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(54) Title: DIAGNOSTICS AND TREATMENTS OF ANESTHETIC INSENSITIVE SUBJECTS

(57) Abstract: This invention provides methods for diagnosing and treating human subjects (e.g., pregnant females, subjects with a stress disorder, subjects about to undergo a dermatological procedure, an injection, or a catheterization) who are insensitive to an anesthetic, e.g., lidocaine by first administering the anesthetic, e.g., lidocaine, and determining its effectiveness. Some patients are then further administered a second anesthetic if they are found to be insensitive to the anesthetic, e.g., lidocaine. Other embodiments include treating these patients with an agent that increases potassium serum levels and/or additional therapeutic agents.



DIAGNOSTICS AND TREATMENTS OF ANESTHETIC INSENSITIVE SUBJECTS

BACKGROUND OF THE INVENTION

Lidocaine is a common anesthetic used to numb pain in a patient before a medical procedure.

5 A subset of people is insensitive to lidocaine and therefore require the use of an alternative anesthetic before a medical procedure to ensure comfort and safety. Accordingly, new approaches to identifying these patient populations and accurately diagnosing their sensitivity to lidocaine are needed. Furthermore, some members of these patient populations require treatments to reduce symptoms associated with their conditions. Thus, new methods of treatment are needed.

SUMMARY OF THE INVENTION

10 In one aspect, the invention features a method of determining the effectiveness of an anesthetic (e.g., lidocaine) in a subject by applying an aliquot of a formulation including the anesthetic topically to a location of the subject and determining tactile, taste, or temperature sensation at the
15 location, wherein no reduction in the sensation at the location indicates that the anesthetic is ineffective for the subject. The subject is, for example, a pregnant subject, a subject undergoing a dermatological procedure, an injection (e.g., an injection to a joint, e.g., including a steroid), or a catheterization, or a subject having a stress disorder (e.g., PTSD or ATSD). In some embodiments, the method further includes the steps of applying an aliquot of a second formulation, including a
20 second anesthetic (e.g., benzocaine, articaine, bupivacaine, chloroprocaine, and mepivacaine), topically to a second location of the subject and determining tactile, taste, or temperature sensation at the second location, wherein a reduction in the sensation at the second location indicates that the second anesthetic is effective for the subject. In alternative embodiments, the method includes determining tactile, taste, or temperature sensation at a second location with a control formulation,
25 wherein the control formulation includes no anesthetic, wherein no difference in the sensation between the location with the anesthetic and the second location with the control formulation indicates that the anesthetic is ineffective for the subject. In further embodiments, the method includes the step of administering the anesthetic to the subject if the anesthetic is effective for the subject or administering the second anesthetic (e.g., benzocaine, articaine, bupivacaine, chloroprocaine, and
30 mepivacaine) if the anesthetic is ineffective for the subject.

In some embodiments, the location is in the mouth (e.g., tongue) of the subject. The determining may include applying pressure, a pin prick, or elevated or reduced temperature to the location. In particular, the determining may include applying a temperature probe to the location. The temperature probe may be at least 10 degrees Fahrenheit colder than subject body temperature. The
35 determining may include applying a taste agent to the location. The taste agent may be sweet, sour, salty, or bitter. The determining may include determining the sensation at the location up to two minutes after the anesthetic or control is applied.

In some embodiments, the pregnant subject is in labor, and the anesthetic or the second anesthetic (e.g., chloroprocaine) may be used for pain management during labor. In some
40 embodiments, the dermatological procedure is selected from skin removal, spot removal,

administration of stitches, plastic surgery, and a cosmetic procedure (e.g., botulinum toxin administration, chemical peel, dermabrasion, face lift, or hair transplant). In some embodiments, the catheterization is an intravenous catheterization. For subjects with a stress disorder, the method may further include treating the subject. For subjects undergoing an injection, the method may further
5 include administering a pharmaceutical, e.g., a steroid, by injection.

In another aspect, the invention features a method of treating a subject with a stress disorder, e.g., a subject in whom an anesthetic such as lidocaine is ineffective, by administering potassium or a potassium elevating agent. The potassium may include potassium gluconate or potassium chloride. 90 mg to 5,000 mg of elemental potassium may be administered. The potassium or potassium
10 elevating agent may be administered to the subject in 1 to 30 dosage forms. The potassium or potassium elevating agent may be packaged in a kit. The potassium or potassium elevating agent may be formulated in a pill, tablet, capsule, powder, liquid, or food conveyance. The potassium or potassium elevating agent may be formulated for oral, subdermal, ocular, otic, vaginal, rectal, intravenous, intranasal, or transdermal administration. The potassium or potassium elevating agent
15 may be formulated for extended release.

In some embodiments, the potassium-elevating agent is a renin-angiotensin-aldosterone system antagonist. The renin-angiotensin-aldosterone system antagonist may be selected from the group consisting of an ACE inhibitor, an angiotensin receptor antagonist, an aldosterone antagonist, and a renin inhibitor.

In some embodiments, the ACE inhibitor may be selected from the group consisting of captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril,trandolapril, cilazapril, fosinopril, moexipril, spirapril, alacepril, deparil, temocapril, and teprotide. The angiotensin receptor antagonist may be selected from the group consisting of losartan, candesartan, valsartan, irbesartan, telmisartan, eprosartan, olmesartan, azilsartan, and firmasartan. The
20 aldosterone antagonist may be selected from the group consisting of spironolactone and eplerenone. The renin inhibitor may be aliskiren.

In some embodiments, the treatment further includes administering a second therapeutic agent. The second therapeutic agent may be selected from the group consisting of a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), a serotonin
30 reuptake inhibitor (SRI), a tricyclic antidepressant (TCA), and a monoamine oxidase inhibitor (MAOI).

The SSRI may be selected from the group consisting of sertraline, paroxetine, and fluoxetine. The SNRI may be venlafaxine. The SRI may be nefazodone. The TCA may be imipramine. The MAOI may be phenelzine.

In another aspect, the invention features a kit including an aliquot of a first formulation for
35 topical administration including lidocaine; and an aliquot of a second formulation for topical administration wherein the second formulation includes chloroprocaine, and wherein the first formulation and second formulation are visually distinguishable when applied to a subject. In some embodiments, the aliquot of the first and/or second formulation is disposed in gauze or a swab. The kit may further include a physical barrier configured to adhere topically to the subject. The physical
40 barrier may include an absorbent material. In other embodiments, the kit further includes a probe for

tactile, taste, or temperature sensitivity. In further embodiments, the first formulation and second formulation are visually distinguishable by color, reflectivity, light scattering, opacity, or inclusion of particles.

In another aspect, the invention features a kit including an aliquot of a formulation for topical administration including an anesthetic and an esthesiometer, e.g., one or more von Frey filaments. The esthesiometer, e.g., one or more von Frey filaments, may be sterile. The kit may be used in a method of determining the effectiveness of an anesthetic in a pregnant subject (e.g., a subject in labor) by applying an aliquot of the formulation that includes the anesthetic topically to a location of the subject, and determining tactile sensation at the location with the esthesiometer (e.g., using one or more von Frey filaments). No reduction in the sensation at the location indicates that the anesthetic is ineffective for the subject. The pregnant subject may be about to undergo a Cesarean section, e.g., in an urgent, non-STAT circumstance.

In another aspect, the invention features a kit including an aliquot of a formulation comprising an anesthetic (e.g., lidocaine), an esthesiometer (e.g., one or more von Frey filaments), and a delivery device (e.g., syringe).

In some embodiments, the subject does not have or is not diagnosed with a disorder of attention (e.g., attention deficit disorder (ADD) or attention deficit hyperactive disorder (ADHD)), Asperger Syndrome, pain syndrome, Premenstrual Syndrome (PMS), Sensory Overstimulation Syndrome (SOS), Sensory Processing Disorder, Sensory Integration Disorder, Fibromyalgia, a Hypokalemic Condition, Hypokalemic Periodic Paralysis (HypoPP), or a Lidocaine-Ineffective Condition.

DEFINITIONS

As used herein, the term "about" refers to a value that is within 10% above or below the value being described.

