METHOD OF TREATING DISEASE BY AURICULAR ANESTHESIA OF CRANIAL NERVES

This application claims benefit of and priority to U.S. Provisional Application No. 61/819,023, filed May 3, 2013, by Thomas M. Crews, and is entitled to that filing date for priority. The specification, figures and complete disclosure of U.S. Provisional Application No. 61/819,023 are incorporated herein by specific reference for all purposes.

FIELD

The present disclosure relates to methods for treating a variety of diseases by performing auricular anesthesia of the fifth cranial nerve (trigeminal nerve), the seventh cranial nerve (facial nerve), ninth cranial nerve (glossopharyngeal nerve), and the tenth cranial nerve (vagus nerve).

BACKGROUND

The vagus nerve, also known as cranial nerve X, is the tenth of twelve paired cranial nerves and is the longest of the cranial nerves. Upon leaving the medulla between the medullary pyramid and the inferior cerebellar peduncle, it extends through the jugular foramen, then passes into the carotid sheath between the internal carotid artery and the internal jugular vein down below the head, to the neck, chest and abdomen, where it contributes to the innervation of the viscera. The anatomy of the vagus nerve is illustrated in FIGS. 1 and 2.

Upon exiting the jugular foramen, the vagus nerve forms the jugular ganglion and the ganglion nodosum or the superior and inferior vagal ganglion. The jugular ganglion is joined by filaments from the petrous ganglion of the glossopharyngeal nerve. The auricular branch of the vagus nerve also has connections from the jugular ganglion of ten and the petrous ganglion of the glossopharyngeal nerve as it enters the mastoid canaliculus from the lateral wall of the jugular fossa. Brushing the temporal bone, the auricular branch of vagas exits the tympanomastoid fissure and divides into two branches; one joins the post-auricular nerve and the other is distributed to the skin of the back of the ear and to the posterior external acoustic meatus.

The vagus nerve conveys sensory information about the state of the body's organs to the central nervous system. Approximately 80% of the nerve fibers in the vagus nerve are afferent, or sensory nerves, communicating the state of the viscera to the brain, while the remaining 20% are efferent, or functional nerves.

The vagus nerve is responsible for regulating a host of bodily functions, including, but not limited to, breathing, speech, sweating, facilitating in keeping the larynx open during breathing, monitoring and regulating heartbeat, and digestion of food in the stomach, along with a host of other physiological functions.

Consequently, manipulation of the vagus nerve and subsequent alteration of its normal physiological function may have profound effects upon a wide range of human ailments that are associated with vagus nerve regulation. However, the present procedures available in the art for altering the function of the vagus nerve are highly invasive. These current procedures often rely upon the implantation of artificial mechanical devices into the body of a patient. Besides being highly invasive surgical procedures, these methods are very costly.

For instance, the United States Food and Drug Administration approved a procedure called vagus nerve stimulation (VNS) in the late 1990s for the treatment of partial onset epilepsy. VNS is performed as a surgical procedure to install a pacemaker-like device into a subject suffering from epileptic seizures. The device, implanted inside a patient's neck area, is used to send mild electrical impulses through the vagus nerve. The device is battery operated, and has an electrical pulse generator. After it is implanted, electrodes with insulated plastic are run into the vagus nerve from under the skin on the patient's neck. The pulse is set to operate alternately, by turning on every few seconds and then turning off.

Researchers have also begun to investigate the possibility of utilizing these pacemaker-like devices in the stomach of obese patients to block the function of the vagus nerve, in order to suppress appetite. Again, these procedures are highly invasive and involve the implantation of artificial devices into the body of a patient.

Some surgeons have even performed vagotomy procedures to treat obesity. In these procedures, the surgeon completely severs a patient's vagus nerve. While these procedures successfully allowed the subjects to lose weight, it is apparent that such an invasive and permanent surgical procedure is problematic for many patients.

