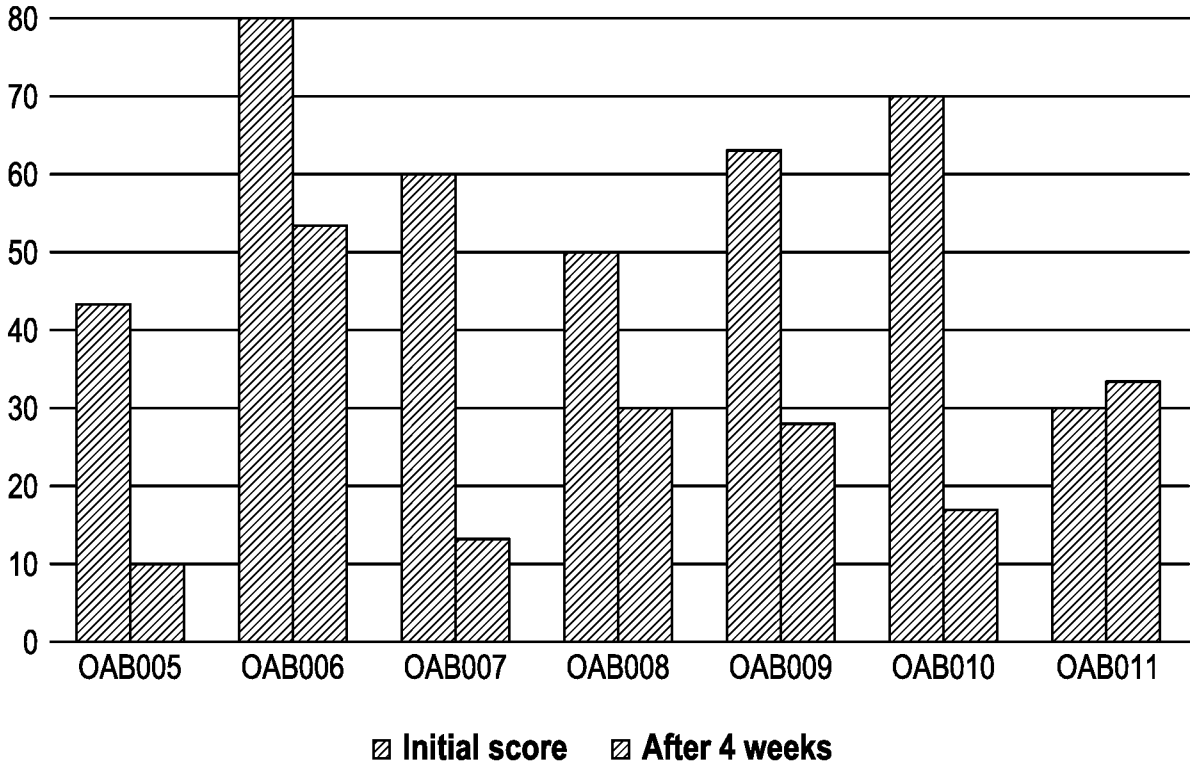

80
70
60
50
40
30
20
10
0
OAB005
OAB006
OAB007
OAB008
OAB009
OAB010
OAB011
Initial score
After 4 weeks

FIG. 16C

Subject baseline parameters

Age (years)	73.5 (±8.4) N = 4
OAB-V8 Score*	21.5 (±7.5)
Frequency (Episodes/24 hours)	11.7 (±0.5)
Incontinence (Episodes/24 hours)	2.4 (±1.0)
Nocturia	2.7 (±2.0)

* OAB-V8 Score > 8 is consistent with overactive bladder

FIG. 17A

Responder rate

	Nocturia	Incontinence	Frequency
Responder rate	4/4 (100%)	2/3 (67%)*	3/4 (75%)

Responder rate: > 30% improvement in symptom parameter; for nocturia and incontinence, improvement was 50% in all subjects seen