As used herein, the term "aldosterone antagonist" refers to a compound having the ability to counteract the effect of aldosterone, for example, by competitive blockage aldosterone receptors found in renal tubules. Aldosterone antagonists useful in conjunction with the compositions and methods described herein include those known in the art, such as those described in US Patent Application Publication No. 2006/0286105, the disclosure of which is incorporated herein by reference as it pertains to aldosterone antagonists.

As used herein, the term "angiotensin-converting enzyme inhibitor" or "ACE inhibitor" refers to a substance having the ability to inhibit the cleavage of the N-terminal decapeptide angiotensin I to the vasoactive octapeptide angiotensin II. ACE inhibitors useful in conjunction with the compositions and methods described herein include those known in the art, such as those described in, for example, US Patent Nos. 4,046,889 and 4,374,829, the disclosures of each of which are incorporated herein by reference as they pertain to ACE inhibitors.

As used herein, the term "angiotensin receptor antagonist" refers to a compound having the ability to inhibit the vasoactive effects of endogenous angiotensin II by competitive blockade at the angiotensin receptor sites located in vascular smooth muscle and within the adrenal gland.

Angiotensin receptor antagonists include compounds capable of binding the angiotensin receptor as well as those capable of binding angiotensin II to compete with or otherwise preclude interaction between angiotensin II and the angiotensin II receptor. Angiotensin receptor antagonists useful in conjunction with the compositions and methods described herein include those known in the art, such as those described in, for example, US Patent Nos. 4,355,040 and 4,880,804, the disclosures of each of which are incorporated herein by reference as they pertain to angiotensin receptor antagonists.

As used herein, the term "disorder of attention" refers to a condition characterized by inattention, over-activity, and/or impulsiveness. Disorders of attention include, without limitation, Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder, Hyperkinetic Disorder, Sensory Processing Disorder, Sensory Integration Disorder, Sensory Overstimulation Syndrome (SOS), Hypokalemic Sensory Overstimulation and Premenstrual Syndrome (PMS). Attention Deficit Hyperactivity Disorder, which is also referred to in the literature as Attention Deficit Disorder/Hyperactivity Syndrome (ADD/HS), is a condition (or group of conditions) characterized by impulsiveness, distractibility, inappropriate behavior in social situations and hyperactivity. Other disorders, such as Asperger Syndrome, may include a finding of attention deficit and are included in this definition.

As used herein, the term "dermatological procedure" refers to a medical procedure involving the manipulation of the skin of a patient requiring local anesthesia. Exemplary dermatological procedures are skin removal, administration of stitches, spot removal, plastic surgery, and cosmetic procedures (e.g., botulinum toxin administration, chemical peel, dermabrasion, face lift, or hair transplant).

As used herein, the term "food conveyance" is a substance that can be consumed for nutrition. For example, a food conveyance can be a food or beverage.

As used herein, the term "hypokalemia" means low serum potassium, as defined as below 3.5 mEq/L.

As used herein, the term "hypokalemic condition" refers to a condition characterized by or exacerbated by serum potassium falling into the hypokalemic range. A patient with a hypokalemic condition will have potassium serum concentration low during exacerbation of the condition or all the time in certain conditions. Examples of hypokalemic conditions include Bartter syndrome.

As used herein, the term "stress disorder" refers to mental disorders that develop after a person is exposed to a traumatic event (e.g., sexual assault, warfare, traffic collision, or other threat on a person's life). Acute traumatic stress disorder (ATSD) refers to clinically significant dysfunction or distress less than one month after the trauma, while post-traumatic stress disorder (PTSD) refers to clinically significant dysfunction or distress more than one month after the trauma.

As used herein, the term "pharmaceutical composition" means a mixture containing a therapeutic compound to be administered to a subject, such as a mammal, e.g., a human, and a carrier to prevent, treat, or control a particular disease or condition affecting the mammal or to meet the distinctive dietary requirements of the condition.

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms, which are suitable for contact with the tissues of a subject, such

as a mammal (e.g., a human) without excessive toxicity, irritation, allergic response and other problem complications commensurate with a reasonable benefit/risk ratio.

As used herein, the term "potassium elevating agent" refers to a substance that increases the serum concentration of potassium by a mechanism other than direct administration of potassium.

5 Examples are provided herein.

As used herein, the term "Premenstrual Syndrome" or "PMS" refers to a combination of physical and emotional disturbances that occur after a woman ovulates and ends with or shortly after menstruation.

As used herein, the term "renin inhibitor" refers to a substance capable of inhibiting the initial,
10 rate-limiting step in the renin-angiotensin system cascade: renin-mediated proteolytic conversion of angiotensinogen into the N-terminal decapeptide angiotensin I, the penultimate precursor to angiotensin II. Renin inhibitors include compounds that specifically bind renin, such as compounds that bind the proteolytic active site of renin to preclude the binding and subsequent cleavage of angiotensin. Renin inhibitors useful in conjunction with the compositions and methods described
15 herein include those known in the art, such as those described in, for example, US Patent Nos. 4,814,342; 4,855,303; and 4,895,834, the disclosures of each of which are incorporated herein by reference as they pertain to renin inhibitors.

As used herein, the term "Sensory Overstimulation Syndrome" refers to a condition that can present with findings of inattention, pain, cramps, migraines, or Premenstrual Syndrome (in females),
20 as well as being lidocaine insensitive. During episodes of overstimulation, patients will find that small stimuli will produce outsized reactions. For example, sounds will seem louder (and even hostile), clothing will seem intolerably irritating and visual cues will be completely distracting. The syndrome is believed to be the result of a channelopathy affecting the sensory nerves.

As used herein, the terms "subject" and "patient" are interchangeable and refer to an
25 organism that receives treatment for a particular disease or condition as described herein or that is diagnosed as having a disease or condition according to the methods described herein. Such subject or patient can be a mammal, including a human.

As used herein, the term "therapeutically effective" refers to an amount of a therapeutic agent sufficient to result in prevention, delay of onset, and/or amelioration of one or more symptoms of a
30 disease or condition.

As used herein, the terms "treat" or "treatment" refer to therapeutic treatment, in which the object is to alleviation or amelioration of one or more symptoms or conditions; diminishment of extent of disease, disorder, or condition; stabilization (i.e., not worsening) of a state of disease, disorder, or condition; delay or slowing the progress of the disease, disorder, or condition; amelioration or
35 palliation of the disease, disorder, or condition; and remission (whether partial or total), whether detectable or undetectable. In some examples, treating also includes meeting the distinct dietary requirements of a condition.

As used herein, the term "urgent, non-STAT" refers to circumstances with maternal or fetal compromise with no immediate threat to the life of either.

40

DETAILED DESCRIPTION

Lidocaine is a commonly used anesthetic to numb tissues. However, for a subset of people, lidocaine is ineffective. People with relative insensitivity to lidocaine need at least several injections of lidocaine to achieve even partial anesthesia. Patients who are insensitive to lidocaine require a second, different anesthetic for effective numbing. Such patients include, for example, pregnant females and those undergoing a procedure as described herein (e.g., a medical, surgical, or dental procedure, e.g., a dermatological procedure, an injection (e.g., a joint injection, e.g., including a steroid), or a catheterization). The insensitivity to lidocaine may also be used as a diagnostic for certain disorders, such as a stress disorder (e.g., PTSD and ATSD).

Certain patients with a stress disorder (e.g., PTSD and ATSD) that are insensitive to lidocaine may be treated by elevating their potassium levels. These patients may be treated with potassium or a potassium elevating agent, e.g., following a diagnosis of lidocaine insensitivity. The level of potassium in the blood (serum potassium) regulates sensory signaling. Normal ranges of serum potassium in adults are 3.5 – 5.3 mEq/L. While serum potassium levels fluctuate within the normal range throughout the day in everyone, some people have episodes where their serum potassium falls below the normal level. Others have potassium levels that remain within the normal range. However, for many patients who are insensitive to lidocaine, serum potassium is neither chronically low nor outside the normal range of serum potassium levels most of the time. Nonetheless, these patients benefit from increasing their level of serum potassium.