Cranial nerve seven or the facial nerve is one of the twelve paired cranial nerves (see FIG. 3). It is so named because its main function is to supply motor innervation to the muscles of the face. Other muscles it innervates are the platysma, the posterior belly of the digastric, and the stapedius muscle. The sensory and parasympathetic portion of the facial nerve travels in the nervus intermedius and supplies the following components: (1) taste to the anterior two-thirds of

the tongue; (2) secretory and vasomotor fibers to the lacrimal gland, the mucus glands of the nose and sinuses, mouth, and the submandibular and sublingual salivary glands; and (3) cutaneous sensory impulses from the external auditory meatus and regions of the back of the ear. It is also thought that a parasympathetic impulse from the nervus intermedius, to the sphenopalatine ganglion, to the mucosa and submucosa of the nose and paranasal sinuses determines their venous capacitance and level of congestion.

The parasympathetic portion of the seventh cranial nerve takes its origin in the nucleus salivatorius in the brain stem and enters the interior acoustic meatus separate from the motor division of the facial nerve. It combines with the facial nerve proximal to the geniculate ganglion. The fibers leave the geniculate ganglion through the great superficial petrosal nerve and are joined by the large deep petrosal nerve to form the vidian nerve, or the nerve of the pterygoid canal, where together they move forward to synapse in the sphenopalatine ganglion. There they provide parasympathetic innervation to the eye, nose, sinus, palate, pharynx, and salivary glands. The geniculate ganglion receives general somatic afferent fibers from the external auditory canal via the auricular branch of the vagus nerve and its connection to the seventh cranial nerve. General somatic sensory afferent fibers synapse in the geniculate ganglion.

The trigeminal nerve or the fifth cranial nerve is the fifth of twelve paired cranial nerves and is the largest of all the cranial nerves (see FIG. 4). It is the great sensory nerve of the skin of the face, scalp, ear canal, the mucus membranes and other internal structures of the head. It also has functions as motor innervation to the muscles of mastication and contains proprioceptive fibers. It further carries sensory innervation from the dura of the brain with its various branches. The fifth cranial nerve is quite extensive. The main sensory nucleus extends from the pons to the upper spinal cord. The nucleus receives its afferent fibers from the semi-lunar ganglion, also known as the Trigeminal ganglion or the Gasserian ganglion. The Trigeminal ganglion contains the cell bodies of the sensory fibers for its three main divisions. It receives three large sensory division: the ophthalmic, maxillary, and mandibular divisions. The sensory root fibers leave the ganglion posteriorly to pass their insertion into the pons.

The glossopharyngeal nerve, also known as the ninth cranial nerve, is the ninth of twelve paracranial nerves that is known as the tympanic nerve and has both sensory and secretory fibers (see FIGS. 5 and 6). The nerve is a mixed sensory and motor nerve. The sensory component consists of somatic afferent fibers supplying sensation to the mucus membranes of the pharynx

and tonsillar region and back of the tongue. The superficial origin of the glossopharyngeal nerve from the brain stem is by three or four rootlets in the groove between the olive and the inferior peduncle. It exits the skull through the jugular foramen and runs anteriorly between the internal carotid artery and the internal jugular vein. Upon exiting the jugular foramen, it forms a pair of ganglionic swellings: the superior or jugular ganglion, and the inferior or petrosal ganglion. The ganglion contains cell bodies of the sensory fibers of the nerve. The ninth nerve communicates with the vagus nerve or the tenth cranial nerve, the facial nerve, and the sympathetic ganglion.

The glossopharyngeal nerve has five distinct general functions: (1) motor (special visceral efferent) supplies the stylopharyngeus muscle; (2) visceral motor (general visceral efferent) provides parasympathetic innervation of the parotid gland; (3) visceral sensory (general visceral afferent) carries visceral sensory information from the carotid sinus and carotid body; (4) general sensory (general somatic efferent) provides general sensory information from the skin of the external ear, internal surface of the tympanic membrane, upper pharynx, and posterior one-third of the tongue; and (5) special sensory (special afferent) provides taste sensation from the posterior one-third of the tongue, including circumvallate papillae.

Thus, there is a great need in the medical community for methods of treating vagus and other cranial nerve associated diseases that are not dependent upon altering the function of the vagus nerve or other cranial nerves through invasive surgical procedures or artificial devices. Specifically, there is a great need in the art for procedures to alter the function of the vagus and other cranial nerves that are non-invasive, safe, effective, and economical.