* One subject with no urinary incontinence

FIG. 17B

Improvement in Urinary Parameters

	Baseline	Post Stimulation (4 weeks)
Frequency (Episodes/24 hours)	11.7 (±0.5)	8.9 (±2.0)
Incontinence (Episodes/24 hours)	2.4 (±1.0)	1.3 (±0.3)
Nocturia	2.7 (±2.0)	1.4 (±0.4)

FIG. 17C

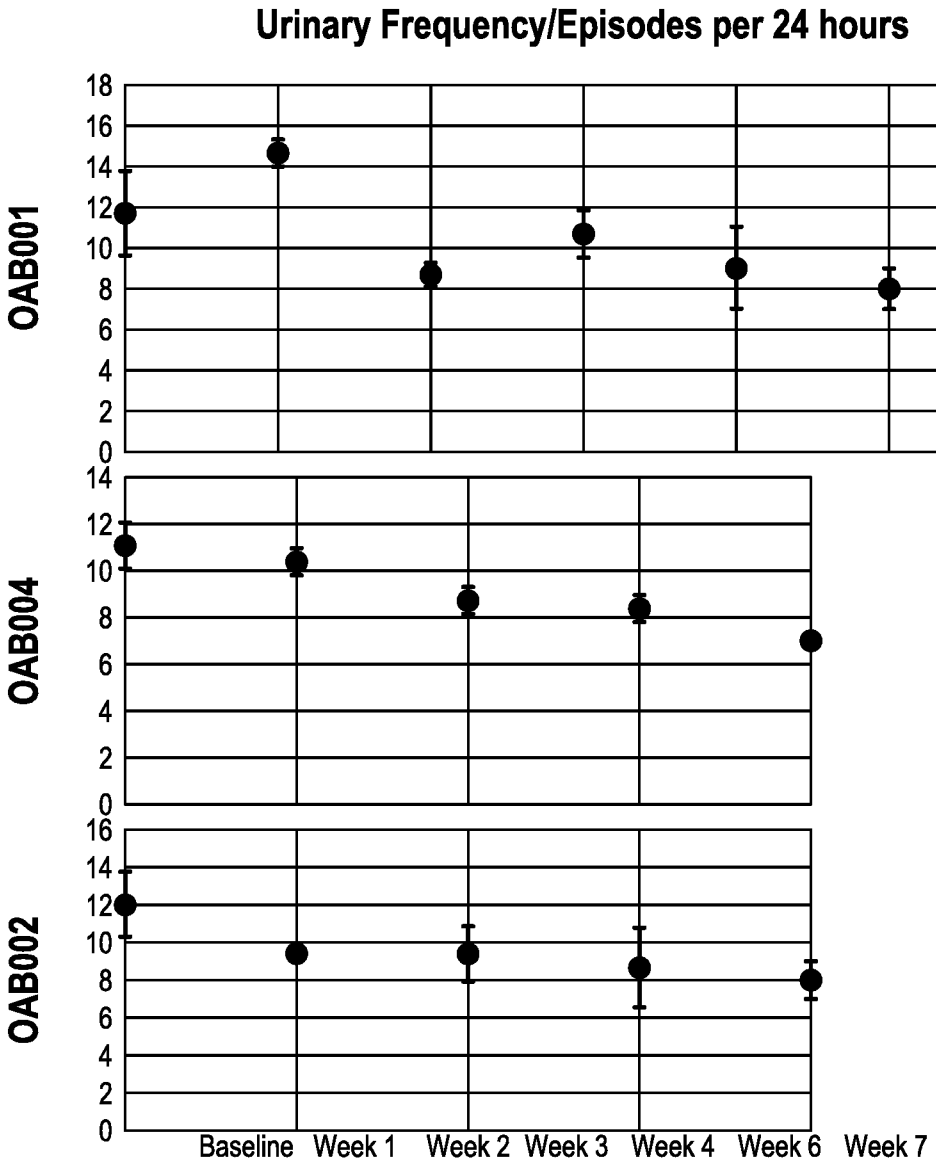


FIG. 17D

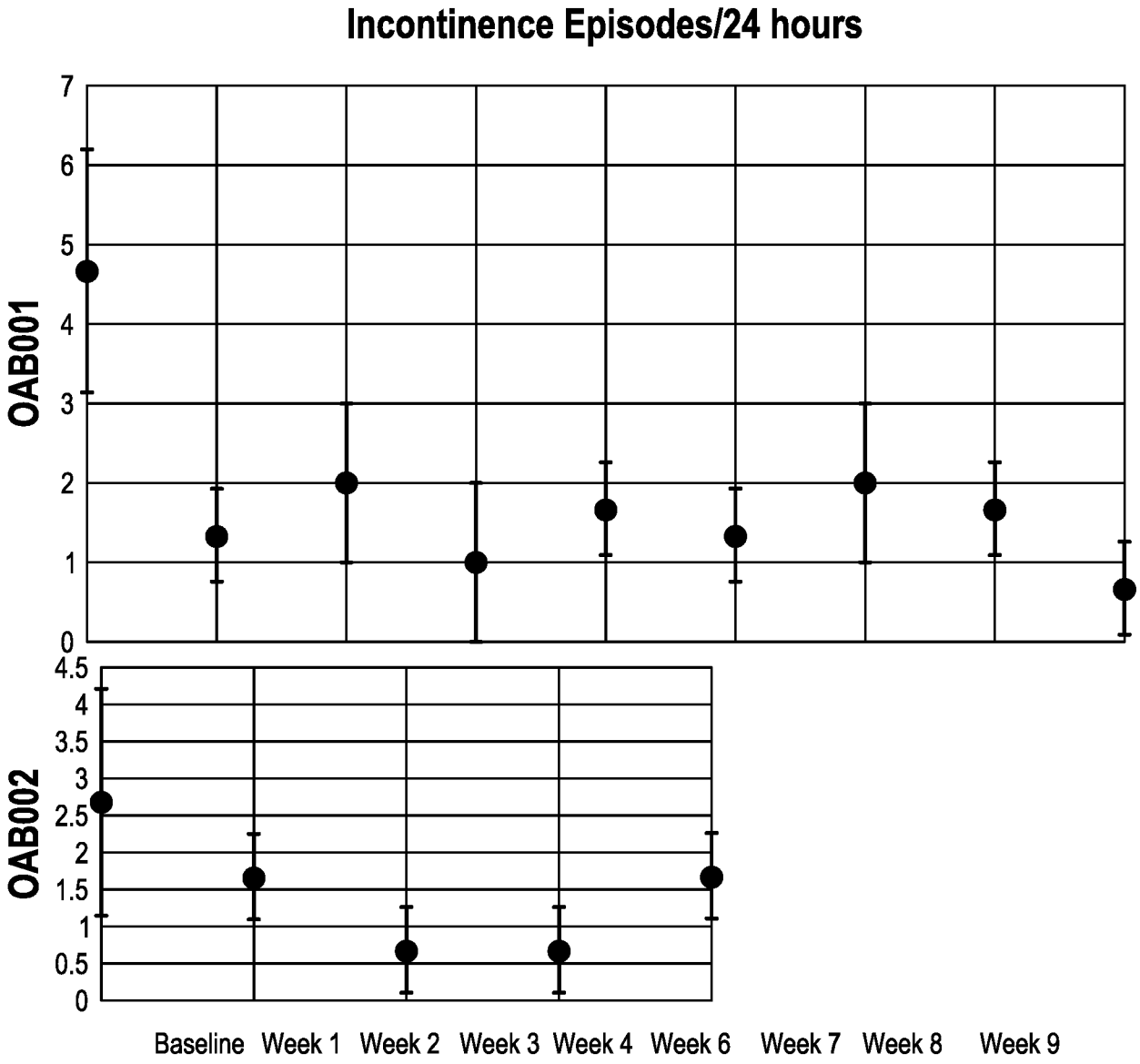

Incontinence Episodes/24 hours
OAB001
7
6
5
4
3
2
1
0
OAB002
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Baseline
Week 1
Week 2
Week 3
Week 4
Week 6
Week 7
Week 8
Week 9