The present invention features methods and kits for determining the ineffectiveness of an anesthetic (e.g., lidocaine) in a subject and, in some instances, further administering the anesthetic (or a different anesthetic) or treating the subject with a potassium agent. Determining ineffectiveness is often difficult because simple, topical administration of an anesthetic (e.g., lidocaine) to a subject may not allow for accurate determination of the effectiveness of the anesthetic. Applying the anesthetic directly without a double-blind technique creates the risk of the user influencing the outcome, as the determination requires patient-reported outcomes.

Another complication is that individuals, especially children, may not have experience with anesthesia and be unable to describe when an area is numb; this lack of familiarity with numbness is complicated when the administration is performed topically as the areas underlying and surrounding the site of administration are still capable of feeling. Numbness, (e.g., from lidocaine), is also time delayed in some individuals, and lack of numbness immediately after administration may not be indicative of true ineffectiveness. Finally, numbness from anesthetics, (e.g., lidocaine), may also present differently in individuals, (e.g., pins and needles or puffiness versus no sensation), making a true determination of ineffectiveness difficult.

The present invention includes approaches that solve these problems by testing sensation (e.g., tactile, taste, or temperature sensitivity) in a double-blind way against the two sides of the tongue, the area found to be most reliable. Thus, some devices, kits, and methods employ a refrigerated kit with one aliquot of a first formulation including an anesthetic and a second formulation not including an anesthetic for comparison of feeling of cold when two cold thermally conductive

pieces are applied, where no difference in the sensation of cold would indicate the ineffectiveness of the anesthetic.

These devices and kits can generally be used to determine the effectiveness of a particular anesthetic prior to a procedure as described herein. In addition, the lack of effectiveness of certain anesthetics (e.g., lidocaine) is diagnostic for certain stress disorders. These stress disorders are described herein and can be further treated with potassium treatments and/or additional therapeutic agents. Potassium therapies often require high and frequent dosages. Thus, in some embodiments, potassium treatments may be formulated in a kit to ensure patient compliance and a regular treatment regimen.

Methods of Diagnosis and Anesthetic Treatment

The diagnostic compositions, kits, and methods described herein may be used on any patient with or without a lidocaine insensitivity. In some embodiments, the patient to be treated includes, for example, a pregnant female (e.g., a pregnant female in labor, e.g., a female about to undergo a Cesarean section delivery, e.g., in an urgent, non-STAT circumstance), a subject with a stress disorder such as PTSD or ATSD, or a patient about to undergo a dermatological procedure, an injection (e.g., a joint injection, e.g., including a steroid), or a catheterization. Any of these patients may or may not have a lidocaine insensitivity but would still benefit from establishing whether they are sensitive to lidocaine.

In some embodiments, the dermatological procedure is, for example, skin removal, spot removal, administration of stitches, plastic surgery, or a cosmetic procedure. The cosmetic procedure may be, for example, botulinum toxin administration, chemical peel, dermabrasion, face lift, or hair transplant.

To assess whether a patient has a lidocaine insensitivity using the devices and kits described herein, one of skill in the art can determine whether the patient is sensitive to lidocaine anesthesia, as described in PCT Publication No. WO2017/035470, the disclosure of which is hereby incorporated by reference in its entirety.

Devices and Kits

The devices and kits of the invention may include several components:

1. Determination of effectiveness by use of a second formulation, which can be a reference anesthetic that is assumed to be effective, (e.g., benzocaine, articaine, bupivacaine, chloroprocaine, or mepivacaine) or a control such as the base un-medicated gel for lidocaine that is assumed to be ineffective;
2. Visual indication of the formulations so that adequate coverage can be determined reliably;
3. Applicators and application technique can include either an integrated applicator that separates the two formulations or two independent applicators and various procedures to ensure effective application;
4. Metrics of effectiveness, include tactile sensations, such as numbness, temperature sensitivity, or taste sensitivity; or

5. Double-blind mechanism for determining the effectiveness, thus increasing the confidence in a test requiring patient reported outcomes.

The kit or device may be used to ascertain whether a particular anesthetic (e.g., lidocaine) will work for a given patient (e.g., a pregnant female, or a patient undergoing a dermatological procedure, injection (e.g., a joint injection, e.g., including a steroid), or a catheterization). It can also be used to diagnose a type of stress disorder, such as PTSD or ATSD.

The diagnostic compositions, kits, and methods described herein may further include an esthesiometer, a device for measuring the tactile sensitivity of the skin. One type of esthesiometer is a von Frey filament. Von Frey filaments are elastic columns that will buckle elastically at a predetermined force when under compression. This force is dependent on the length, diameter, and modulus of the material within the filament. Once the filament buckles, the force imparted by the column is constant, regardless of the degree of buckling. The filaments are used to provide a range of forces to the skin of a test subject (e.g., a pregnant female) to determine the force at which the subject senses tactile stimulation, e.g., pain (e.g., at a specific location on the skin, such as the surgical area). A kit may include one or more filaments, all with approximately the same length, but of various diameters so as to provide a range of forces (e.g., from 0.008 grams force up to 300 grams force).

A kit may include, for example, any of the components described above in addition to the esthesiometer, e.g., one or more von Frey filaments. The one or more von Frey filaments may be used to determine effectiveness of an anesthetic (e.g., lidocaine or a second, different anesthetic such as chloroprocaine). The kit may also include, for example, an injectable anesthetic (e.g., lidocaine) and a syringe. A pregnant female who is in labor may require a cesarean section (C-section). C-sections are generally categorized as urgent (e.g., STAT or non-STAT) or non-urgent. In the case of an urgent non-STAT C-section, timely retrieval of the baby is critical. However, a medical provider may have time to test the effectiveness of an anesthetic (e.g., with one or more von Frey filaments) and administer a local rather than general anesthetic to the subject in order to numb the area prior to the C-section. An esthesiometer, e.g., one or more von Frey filaments, can be used to test effectiveness of the anesthetic. If the von Frey filaments do not induce tactile sensation, e.g., pain, after administration of the anesthetic (e.g., as compared to a reference anesthetic or no anesthetic), it may be determined that the subject is sensitive to the anesthetic. However, if the von Frey filaments do induce tactile sensation, e.g., pain, after application of the anesthetic, then the subject is insensitive to the anesthetic and an alternative anesthetic may be required. As a C-section is a medical procedure, it may be desirable to use sterile von Frey filaments not to contaminate the surgical area.

Determination of Effectiveness

In a reference model embodiment, it is typically known that one of the anesthetics is effective for the subject and is used as reference for a positive response to compare to the other anesthetic being tested for effectiveness. Suitable first anesthetics include lidocaine, benzocaine, articaine, bupivacaine, butamben, dibucaine, mepivacaine, oxybuprocaine, pramoxine, procaine, proparacaine,

proxymetacaine, chloroprocaine, or tetracaine, and suitable second anesthetics include benzocaine, articaine, bupivacaine, butamben, dibucaine, mepivacaine, oxybuprocaine, pramoxine, procaine, proparacaine, proxymetacaine, chloroprocaine, or tetracaine. Preferably, the anesthetic being tested for effectiveness is lidocaine. Preferably, the anesthetics will be formulated for oral administration.

- 5 The reference anesthetic is preferably benzocaine, articaine, bupivacaine, or mepivacaine. In the reference model, a difference in tactile, temperature, or taste sensitivity indicates that the first anesthetic is ineffective for the subject.

In a control model embodiment, the second formulation does not include an anesthetic, e.g., a control base without the medication. The control model has the advantage of not needing to know if other anesthetics are normally effective for the patient, when testing the first anesthetic, while at the same time preserving the double-blind nature of the test, e.g., by having both formulations have the same feel in the mouth. Here too, preferably the anesthetics will be formulated for oral administration. In the control model, no difference in tactile, temperature, or taste sensitivity indicates that the first anesthetic is ineffective for the subject.

- 10 In some embodiments, the first anesthetic being tested is lidocaine, and if the patient is found to be insensitive to lidocaine, a second anesthetic (e.g., chloroprocaine) is used. If the patient is found to be sensitive to lidocaine, then it can be administered. This embodiment may be used for a pregnant female, a subject undergoing a dermatological procedure, a steroid injection, or catheterization (e.g., intravenous catheterization), or a subject with a stress disorder (e.g., PTSD or ATSD).