SUMMARY OF THE INVENTION

In various embodiments, the present invention provides a safe and non-invasive procedure, by which to treat a host of human diseases, and their symptoms, that are associated with the fifth cranial nerve (trigeminal nerve), the seventh cranial nerve (facial nerve), ninth cranial nerve (glossopharyngeal nerve), and the tenth cranial nerve (vagus nerve). The present disclosure provides a method of disrupting the normal physiological function of the nerve that does not rely upon an invasive and costly surgical procedure. The disclosed methods are able to "block" the transduction of both afferent and efferent signals from being transmitted via the trigeminal, facial, glossopharyngeal or vagus nerves. Such blockage of the transduction of signals on the nerve is achieved by a topical auricular anesthesia procedure, whereby a pharmaceutical composition is administered to the ear canal of a subject. It is the cutaneous

auricular anesthesia of those nerves and their particular close proximity and relationship to their respective ganglia that allows for their modulation in function. It is that modulation of function which results in the modulation of expression of specific disease processes.

In an exemplary embodiment, the present disclosure provides a method for treating symptoms of a disease, which comprises topically administering to an ear canal of a subject a pharmaceutical composition, comprising: (i) an analgesic and (ii) an anesthetic. In an embodiment, the analgesic is at least one pyrazolone derivative selected from the group consisting of ampyrone, dipyrone, antipyrine, aminopyrine, and propyphenazone. In a preferred embodiment, the analgesic is antipyrine. In an embodiment, the anesthetic is at least one selected from the group consisting benzocaine, chloroprocaine, cocaine, cyclomethycaine, dimethocaine, larocaine, piperocaine, propoxycaine, procaine, novocaine, proparacaine, tetracaine, amethocaine, articaine, bupivacaine, cinchocaine, dibucaine, etidocaine, levobupivacaine, lidocaine, lignocaine, mepivacaine, prilocaine, ropivacaine, trimecaine, and pharmaceutically acceptable derivatives thereof. In a preferred embodiment, the anesthetic is benzocaine.

The diseases that are treatable by the disclosed methodology are numerous. Any disease that is associated with an organ or bodily tissue that is innervated by the particular nerve could potentially be treated by the present methods. Particular mention of the following diseases treatable by the present methods is made: asthma, neurogenic cough, globus hystericus, spasmodic dysphonia, gastroesophageal reflux disease, and obesity. The present methods are also suitable for treating post-tonsillectomy or post-adenoidectomy pharyngeal pain, or oropharyngeal pain.

In yet other embodiments, the diseases treatable by the disclosed methodology include, but are not limited to: cardiac diseases, paroxysmal (lone) (vagal) atrial fibrillation, reflex systolic syncope, postural orthostatic tachycardia syndrome (POTS), excessive gag reflex, esophageal dysphagia, vomiting, nausea, odynophagia, esophageal pain, esophageal neuralgia, gastritis, dyspepsia, gall bladder disease, colecistitis pain, abdominal pain, esophageal motility disorder or esophageal dysmotility, spastic colon, pancreatic pain or spasms, pediatric colic, rectal spasms and pain, bladder spasm (overactive bladder), interstitial cystitis, dysmenorrhea, premature labor, pelvic pain, chronic pelvic pain, chronic prostatitis pain, eclampsia, preeclampsia, HELLP syndrome, cystitis pain, irritable bowel syndrome, Cohn's disease,