FIG. 17E

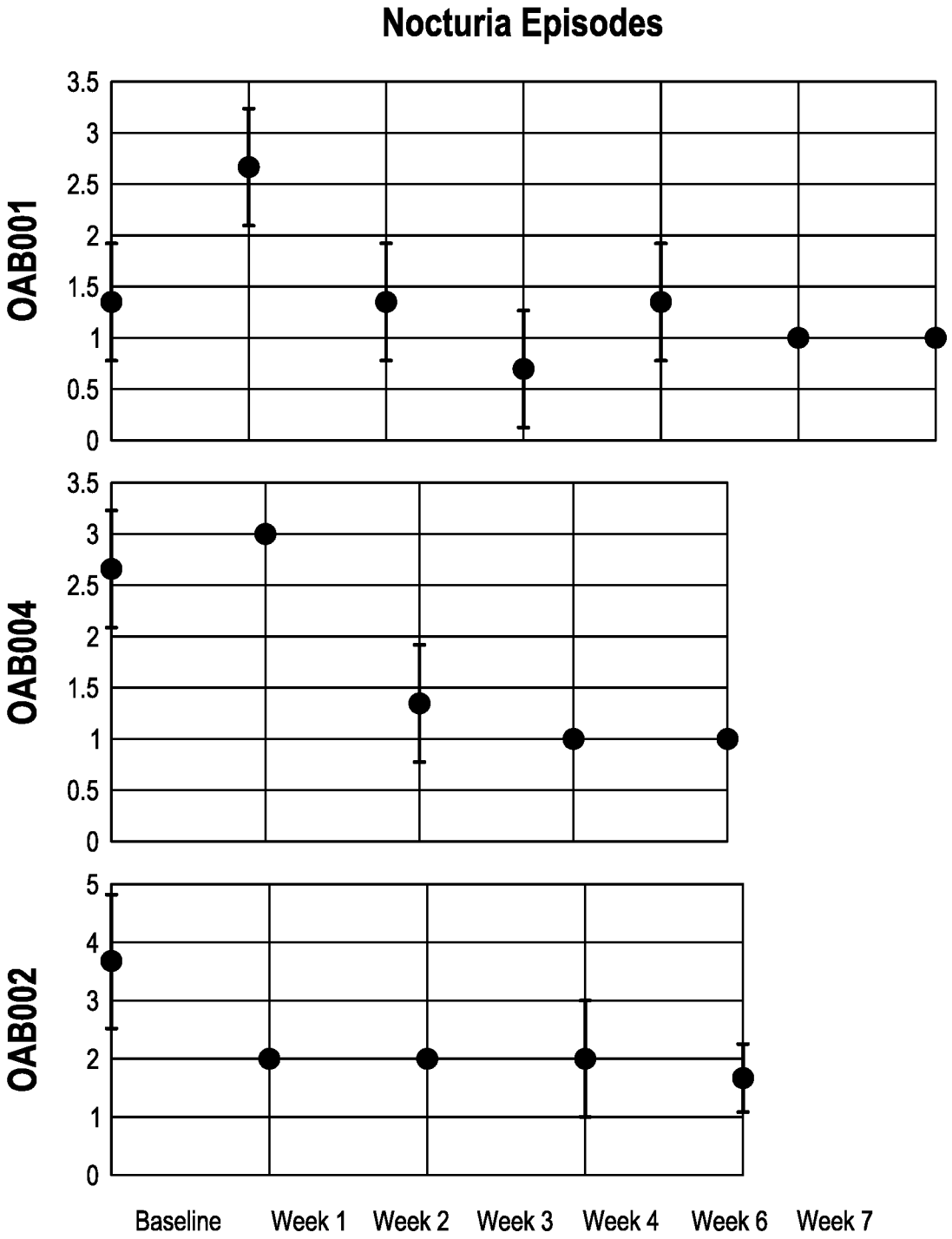
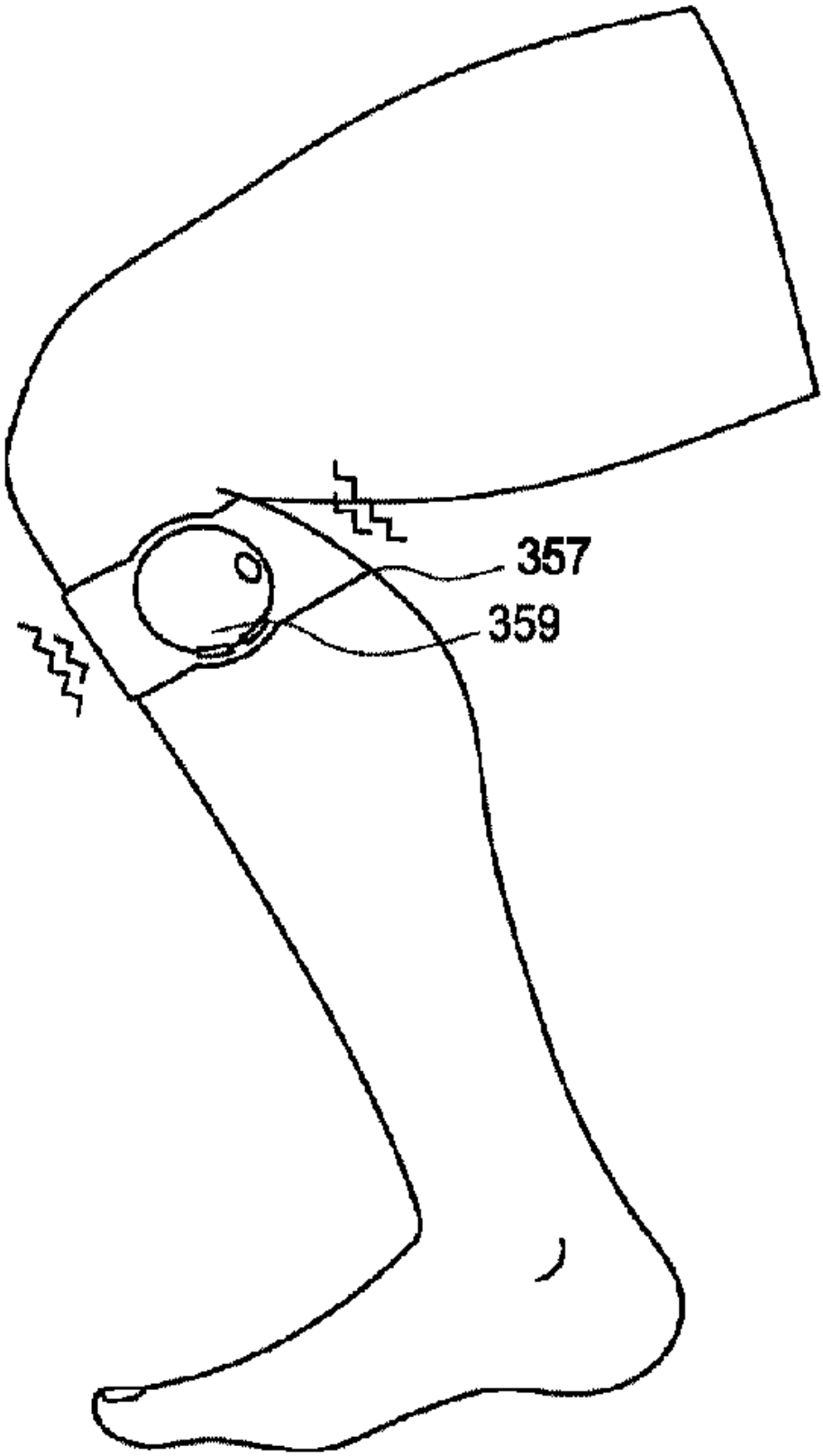

Nocturia Episodes
OAB001
OAB004
OAB002
3.5
3
2.5
2
1.5
1
0.5
0
5
4
Baseline
Week 1
Week 2
Week 3
Week 4
Week 6
Week 7

FIG. 17F


357
359