Visual Indication of the Formulations

The user may need a mechanism to ensure adequate coverage of both formulations, which is achieved by providing a visual indicator in each formulation. Suitable visual indicators include color, reflectivity, light scattering, opacity, or inclusion of particles (e.g., colored or reflective beads or flakes). To mitigate the risk that the indicator, e.g., color, is associated in the mind of the tester with an outcome and that the tester influences the subject's response, the indicator, e.g., color, of first anesthetic, (e.g., lidocaine), may alternate between indicator, e.g., color, 1 and indicator, e.g., color, 2. A box of kits, as ordered by a medical professional may contain a random mix of kits where the first anesthetic has indicator, e.g., color, 1 and where the first anesthetic has indicator, e.g., color 2.

Applicators and Application Techniques

Devices of the invention will preferably be inserted into the mouth of the subject as this generates the most reliable results, and are preferably configured for use on each side of the tongue for the same reason. Devices may, however, be configured for use on the area from the lip to the gum or cheek. Devices of the invention include integrated applicators containing both formulations, and independent applicators each containing one of the formulations. In the embodiment of the integrated applicator, the aliquots of the first formulation and second formulations, e.g., either containing a second anesthetic or control un-medicated gel for the first anesthetic, are placed on the body of a device. The formulations are spaced apart on the body of the device to prevent mixing when applied

to the subject and to allow sufficient spatial separation for the subject to discern a difference in tactile, temperature, or taste sensitivity. The spacing between the two formulations is typically either side of the tongue, although in some embodiments it could be under the upper lip on either side of buccal fold. Bodies may be formed of any suitable material, such as wood, metal, heavy paper or plastic.

- 5 Devices may also include a barrier that may or may not be absorbent between the two formulations. Such barriers may aid in preventing the formulations from mixing during administration.

In another embodiment, the integrated device is a flexible strip where the two formulations are placed on the same face of the strip. The device may be a thin strip, sized to fit comfortably between the gum and lip, (e.g., upper lip), where the two formulations are spaced apart on the strip. The strip
10 may include a cutout to accommodate the buccal frenulum and/or a physical barrier to reduce possible mixing of the two formulations. In another embodiment, the body of the device includes a handle and an application region, (e.g., with a Y- or T-shape). Typically, the formulations are placed on the same face of the body, but can be placed on opposite faces or on both faces. Formulations may also be placed on the tip ends of a Y- or U- shaped body. The integrated applicator may also be
15 covered with a protective film that can be removed prior to use.

In an independent applicator embodiment, the two formulations are provided on physically separate applications, e.g., a swab or gauze pad. The independent applicators and their formulations may also be covered with a protective film that can be removed prior to use.

A formulation may be placed directly on a non-absorbent portion of the body if appropriately
20 formulated as a gel, ointment, or cream. Alternatively, formulations may be absorbed into an absorbent portion of the body, (e.g., if formulated as a liquid).

Formulations in kits may be disposed in any suitable container. Examples include cotton swabs, cotton balls, gauze pads, bandages, wooden sticks, vials, squeeze tubes, capsules, and syringes. Kits may also include a barrier that will adhere to the tissue being treated. Suitable barriers
25 include gauze, cotton, and plastics. Such barriers may be adhered to skin or oral mucosa using known temporary adhesives. Absorbent materials, (e.g., gauze), may also naturally adhere to oral mucosa without use of an adhesive.

Various topical formulations and dosages of anesthetics are known in the art. The invention will employ a formulation suitable for the location of administration and a dosage sufficient to induce
30 loss of tactile, temperature, or taste sensation in a sensitive subject. For example, using a reference model, lidocaine may be administered as an ointment at 1-10%, (e.g., 5%), and benzocaine may be administered as a gel at 10-30 %, (e.g., 20%), or using a control model, lidocaine may be administered as an ointment at 1-10%, (e.g., 5%), and a control of the base for the lidocaine without the anesthetic.

35 When administered orally, the area of application may first be dried, (e.g., by blotting or spraying with air), prior to administering the anesthetics.

Probes for tactile, temperature, or taste sensitivity may also be provided with devices or kits of the invention. One probe may be used for each location, but separate probes are preferable. Alternatively, an integrated probe with two prongs spaced for each location may be employed.
40 Appropriate materials for tactile sensitivity are known in the art, e.g., wood, metal, and plastic. For

temperature sensitivity, the probe may be a thermally conductive material, e.g., metal, that is heated or cooled to the desired temperature. Typically, such probes are heated or cooled to the desired temperature, e.g., in a refrigerator, freezer, oven, or water bath. Alternatively, probes may be heated or cooled thermoelectrically, by chemical reaction, or by liquids circulating in the probe. Heated probes may also include a resistive heating element. The probes may also expel heated or cooled gas or liquid (e.g., air or water), or the probes may include an edible solid material that produces a warm or cold feeling upon dissolution in the mouth. The temperature of the probes is typically at least 10 degrees Fahrenheit warmer or colder than the body temperature of the subject. Probes for taste will typically be made of an inedible material, such as wood, paper, plastic, or metal. The probes will include a taste agent, e.g., in liquid, gel, or dissolvable form, that produces a sweet, sour, salty, or bitter taste.

Metrics of Effectiveness

Any differences in sensitivity can then be determined by the subject. For example, the subject can describe any difference in feeling of cold, heat, taste, numbness, puffiness, or pins and needles between the two locations. Under some circumstances, the two locations may also be probed, (e.g., by a blunt probe, pin, or heated or cooled probe), to aid in determining difference in sensation in the two areas. The subject can also indicate the sensation using a numerical scale, such as on a visual analog scale as modified for the tactile, temperature, or taste being employed as the metric. Determining the effectiveness occurs after administration of the two formulations, e.g., up to 2 minutes after.

In one embodiment, the metric is the difference in tactile sensation. When the second formulation includes a second anesthetic, a difference in the tactile sensation between the first and second locations indicates that the first anesthetic is ineffective for the subject. When the second formulation does not include an anesthetic, no difference in the tactile sensation between the first and second locations indicates that the first anesthetic is ineffective for the subject. In certain embodiments, the determining may include questioning the subject regarding feeling of numbness, puffiness, or pins and needles. Alternatively, the determining includes applying pressure or a pin prick to the first and second regions. In other embodiments, the determining may include applying an esthesiometer, e.g., one or more von Frey filaments, to an area to probe for sensitivity at the location that has received the anesthetic.

In another embodiment, the metric is temperature sensitivity. In this embodiment, probes that are warmer or colder than the body temperature are employed. For example, a kit may include 2 pieces of thermally conductive material (e.g., metal) suitable for use in humans. The thermally conductive material is preferably slow to adjust to room temperature. The probes may be cooled to ~32 degrees Fahrenheit, and the probes may be applied to the locations in the mouth treated with the two formulations. The subject may then be asked to indicate by raising arms to indicate which side feels cold: (1) Left colder; (2) Both sides cold (both arms raised); (3) Right colder; (4) Neither cold (both arms down). The kits are stable at room temperature, and only need to be refrigerated so that the metal or plastic pieces are cold. For temperature sensitivity and no anesthetic in the second

formulation, if the perception of temperature is the same between the first and control regions that indicates that the first anesthetic is ineffective for the subject. In the case of the second formulation having a second anesthetic, if the perception of temperature is different between the first and reference regions that indicates the test anesthetic is ineffective for the subject.

5 In another embodiment, the metric is taste sensitivity. In this embodiment, taste agents are applied to the two locations, and the subject is asked whether there is a difference in taste. For taste sensitivity and no anesthetic in the second formulation, if the taste is the same between the first and control regions that indicates that the first anesthetic is ineffective for the subject. In the case of the second formulation having a second anesthetic, if the taste is different between the first and reference
10 regions that indicates the test anesthetic is ineffective for the subject.

Double-Blind Mechanism for Determining Effectiveness

Directions on how the test subject is to indicate the side where they feel the effect, together with a recording mechanism that avoids confusion about left and right (for example, allowing the
15 invention to be used with younger children) and my left/your left confusion between subject and user may be provided. Furthermore, a peel off or scratch off key that indicates the interpretation for each of the 4 possible responses for this particular combination of materials and left-right orientations of the kit may also be provided, allowing the user to collect the responses in a manner that is double-blinded. In addition, the subject may be asked about the difference in sensation they are
20 experiencing, reflecting that the ineffectiveness may not be absolute.