ulcerative colitis, reflux disease, gastritis, gastroenteritis symptoms, hyperemesis gravidarum, pediatric colic, hepato-renal syndrome, appetite suppression, gall bladder pain, inflammation of the esophagus, inflammation of the stomach, inflammation of the colon, kidney pain (from stone, infection, or tumor), enuresis, dysuria, dyspareunia, encopresis, heavy flow periods, frequent urination, prolonged vaginal bleeding, inhibit erections, prevention of premature ejaculation, inhibit excessive sweating, ureteral spasms, menstrual cramps, uterine spasms, ovarian pain and spasms, fallopian tube pain and spasms, pediatric asthma, adult asthma, chronic obstructive pulmonary disease (COPD), bronchial mucus, acute bronchitis, asthmatic bronchitis, chronic bronchitis, bronchospasm, cystic fibrosis, inflammation of the lung, emphysema, pleuritic chest pain, intercostal muscle pain, nerve pain, bronchospasm secondary to intubation and extubation, angina pectoris, cardiac vagal blockage, vasovagal reflex blockage, bradycardia, hypotension, orthostatic hypotension, hypertension, diabetes, shock, septic shock, reduction of blood sugar, inflammation of the pancreas, syncope secondary to vagal or cardiac reasons, vasovagal syncope, bradyarrhythmias, vasodilation of the skin, neuralgia, laryngospasm, acute laryngitis, laryngeal pain, chronic laryngitis, post extubation and intubation laryngospasms, palatal myoclonus, post-tonsillectomy pain, snoring, allergic rhinitis, vasomotor rhinitis, inflammatory polyposis (nasal), chronic sinusitis, chronic nasal congestion, allergic conjunctivitis, sneezing, hiccups, rhinitis, tinnitus, dysphagia, croup, chronic fatigue syndrome, fibromyalgia (chronic), epilepsy, obsessive compulsive disorder, panic attacks, post-traumatic stress disorder, Tourette's syndrome, focal dystonia, tic doloreaux, bulimia, anxiety, depression, restless leg syndrome, dysautonomia, familial intentional tremor, migraines, autism spectrum, anxiety headaches, insomnia or sleep disorders, multiple sclerosis, modulation of the reticular activating system, peripheral neuropathy, apraxia, neck and shoulder pain, and Parkinson's disease.

Thus, it is apparent that the present method applies generally to the treatment of any disease, ailment, or bodily condition that may benefit from the “blockage” of the particular nerve function. That is, any condition that would benefit from the hampered ability of the nerve to transmit neurological signals are encompassed by the disclosed method.

In methods disclosed herein, the pharmaceutical composition is administered to the ear canal of a subject in a concentration sufficient to physiologically alter the activity of the subject’s nerve compared to the physiological activity of a nerve in a subject not administered the

pharmaceutical composition. Thus, the present pharmaceutical composition utilized in a method as disclosed, is able to disrupt the natural ability of the nerve to transmit neurological signals along its length. These signals, both afferent and efferent, are blocked or hampered by the present methods.

The amount of analgesic present in the pharmaceutical composition my comprise from about: 1 to 100 mg per mL, 10 to 100 mg per mL, 20 to 100 mg per mL, 30 to 100 mg per mL, 40 to 100 mg per mL, 50 to 100 mg per mL, 60 to 100 mg per mL, 70 to 100 mg per mL, 80 to 100 mg per mL, 90 to 100 mg per mL, or 100 mg per mL. In some embodiments, the amount of analgesic present is from about 50 to 60 mg per mL, or about 54 mg per mL, or about 50 to 55 mg per mL, or about 55 to 60 mg per mL.

The amount of anesthetic present in the pharmaceutical composition my comprise from about: 1 to 100 mg per mL, 10 to 100 mg per mL, 20 to 100 mg per mL, 30 to 100 mg per mL, 40 to 100 mg per mL, 50 to 100 mg per mL, 60 to 100 mg per mL, 70 to 100 mg per mL, 80 to 100 mg per mL, 90 to 100 mg per mL, or 100 mg per mL. In some embodiments, the amount of anesthetic present is from about 1 to 20 mg per mL, or about 1 to 15 mg per mL, or about 5 to 15 mg per mL, or about 10 to 20 mg per mL, or about 10 to 15 mg per mL, or about 14 mg per mL.

The total amount of the pharmaceutical composition administered to a patient during one dosage may comprise from about: .001 to .01 mL of solution, or .01 to .1 mL of solution, or .1 to .5 mL of solution, or .1 to 1mL of solution, or 1 to 1.5 mL of solution, or 1.5 to 2 mL of solution, or 2 to 5 mL of solution, or 5 to 10 mL of solution. The administration may comprise using a "dropper" bottle that applies "drops" of solution to the patients ear canal during a typical dosage. Such administration may comprise 1mL ≈ 15-20 drops, 0.5 mL ≈ 10 drops, 0.25 mL ≈ 5 drops.

As used herein, unless otherwise expressly specified, all numbers such as those expressing values, ranges, amounts, or percentages may be read as if prefaced by the word "about," even if the term does not expressly appear. Any numerical range recited herein is intended to include all sub-ranges subsumed therein. Plural encompasses singular and vice versa; *e.g.*, the singular forms "a," "an," and "the" include plural referents unless expressly and unequivocally limited to one referent.

In certain embodiments, the subject treated by the present methods does not have an ear infection. Furthermore, in certain embodiments, the subject treated by the present methods does not have an ear ache or is not experiencing ear pain.

In particular aspects, the present method is not utilized on patients with ear infections. That is, the present methods, in certain embodiments, specifically exclude utilization on patients with an ear infection or ear pain associated with an ear infection. Certain embodiments specifically exclude utilizing the method on subjects experiencing an ear ache or ear pain. In these embodiments, a first step of the method may comprise an ear examination by a treating physician to assure that the patient does not have ear pain, or an ear ache, or swelling of the tissue in the ear that may cause ear pain, or an ear infection. In some aspects, after the ascertainment that a patient does not have any of the aforementioned, the patient's ear canal may be treated with the disclosed pharmaceutical composition, which in a preferred embodiment comprises antipyrine and benzocaine.

The disclosed pharmaceutical compositions utilized in the present methods may comprise additional components such as: antibiotics, vasoconstrictors, glycerin, and acetic acid.

The pharmaceutical compositions may comprise any pharmaceutically acceptable carrier, or adjuvant, and may be formulated as: solutions, foams, gels, creams, pastes, lotions, emulsions, and combinations of the aforementioned.

The pharmaceutical composition may be administered once a day, twice a day, three times a day, four times a day, five times a day, six times a day, seven times a day, eight times a day, nine times a day, 10 to 20 times a day, or up to continuously throughout the day as needed. Further, in certain embodiments, the pharmaceutical composition is administered upon the onset of an asthma attack. In other embodiments, the pharmaceutical composition is administered upon a person feeling hungry. Some aspects of the methods entail administration of the pharmaceutical composition upon a patient feeling pain in their pharyngeal region. Certain embodiments contemplate not utilizing the taught compositions on patients that are experiencing ear pain, or that have an ear infection, or swelling in the ear associated with an ear infection. In these embodiments, the disclosed method of treating diseases associated with the vagus nerve may be immediately halted or stopped upon a patient developing ear pain.

A specifically preferred ailment to be treated by the disclosed method is the pharyngeal or oropharyngeal pain associated with a post-operative tonsillectomy or a post-operative adenoidectomy. These embodiments treat pain that patients feel after the aforementioned surgical procedures. In these embodiments, the pharmaceutical composition is applied to the ear canal of a subject that has had a tonsillectomy or adenoidectomy within: the preceding 168 hours (or 7

days), preceding 48 hours, preceding 24 hours, preceding 12 hours, preceding 4 hours, or immediately post-operation, prior to administering the pharmaceutical composition. Thus, the present method contemplates doctors prescribing the disclosed procedure and pharmaceutical composition to patients to utilize immediately upon feeling pain in the pharyngeal or oropharyngeal regions post-surgery.

Another particularly preferred ailment, or disease, to be treated by the disclosed method is asthma. In certain embodiments, acute asthma attacks are treated by the present methods. These embodiments involve administering the pharmaceutical composition to the ear canal of a subject that is presently experiencing an acute asthma attack. Further, these embodiments may comprise treatment of a subject that has experienced an asthma attack in the last 48, 24, 12, 6, or 1 hours. Thus, the methods taught herein may be used in conjunction with normal bronchodilators and corticosteroids for the treatment and management of a patient's asthma. The methods may be suitable for use on asthma patients experiencing a peak expiratory flow rate (PEFR) of 50 to 79% of the patient's normal peak flow readings, *i.e.* "the yellow zone" as classified by the American Lung Association. The methods are also suitable for use on a patient experiencing a peak expiratory flow rate of less than 50% of the patient's normal peak flow reading, *i.e.* "the red zone." The methods can be utilized in conjunction with a rescue inhaler when a patient experiences a severe asthma attack. Consequently, in some embodiments, the present pharmaceutical composition is a component of a kit, wherein said kit comprises a rescue inhaler and a pharmaceutical composition comprising antipyrine and benzocaine. The kit is intended to be kept with a patient that is in danger of suffering a severe asthma attack. Further, in some embodiments, the pharmaceutical composition is part of an emergency first aid kit that is kept in school classrooms, for example. In these embodiments, teachers could utilize the present pharmaceutical composition in times of emergency, such as when a student suffers a severe asthma attack, but yet there is no rescue inhaler readily available.