Single Formulation Embodiments

The invention may also be employed with a single formulation including the first anesthetic. In these embodiments, the formulation may include a visual indicator, as described above. The
25 formulation may be applied by any suitable device as described herein, e.g., swab or gauze pad or a single applicator. Determination of effectiveness may be performed using any of the metrics provided herein, tactile, temperature, or taste sensitivity. Kits including a single formulation may include any of the probes for tactile, temperature, or taste sensitivity as described herein. The contacting for determining tactile, temperature, or taste sensitivity can be performed only on the location treated with
30 the formulation or on both the location of the formulation and an untreated location, as described herein when two formulations are employed. When only the location treated is tested, the subject can respond to contacting with a probe by indicating the absence of the feeling, perception of temperature change, or taste. When the treated location and an untreated location are tested, the sensitivity can be determined in the same manner as described herein for two formulations where the second
35 formulation does not include anesthetic.

Methods of Potassium Treatment

The present invention may involve administering either potassium or a potassium-elevating agent, e.g., a renin-angiotensin-aldosterone system antagonist, with or without additional agents, for
40 the treatment of a stress disorder such as PTSD or ATSD, e.g., in a subject in which lidocaine is

ineffective. When multiple agents are employed, administration may occur in the same or different dosage forms. When two or more agents are employed, they also may or may not be administered at the same time point. For example, the agents may be administered within 6 hours, e.g., within 3, 2, 1, 0.5, or 0.25 hours of each other. Preferably, the amount of therapeutic typically administered to treat a condition is reduced when the renin-angiotensin-aldosterone system antagonist or potassium is co-administered; for example, the amount of another therapeutic agent is reduced by at least 25, 50, 75, 80, 85, 90, or 95%.

Potassium Supplementation Agents

One type of potassium treatment involves treating a patient by administering potassium. For example, you can treat a condition in a patient by administering to the patient a therapeutically effective amount of potassium or a potassium salt. The patient can be one who has been diagnosed as having a lidocaine insensitivity, whether or not lidocaine effectiveness was tested, or a hypokalemic condition. In some embodiments, the method further includes diagnosing the patient as having a partial or complete lidocaine ineffectiveness prior to the administering the therapy. The method can include mineral treatments at adequate doses required to directly elevate serum potassium to levels that reduce or eliminate symptoms.

In some embodiments, the potassium salt can be potassium gluconate or chloride.

In some embodiments, the potassium is administered using a time-release (i.e., extended release) form to deliver a dose in a steady amount over a longer time.

Pharmaceutical compositions suitable for use in these methods can be provided in any suitable form, e.g., a (1) tablet (with or without coatings) or (2) capsule or in (3) liquid or (4) powder form or (5) a consumable food conveyance to accommodate the bulkiness of mineral salts and the required doses, especially for those unable to swallow pills. In addition, pharmaceutical compositions can be provided in ways that minimize significant carbohydrates and sugar to avoid the insulin effect that lowers serum potassium; and in ways that avoid surges in sodium consumption.

These ingredients may be prepared and packaged in ways that make compliance with the required regimen as easy and reliable as possible (for example, in kits).

The potassium dose over a 24-hours will vary by age and size of the patient. An adult will typically take 4 – 5 doses of 600 mg of elemental potassium, resulting in a dose over 24-hours of 2.4 g of elemental potassium, such as might be achieved with 13 g or 60 mEq or more of potassium gluconate; children will typically take doses of half that amount.

In some embodiments, the potassium is administered to the patient in multiple doses, e.g., from 1 to 30 dosage forms (e.g., pills or a food conveyance such as a potassium-enriched nutritional bars), such as such as in 1 to 24, 2 to 20, 2 to 15, 2 to 12, 2 to 9, 3 to 8, 2 to 7, or 3 to 6 dosage forms (e.g., 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, or 30 dosage forms). A total of dose may be administered to a patient per 24 hours, for example, in the range of approximately 90 mg to 5,000 mg of elemental potassium, e.g., 90 to 1000 mg, 250 to 4000 mg, 500 to 4000 mg, 750 to 4000 mg, 1000 to 4000 mg, 1250 to 4000, 1500 to 4000 mg, 2000 to 4000 mg, 1000 to 2000 mg, 1000 to 3000, or 3000 to 5000 mg. Such daily doses could be about:

90 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 500 mg, 750 mg, 1,000 mg, 1,050 mg, 1,100 mg, 1,150 mg, 1,200 mg, 1,250 mg, 1,300 mg, 1,350 mg, 1,400 mg, 1,450 mg, 1,500 mg, 1,550 mg, 1,600 mg, 1,650 mg, 1,700 mg, 1,750 mg, 1,800 mg, 1,850 mg, 1,900 mg, 1,950 mg, 2,000 mg, 2,150 mg, 2,200 mg, 2,250 mg, 2,300 mg, 2,350 mg, 2,400 mg, 2,450 mg, 2,500 mg, 2,550 mg, 2,600 mg, 2,650 mg, 2,700 mg, 2,750 mg, 2,800 mg, 2,850 mg, 2,900 mg, 2,950 mg, 3,000 mg, 3,500 mg, 4,000 mg, 4,500 mg, or 5,000 mg of elemental potassium per day. For example, a child may be administered from about 250 mg per dose of elemental potassium, and an adult may be administered from about 500 mg per dose of elemental potassium, and each may take 4-5 such doses in 24 hours.

Potassium-Elevating Agents

Another type of potassium treatment can involve administering to the patient a therapeutically effective amount of a potassium-elevating agent. One such agent that elevates serum potassium is a renin-angiotensin-aldosterone system antagonist. The patient can be one who has been diagnosed as having a lidocaine insensitivity, whether or not lidocaine effectiveness was tested, or hypokalemic condition. In some embodiments, the method further includes diagnosing the patient as having a partial or complete lidocaine ineffectiveness prior to the administering.

The methods include elevating serum potassium indirectly (e.g., through renin-angiotensin-aldosterone system antagonists) to levels that reduce or eliminate symptoms. The methods may further include administering blood pressure boosting drugs (e.g., by a mechanism other than the renin-angiotensin-aldosterone system such as fludrocortisone or midodrine), to allow those (e.g., children) with normal or low blood pressure to be treated safely.

A variety of renin-angiotensin-aldosterone system antagonists and other potassium-elevating drugs may be used in the compositions and methods described herein. Renin is a protease that converts angiotensin to angiotensin I, which is in turn cleaved by angiotensin-converting enzyme (ACE) to form angiotensin II, which acts on the adrenal cortex to induce the release of aldosterone and the subsequent excretion of aqueous potassium. An inhibitor of one or more of the components of the renin-angiotensin-aldosterone system results in elevated retention of potassium. Renin-angiotensin-aldosterone system antagonists include compounds capable of inhibiting one or more components of the renin-angiotensin system cascade, thereby attenuating the excretion of potassium and elevating serum potassium concentration. Exemplary renin-angiotensin-aldosterone system antagonists are renin inhibitors, ACE inhibitors, angiotensin receptor antagonists, and aldosterone antagonists, such as those described herein and known in the art.

Exemplary renin inhibitors that may be used in conjunction with the compositions and methods described herein are aliskiren and compounds structurally related thereto, such as those described, for example, in US Patent No. 5,719,141 and International Patent Application No. WO 2001/009079, the disclosures of each of which are incorporated herein by reference, as they pertain to renin inhibitors. Additional exemplary renin inhibitors useful in conjunction with the compositions and methods described herein are enalkiren and compounds structurally related thereto, remikiren and compounds structurally related thereto, among other renin inhibitors, such as those described in

US Patent Nos. 4,814,342; 4,855,303; 4,895,834; and 5,696,116, the disclosures of each of which are incorporated herein by reference as they pertain to renin inhibitors.