The present methods are also suitable for use in treating chronic asthma. In these embodiments, patients utilize the disclosed compositions as taught in the present disclosure to prevent the onset of an acute asthma attack. In these methods, chronic asthma is managed by continuous use of the present methods. Thus, in certain embodiments, patients with asthma are administered the pharmaceutical compositions presented herein before the onset of an asthma attack. For example, certain embodiments of the present methods are effective at controlling

asthma in patients that play sports. Often, patients suffering from asthma will experience a decreased ability to breathe upon physical exertion, which in some cases may lead to a severe asthma attack requiring the use of an inhaler. The present methods allow the treatment of a subject's ear canal with a pharmaceutical composition comprising antipyrine and benzocaine before the subject engages in playing a sport. In this manner, the present methods may be an effective therapy for patient's to utilize before engaging in physical activity, in order to reduce the likelihood of having an asthma attack.

Another particularly preferred condition, or disease, to be treated by the disclosed method is obesity. The present methods treat obesity by providing a mechanism to suppress a patient's appetite. By suppressing a patient's appetite, the present methods provide another tool for doctor's to utilize in managing a patient's weight. Thus, obesity may be treated by administering the taught pharmaceutical composition to a subject's ear canal. In some embodiments, subjects are treated with the taught pharmaceutical composition whenever the subjects experience a sensation of hunger. Further, some embodiments administer the disclosed pharmaceutical compositions to the subject's ear canal immediately before a meal is eaten, or 10 minutes to 60 minutes before a meal is eaten, or 20 to 60 minutes before a meal is eaten, or 30 to 60 minutes before a meal is eaten, or concurrently with the consumption of a food. Thus, in some aspects, the present method of auricular anesthesia of the vagus nerve is utilized on a patient within an hour prior to the patient eating any food. In this way, the patient's appetite is satiated and less food will be consumed. Further, some embodiments administer the disclosed pharmaceutical compositions to the subject's ear canal in the morning, preferably before the subject eats breakfast, thus providing an effective appetite suppressant that lasts until at least lunch.

In some embodiments, the present pharmaceutical compositions and treatment methodology are part of a comprehensive weight loss program that involves not only utilization of the pharmaceutical composition to curb a patient's appetite, but also may include a specific diet and exercise regime.

In some aspects, a person applying the topical pharmaceutical composition to a patient's ear canal should have good light, so as to get a superficial look into the patient's ear, so as to check for any gross obstructions, *i.e.* wax, skin, infection, purulence, or swelling. The person may gently pull the ear pinna outward and upward, so as to straighten out the ear canal. Ear drops comprising the taught pharmaceutical composition that have been previously warmed and

are quite viscid should be applied to the posterior or back wall of the lateral ear opening. The drops should be applied very slowly and deliberately, one drop at a time, allowing for each drop to slowly migrate down the ear canal. The patient's head should be resting on its side on a flat soft surface for optimal application. The back wall of the canal and eardrum have a large portion of the vagal nerve fibers, and thus pointed application to this area is desired. In some aspects, children under 10 will require 4 to 8 drops per ear, while adults and children over 12 usually require 6 to 10 drops for anesthesia. In some embodiments, drops are always followed by a cotton ball in the lateral ear canal for about one hour to insure the maintenance of the medicine in the ear canal to provide the required topical anesthesia to the vagus nerve. After an hour the cotton may be removed.

The administration of a pharmaceutical composition to a patient's ear canal for the purpose of auricular anesthesia of the vagus nerve to treat a disease affected by vagus nerve physiological alteration is referred to in some embodiments as the "Crews Maneuver." The Crews Maneuver of utilizing the ear canal as a conduit to anesthetizing the vagus nerve does not suffer from the drawbacks present in the art.

These and other features, aspects, and advantages of embodiments of the present disclosure will become better understood with regard to the following description, claims, and accompanying drawings explained below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an illustration of the complex anatomy of the vagus nerve. The auricular branch is noted.

FIG. 2 is an illustration of the complex anatomy of the vagus nerve showing the innervation of the parasympathetic division on one side of the body.

FIG. 3 is an illustration of the anatomy of the facial nerve.

FIG. 4 is an illustration of the anatomy of the trigeminal nerve.

FIG. 5 is an illustration of the anatomy of the glossopharyngeal nerve.

FIG. 6 is an illustration of the glossopharyngeal nerve.

FIG. 7 is an illustration of the interior of a human ear. The ear canal is noted.

DETAILED DESCRIPTION

Detailed descriptions of one or more preferred embodiments are provided herein. It is to be understood, however, that the present disclosure may be embodied in various forms. Therefore, specific details disclosed herein are not to be interpreted as limiting, but rather as a basis for the claims and as a representative basis for teaching one skilled in the art to employ the present disclosure in any appropriate manner.

A. Disruption of the Transduction of Neurological Signals Along the Cranial Nerves

The tenth cranial nerve (vagus nerve) is associated with numerous bodily organs and alteration of its normal physiological function can have profound effects on a host of human ailments. That is, by "blocking" or "disrupting" or "numbing" the conduction of neurological signals in the particular nerve, one is able to influence a host of organs that are innervated by that nerve. Consequently, blocking the transduction of signals transmitted along the nerve, whether those signals are afferent or efferent in nature, will alter the normal physiological response of various organs and tissues. This, in turn, can have profound implications for treating a variety of diseases, or ailments, that are associated with human organs and tissues that are innervated by the particular nerve.

Auricular anesthesia of the cutaneous portion of the seventh cranial nerve (facial nerve) carry signals back to the geniculate ganglion where parasympathetic fibers and sensory fibers are anesthetized, blocked, or otherwise modulated. Anesthesia of the geniculate ganglion and its connection to the Sphenopalatine ganglion serve to modulate or block transduction of efferent signals through the facial nerve. This can profoundly affect disease processes such as, but not limited to, allergic rhinitis, vasomotor rhinitis, inflammatory nasal polyposis, chronic sinusitis, chronic nasal congestion, allergic conjunctivitis, sneezing, and rhinitis in all forms.

The sensory aspect of the fifth cranial nerve (trigeminal nerve) deals with information from the dura, the mucus membranes of the eyes, the mucus membranes of the nose and sinuses, the skin of the external auditory canal eardrum. Auricular anesthesia of the skin of the ear canal then signals to the trigeminal ganglion via the auriculotemporal branch of the mandibular division of the trigeminal nerve. Modulation of afferent signals through the trigeminal ganglion has profound effects on multiple disease processes. Modulating those afferent signals from the dura, the eye, the nose and sinuses leads to modulation of various disease processes. Manipulation of dural signals that pass through the ophthalmic, maxillary, and mandibular

divisions have profound effects in the treatments of headaches and migraine headaches. Manipulation or modulation or blockage of afferent signals from the ophthalmic and maxillary divisions of the trigeminal nerve will result in modulated efferent signals from the motor division of the seventh cranial nerve that deal with allergic rhinitis, vasomotor rhinitis, all forms of rhinitis, inflammatory nasal polyposis, chronic sinusitis, chronic nasal congestion, allergic conjunctivitis and sneezing.

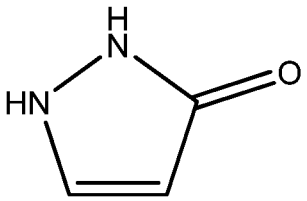
Auricular anesthesia of the cutaneous portion of the ninth cranial nerve (glossopharyngeal nerve) and its proximity to the petrous ganglion and its connection to the seventh cranial nerve and tenth cranial nerve can have profound effect on certain disease processes. Because of neural connections between the glossopharyngeal nerve and those of the seventh and tenth cranial nerves, disease processes specific to those nerves may also be modulated. Diseases specific to the glossopharyngeal nerve that may be affected by topical auricular anesthesia include,, but are not limited to, pharyngeal pain, post tonsillectomy pain, sneezing, and parotid salivation.