Exemplary ACE inhibitors that may be used in conjunction with the compositions and methods described herein are benazepril and its metabolite benazeprilat and compounds structurally related thereto, such as those described in US Patent No. 4,410,520, the disclosure of which is incorporated herein by reference as it pertains to ACE inhibitors. Additional examples of ACE inhibitors that may be used in conjunction with the compositions and methods described herein include captopril and compounds structurally related thereto, such as those described in US Patent No. U.S. Pat. No. 4,105,776, the disclosure of which is incorporated herein by reference as it pertains to ACE inhibitors. ACE inhibitors useful in conjunction with the compositions and methods described herein additionally include enalapril, lisinopril and compounds related structurally thereto, such as those described in US Patent Nos. 4,374,829; 6,468,976; and 6,465,615, the disclosures of each of which are incorporated herein by reference as they pertain to ACE inhibitors. Exemplary ACE inhibitors useful in conjunction with the compositions and methods described herein additionally include perindopril erbumine, the ethyl ester thereof, and compounds related thereto, as well as quinapril and compounds related thereto, ramipril, the ethyl ester thereof, and compounds related thereto, fosinopril sodium salt and compounds related thereto, moexipril and compounds related thereto; and imidapril and compounds related thereto, among other ACE inhibitors, such as those described in US Patent Nos. 5,696,116; 6,410,524; and 6,482,797, the disclosures of each of which are incorporated herein by reference as they pertain to ACE inhibitors.

Angiotensin receptor antagonists that may be used in conjunction with the compositions and methods described herein include, without limitation, losartan and various substituted imidazole derivatives and other compounds related thereto, such as those described in US Patent No. 5,138,069; the disclosure of which is incorporated herein by reference as it pertains to angiotensin receptor antagonists. Additional examples of angiotensin receptor antagonists include valsartan and compounds related thereto, such as those described in US Patent No. 5,399,578, the disclosure of which is incorporated herein by reference as it pertains to angiotensin receptor antagonists.

Exemplary angiotensin receptor antagonists additionally are irbesartan and compounds related thereto, such as those described in US Patent Nos. 5,270,317 and 5,352,788, the disclosure of which is incorporated herein by reference as it pertains to angiotensin receptor antagonists. Additional angiotensin receptor antagonists include candesartan and compounds related thereto, such as those described in US Patent No. 5,196,444, the disclosure of which is incorporated herein by reference as it pertains to angiotensin receptor antagonists. Additional exemplary angiotensin receptor antagonists are telmisartan and compounds related thereto, tasosartan and compounds related thereto, such as those described in US Patent No. 5,149,699, the disclosure of which is incorporated herein by reference as it pertains to angiotensin receptor antagonists. Additional exemplary angiotensin receptor antagonists are eprosartan and compounds related thereto, such as those described in US Patent No. 5,185,351, the disclosure of which is incorporated herein by reference as it pertains to angiotensin receptor antagonists. Angiotensin receptor antagonists additionally include saralasin, an octapeptide analog of bovine angiotensin II in which amino acid residues 1 and 8 are substituted with

sarcosine and alanine, respectively. Additional examples of angiotensin receptor antagonists that may be used in conjunction with the compositions and methods described herein include those described in US Patent Nos. 5,484,780; 6,028,091; and 6,329,384, the disclosures of each of which are incorporated herein by reference as they pertain to angiotensin receptor antagonists.

Exemplary aldosterone antagonists useful in conjunction with the compositions and methods described herein are, without limitation, eplerenone and compounds related thereto, such as those described in US Patent No. 4,559,332, the disclosure of which is incorporated herein by reference as it pertains to aldosterone antagonists. Aldosterone antagonists additionally include spironolactone alone or in combination with hydrochlorothiazide, and compounds related thereto. Additional exemplary aldosterone antagonists useful in conjunction with the compositions and methods described herein are those described in US Patent No. 6,410,524, the disclosure of which is incorporated herein by reference.

In certain embodiments, the potassium-elevating agent may be formulated in a pill, tablet, capsule, powder, liquid, or food conveyance. The potassium-elevating agent, e.g., renin-angiotensin-aldosterone system antagonist, may be administered at a dose of from 0.05 mg/day to 600 mg/day, e.g., 0.05 to 50, 10 to 100, 10 to 200, 10 to 300, 100 to 500, 100 to 400, 100 to 300, 200 to 600, or 300 to 600 mg/day (e.g., about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 200 mg/day, 300 mg/day, 400 mg/day, 500 mg/day, or 600 mg/day). The potassium-elevating agent, e.g., renin-angiotensin-aldosterone system antagonist, may be administered to the patient in 1 to 30 dosage forms, such as in 1 to 24, 2 to 20, 2 to 15, 2 to 12, 2 to 9, 3 to 8, 2 to 7, or 3 to 6 dosage forms (e.g., 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, and 30). The potassium-elevating agent may be packaged in a kit. The potassium-elevating agent may be formulated for extended release.

Additional Therapeutic Agents

Potassium or potassium-elevating agents may be administered in combination with one or more additional therapeutic agents. Certain conditions associated with lidocaine insensitivity, including stress disorders (e.g., PTSD or ATSD), may benefit from additional treatments. Accordingly, it is an aspect of the present invention that patients treated for low serum potassium by one of the above methods can often also be treated with other therapeutic agents.

In some embodiments, the additional therapeutic agent is a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant (TCA), or a monoamine oxidase inhibitor (MAOI). Examples of suitable SSRIs include sertraline, paroxetine, and fluoxetine. In some embodiments, the SNRI is venlafaxine. In some embodiments, the SRI is nefazodone. In some embodiments, the TCA is imipramine. In some embodiments, the MAOI is phenelzine.

Pharmaceutical Compositions, Kits, and Routes of Administration

Administration of the compounds described herein may be by any suitable means that results in treatment. The therapeutic agents described herein may be contained in an appropriate amount in

one or more suitable carrier substances and may be present in amounts totaling 1-95% by weight of the total weight of the composition. If appropriate, the composition may be provided in a dosage form that is suitable for oral, parenteral (e.g., intramuscular), rectal, cutaneous, subcutaneous, subdermal (with or without a customized dose delivery pattern), topical, transdermal (e.g., patch, patch pump),
5 transmucosal, buccal, sublingual, nasal, vaginal, epidural, otic, or ocular administration, or by injection (e.g., subcutaneous, intramuscular, and intravenous), inhalation, or direct contact with the nasal or oral mucosa (such as sublingual or buccal). In certain embodiments, the dosage is formulated for extended release, e.g., over a period of 4, 6, 8, 10, 12, 16, 18, 20, 22, or 24 hours.

The pharmaceutical compositions and routes of administration may be in the form of, for
10 example, tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, or aerosols.

In some embodiments, the composition may be in the form of a food conveyance, e.g., food (e.g., medical food) or beverage formulation, that accommodates the bulk of potassium salts (e.g.,
15 treatments mixed into a nutrition bar with appropriately low sugar and salt in order to avoid an insulin effect that lowers serum potassium; and in ways that avoid surges in sodium consumption).

These ingredients may be prepared and packaged in ways that make compliance with the required regimen as easy and reliable as possible (for example, in kits). In the kits of the invention, the active agents may or may not be formulated together, when multiple agents are present. The
20 potassium in the kit may be formulated in a food conveyance or for extended release.

When formulated together for at least one dose, the kit will include multiple dosages. In one embodiment, when an additional therapeutic agent is present (e.g., a stimulant or a blood-pressure raising medicine), the kit includes fewer doses of the additional agent relative to the potassium-elevating agent, e.g., renin-angiotensin-aldosterone system antagonist, or relative to potassium. For
25 example, the kit may include paired doses of another therapeutic agent and the potassium-elevating agent, e.g., renin-angiotensin-aldosterone system antagonist, or potassium, except for one additional dose of the potassium-elevating agent, e.g., renin-angiotensin-aldosterone system antagonist, or potassium intended to be taken before bed time. Alternatively, the kit may include multiple doses of the combined agents with an additional dose, intended for administration prior to bed time, including
30 the potassium-elevating agent, e.g., renin-angiotensin-aldosterone system antagonist, or potassium but not the additional agent. The dose not including the additional agent may have a different appearance, shape, or form to distinguish.

The compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: The Science and Practice of Pharmacy (2012, 22nd ed.) and in The United States
35 Pharmacopeia: The National Formulary (2015, USP 38 NF 33).

Each compound may be formulated in a variety of ways that are known in the art. For example, the therapeutic agents described herein can be formulated together or separately. The individually or separately formulated agents can be packaged together as a kit. Non-limiting examples include but are not limited to kits that contain, e.g., a food conveyance and a pill, two pills, a
40 pill and a powder, a suppository and a liquid in a vial, two topical creams, and the like. The kit can

include optional components that aid in the administration of the unit dose to patients, such as vials for reconstituting powder forms, syringes for injection, customized IV delivery systems, inhalers, etc. Additionally, the unit dose kit can contain instructions for preparation and administration of the compositions.

5 The kit may be manufactured as a single use unit dose for one patient, multiple uses for a particular patient (at a constant dose or in which the individual compounds may vary in potency as therapy progresses); or the kit may contain multiple doses suitable for administration to multiple patients (bulk packaging). The kit components may be assembled in cartons, blister packs, bottles, tubes, and the like. Kits may be packaged for use in a single day, e.g., two to six doses to be taken in
10 a single day, for a week, e.g., one to six doses to be taken for seven days, for a school/work week, e.g., one to six doses to be taken for five days, or a weekend, e.g., one to six doses to be taken for three days.

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert
15 diluents or fillers (e.g., mannitol or microcrystalline cellulose); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, croscarmellose, alginates, or alginic acid); binding agents (e.g., acacia, alginic acid, sodium alginate, gelatin, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose, methylcellulose, hydroxypropyl
20 methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

Two or more compounds may be mixed together in a tablet, capsule, or other vehicle, or may be partitioned. In one example, the first compound is contained on the inside of the tablet, and the
25 second compound is on the outside, such that a substantial portion of the second compound is released prior to the release of the first compound.

Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., microcrystalline cellulose or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an
30 oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders, granulates, and pellets may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Dissolution- or diffusion-controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound into an
35 appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above and/or, e.g., shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-poly(lactic acid), cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-hydroxymethacrylate,
40 methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, and/or polyethylene

glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated methylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, and/or halogenated fluorocarbon.

The liquid forms in which the compounds and compositions described herein can be incorporated for administration orally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

The solid forms of consumable food can be made of the standard ingredients of consumable food, either raw or baked, such as dried fruits, nuts, and various grains. Importantly, the level of salts and carbohydrates need to be carefully considered to avoid reducing the benefit of the potassium.

Compositions suitable for topical application, if appropriate, can be formulated as a useful topical composition, e.g., a cream, an ointment, a paste, a lotion, a gel, a solution, a suspension, a spray, a foam, a patch, or a tincture. Topical compositions may be administered dermally or transdermally. Typical topical compositions are formulated in a pharmaceutically acceptable vehicle suitable for topical application to the skin. Examples of such vehicles include water, alcohol, or an oil, or a mixture thereof. Further excipients that may be used in the topical compositions include colorants, dyestuffs, fragrances, deodorants, thickeners, antioxidants, solvents, surfactants, detergents, gelling agents, fillers, viscosity-controlling agents, preservatives, humectants, moisturizers, emollients, hydration agents, chelating agents, tonicity adjusting agents, solubilizing excipients, dispersants, permeation enhancer agents, plasticizing agents, preservatives, stabilizers, demulsifiers, wetting agents, sunscreens, emulsifiers, and astringents.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve, which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, or gelatin and glycerine. Compositions for rectal or vaginal administration are convenient in the form of suppositories containing a conventional suppository base, such as cocoa butter.

Generally, when administered to a human, the dosage of any of the compounds, alone or in combination, will depend on the nature of the compound, and can readily be determined by one skilled in the art and described herein.

Administration of each drug in a combination therapy, as described herein, can, independently, be one or more times daily for, e.g., from one day to one year or more (e.g., at least 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months), and may even be for the life of the patient.

In some embodiments, the formulation includes various approaches to improve bioavailability, e.g., gut absorption, including (but not limited to) crystalline solid formulations, amorphous formulations, lipid formulations, and self-emulsifying systems.

OTHER EMBODIMENTS

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the invention that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Other embodiments are within the claims.

What is claimed is:

CLAIMS

1. A method of determining the effectiveness of an anesthetic in a pregnant subject, the method comprising the steps of:
 - a) applying an aliquot of a formulation topically to a location of the subject, wherein the formulation comprises the anesthetic; and
 - b) determining tactile, taste, or temperature sensation at the location, wherein no reduction in the sensation at the location indicates that the anesthetic is ineffective for the subject.
2. The method of claim 1, further comprising the steps of:
 - c) applying an aliquot of a second formulation topically to a second location of the subject, wherein the second formulation comprises a second anesthetic; and
 - d) determining tactile, taste, or temperature sensation at the second location, wherein a reduction in the sensation at the second location indicates that the second anesthetic is effective for the subject.
3. The method of claim 1 or 2, further comprising the step of administering the anesthetic to the subject if the anesthetic is effective for the subject or administering the second anesthetic if the anesthetic is ineffective for the subject.
4. The method of claim 2 or 3, wherein the second anesthetic is chloroprocaine.
5. The method of any one of claims 1-4, wherein the pregnant subject is in labor.
6. The method of claim 5, wherein the anesthetic or the second anesthetic is used for pain management during labor.
7. A method of treating a subject undergoing a dermatological procedure, the method comprising the steps of:
 - a) applying an aliquot of a formulation topically to a location of the subject, wherein the formulation comprises an anesthetic;
 - b) determining tactile, taste, or temperature sensation at the location, wherein no reduction in the sensation at the location indicates that the anesthetic is ineffective for the subject; and
 - c) administering the anesthetic to the subject if the anesthetic is effective for the subject or administering a second anesthetic if the anesthetic is ineffective for the subject prior to the dermatological procedure.
8. The method of claim 7, wherein the dermatological procedure is selected from skin removal, spot removal, administration of stitches, plastic surgery, and a cosmetic procedure.

9. The method of claim 8, wherein the cosmetic procedure is selected from botulinum toxin administration, chemical peel, dermabrasion, face lift, or hair transplant.
10. A method of treating a subject undergoing an injection, the method comprising the steps of:
- a) applying an aliquot of a formulation topically to a location of the subject, wherein the formulation comprises an anesthetic;
 - b) determining tactile, taste, or temperature sensation at the location, wherein no reduction in the sensation at the location indicates that the anesthetic is ineffective for the subject; and
 - c) administering the anesthetic to the subject if the anesthetic is effective for the subject or administering a second anesthetic if the anesthetic is ineffective for the subject prior to the injection.
11. A method of treating a subject undergoing a catheterization, the method comprising the steps of:
- a) applying an aliquot of a formulation topically to a location of the subject, wherein the formulation comprises an anesthetic;
 - b) determining tactile, taste, or temperature sensation at the location, wherein no reduction in the sensation at the location indicates that the anesthetic is ineffective for the subject; and
 - c) administering the anesthetic to the subject if the anesthetic is effective for the subject or administering a second anesthetic if the anesthetic is ineffective for the subject prior to the catheterization.
12. The method of claim 11, wherein the catheterization is intravenous.
13. A method of determining the effectiveness of an anesthetic in a subject with a stress disorder, the method comprising the steps of:
- a) applying an aliquot of a formulation topically to a location of the subject, wherein the formulation comprises an anesthetic; and
 - b) determining tactile, taste, or temperature sensation at the location, wherein no reduction in the sensation at the location indicates that the anesthetic is ineffective for the subject.
14. A method of treating a subject with a stress disorder, the method comprising the steps of:
- a) applying an aliquot of a formulation topically to a location of the subject, wherein the formulation comprises an anesthetic; and
 - b) determining tactile, taste, or temperature sensation at the location, wherein no reduction in the sensation at the location indicates that the anesthetic is ineffective for the subject; and
 - c) treating the subject for the stress disorder.
15. The method of claim 13 or 14, wherein the stress disorder is post-traumatic stress disorder (PTSD) or acute traumatic stress disorder (ATSD).

16. The method of claim 14 or 15, wherein the treatment comprises administering potassium or a potassium elevating agent.
17. The method of claim 16, wherein the potassium comprises potassium gluconate or potassium chloride.
18. The method of claim 17, wherein 90 mg to 5,000 mg of elemental potassium is administered.
19. The method of any one of claims 16-18, wherein the potassium or potassium elevating agent is administered to the subject in 1 to 30 dosage forms.
20. The method of any one of claims 16-19, wherein the potassium or potassium elevating agent is packaged in a kit.
21. The method of any one of claims 16-20, wherein the potassium or potassium elevating agent is formulated in a pill, tablet, capsule, powder, liquid, or food conveyance.
22. The method of any one of claims 16-21, wherein the potassium or potassium elevating agent is formulated for oral, subdermal, ocular, otic, vaginal, rectal, intravenous, intranasal, or transdermal administration.
23. The method of any one of claims 16-22, wherein the potassium or potassium elevating agent is formulated for extended release.
24. The method of any one of claims 16-23, wherein the potassium-elevating agent is a renin-angiotensin-aldosterone system antagonist.
25. The method of claim 24, wherein the renin-angiotensin-aldosterone system antagonist is selected from the group consisting of an ACE inhibitor, an angiotensin receptor antagonist, an aldosterone antagonist, and a renin inhibitor.
26. The method of claim 25, wherein the ACE inhibitor is selected from the group consisting of captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, cilazapril, fosinopril, moexipril, spirapril, alacepril, deparil, temocapril, and teprotide; and/or wherein the angiotensin receptor antagonist is selected from the group consisting of losartan, candesartan, valsartan, irbesartan, telmisartan, eprosartan, olmesartan, azilsartan, and firmasartan; and/or wherein the aldosterone antagonist is selected from the group consisting of spironolactone and eplerenone; and/or

wherein the renin inhibitor is aliskiren.

27. The method of any one of claims 16-26, wherein the treatment further comprises administering a second therapeutic agent.

28. The method of claim 27, wherein the second therapeutic agent is selected from the group consisting of a selective a serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant (TCA), or a monoamine oxidase inhibitor (MAOI).

29. The method of claim 28, wherein the SSRI is selected from the group consisting of sertraline, paroxetine, and fluoxetine; and/or
wherein the SNRI is venlafaxine; and/or
wherein the SRI is nefazodone; and/or
wherein the TCA is imipramine; and/or
wherein the MAOI is phenelzine.

30. The method of any one of claims 1-29, wherein the anesthetic is lidocaine.

31. The method of any one of claims 1 and 7-30, wherein the method further comprises determining tactile, taste, or temperature sensation at a second location with a reference formulation comprising a reference anesthetic, wherein the reference anesthetic is effective for the subject; and
wherein a difference in the sensation between the location with the anesthetic and the second location with the reference formulation indicates that the anesthetic is ineffective for the subject.

32. The method of claim 31, wherein the reference anesthetic is selected from the group consisting of benzocaine, articaine, bupivacaine, chloroprocaine, and mepivacaine.

33. The method of any one of claims 1 and 7-30, wherein the method further comprises determining tactile, taste, or temperature sensation at a second location with a control formulation, wherein the control formulation comprises no anesthetic; and
wherein no difference in the sensation between the location with the anesthetic and the second location with the control formulation indicates that the anesthetic is ineffective for the subject.

34. The method of any one of claims 1-33, wherein the location is in the mouth of the subject.

35. The method of claim 34 wherein the location is on the tongue.

36. The method of any one of claims 1-35, wherein step (b) comprises applying pressure, a pin prick, or elevated or reduced temperature to the location.

37. The method of any one of claims 1-36, wherein step (b) comprises applying a temperature probe to the location.
38. The method of claim 37, wherein the temperature probe is at least 10 degrees Fahrenheit colder than subject body temperature.
39. The method of any one of claims 1-38, wherein step (b) comprises applying a taste agent to the location.
40. The method of claim 39, wherein the taste agent is sweet, sour, salty, or bitter.
41. The method of any one of claims 1-40, wherein step (b) comprises determining the sensation at the location up to two minutes after step (a).
42. A kit comprising:
a) an aliquot of a first formulation for topical administration comprising lidocaine; and
b) an aliquot of a second formulation for topical administration wherein the second formulation comprises chloroprocaine, and wherein the first formulation and second formulation are visually distinguishable when applied to a subject.
43. The kit of claim 42, wherein the aliquot of the first and/or second formulation is disposed in gauze or a swab.
44. The kit of claim 42 or 43, further comprising a physical barrier configured to adhere topically to the subject.
45. The kit of claim 44, wherein the physical barrier comprises an absorbent material.
46. The kit of any one of claims 42-45, further comprising a probe for tactile, taste, or temperature sensitivity.
47. The kit of any one of claims 42-46, wherein the first formulation and second formulation are visually distinguishable by color, reflectivity, light scattering, opacity, or inclusion of particles.
48. A kit comprising:
a) an aliquot of a formulation for topical administration comprising an anesthetic; and
b) one or more von Frey filaments.
49. The kit of claim 48, wherein the one or more von Frey filaments are sterile.

50. The kit of claim 48, wherein the anesthetic is chloroprocaine
51. A method of determining the effectiveness of an anesthetic in a pregnant subject, the method comprising the steps of:
- a) applying an aliquot of a formulation topically to a location of the subject, wherein the formulation comprises the anesthetic; and
 - b) determining tactile sensation at the location with an esthesiometer, wherein a reduction in the sensation at the location indicates that the anesthetic is effective for the subject.
52. The method of claim 51, wherein the pregnant subject is in labor.
53. The method of claim 51, wherein the pregnant subject is about to undergo a Cesarean section.
54. The method of claim 53, wherein the Cesarean section is urgent, non-STAT.
55. The method of claim 51, wherein the esthesiometer is one or more von Frey filaments.
56. The method of claim 51, wherein the anesthetic is chloroprocaine.
57. A kit comprising:
- a) an aliquot of a formulation comprising an anesthetic;
 - b) one or more von Frey filaments; and
 - c) a delivery device for the formulation.
58. The kit of claim 57, wherein the anesthetic is lidocaine.
59. The kit of claim 57, wherein the delivery device is a syringe.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/33226

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 9/00, 9/127, 31/192, 31/196, 31/445, 31/573, 47/10, 47/20, 47/24, 47/44 (2019.01)

CPC - A61K 9/00, 9/0024, 9/127, 9/1277, 31/192, 31/196, 31/445, 31/573, 47/10, 47/20, 47/24, 47/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2018/0049985 A1 (PAINREFORM LTD.) 22 February 2018; abstract; paragraphs [0048], [0053], [0071], [0107], [0186], [0189], [0200], [0222], [0236]	48-49, 57, 59 --- 50-56, 58
Y	WO 01/19403 A1 (HUH et al.) 22 March 2001; abstract; page 4, third paragraph; page 5, second paragraph; page 6, second paragraph; page 9, second – third paragraphs; claims 10, 11; figure 5	1-2, 3/1-2, 7-14, 15/13-14
Y	WO 96/32109 A2 (BARDSLEY et al.) 17 October 1996; abstract; page 4, lines 17-19	1-2, 3/1-2
Y	US 2005/0074466 A1 (SUSKIND et al.) 07 April 2005; paragraph [0085]; claims 1-2	7-10
Y	US 2014/0066843 A1 (ZHANG et al.) 06 March 2014; abstract; paragraphs [0010], [0094]	11-12
	US 2015/0224093 A1 (LIPOV) 13 August 2015; abstract	13-14, 15/13-14
Y	US 2010/0234828 A1 (BOYLE et al.) 16 September 2010; abstract; paragraphs [0041], [0043], [0044], [0066], [0069]	42-42, 44/42-43, 45/44/42-43
Y	WO 2004/058329 A2 (SHAFFER et al.) 15 July 2004; abstract; paragraphs [67], [77]	42-42, 44/42-43, 45/44/42-43, 50, 56, 58
Y	US 2005/0165097 A1 (WEBER et al.) 28 July 2005; abstract; paragraphs [0026], [0033], [0042], [0054]	51-56

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

08 July 2019 (08.07.2019)

Date of mailing of the international search report

22 JUL 2019

Name and mailing address of the ISA/

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/33226

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 8,828,452 B2 (ABRAHMSOHN) 09 September 2014; abstract; claim 30	52

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/33226

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-6, 16-41, 46-47
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.