Thus, several embodiments of the present invention comprise a method that blocks the transduction of efferent signals via the vagus, trigeminal, facial, or glossopharyngeal nerves. Another embodiment of the disclosure blocks the afferent transduction of signals vi via the vagus, trigeminal, facial, or glossopharyngeal nerves. The present disclosure also provides a methodology by which both the afferent and efferent signal transduction via the vagus, trigeminal, facial, or glossopharyngeal nerves is blocked.

B. Pharmaceutical Composition

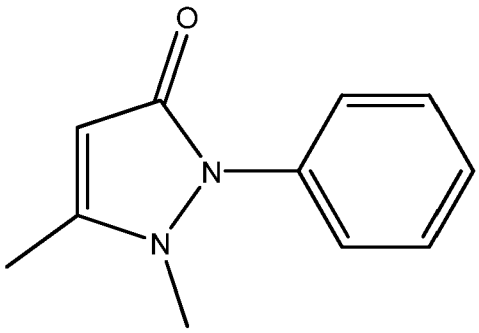
The methods of the present disclosure utilize the application of a pharmaceutical composition to the ear canal of subject in need of such treatment. The ear canal is illustrated in FIG. 7. The pharmaceutical compositions comprise an analgesic and an anesthetic.

The analgesic present in embodiments of the disclosure are pyrazolone ($C_3H_4N_2O$) derivatives. The molecular structure of 3-pyrazolone is as follows:

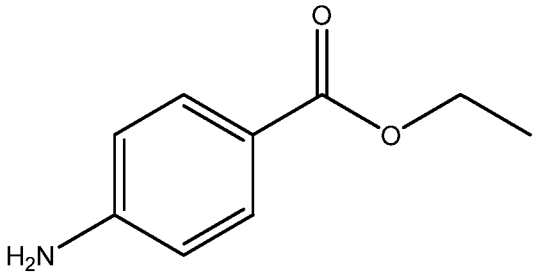


Derivatives of the isomeric form 5-pyrazolone are also encompassed by the disclosure.

Particular embodiments of the present methods utilize antipyrine as the pyrazolone derivative. Antipyrine ($C_{11}H_{12}N_2O$) is also referred to as phenazone. The molecular structure of antipyrine is as follows:



The anesthetic present in some embodiments of the disclosure are ester based anesthetics. In a particular embodiment, the anesthetic is benzocaine ($C_9H_{11}NO_2$), the molecular formula of which is as follows:



Further embodiments of the method utilize amide based anesthetics.

In a preferred embodiment of the present methods, the disclosed pharmaceutical compositions comprise antipyrine as the analgesic and benzocaine as the anesthetic.

The pharmaceutical compositions may be formulated in a host of ways, including, but not limited to, the following: solutions, foams, gels, creams, pastes, lotions, emulsions, and combinations of the aforementioned.

Furthermore, the present disclosure contemplates that active ingredients of the pharmaceutical composition, such as antipyrine and benzocaine, may be infused into material that is then placed into a patient's ear canal. For instance, cotton gauze material could be composed to contain the present pharmaceutical composition, said gauze providing a convenient application method by which to expose the ear canal to the present pharmaceutical composition.

C. Anatomical Site of Application of the Pharmaceutical Composition

The present method contemplates applying the disclosed pharmaceutical composition to the ear canal of a patient. It has been found that the ear canal serves as a convenient point in the human anatomy in which to apply the present pharmaceutical composition and achieve disruption of neurological signals along the vagus or other cranial nerves. That is, by placing a pharmaceutical composition, as described herein, into the ear canal of a patient, it has been discovered that the body will absorb the composition and the vagus or other cranial nerve will be "blocked," such that the normal physiological function of the nerve will be altered. The present methodology of utilizing the ear canal as a conduit to anesthetizing the particular nerve does not suffer from the drawbacks present in the prior art.

The present methods of applying a pharmaceutical composition as described are not invasive and do not pose the risks associated with surgical procedures. Furthermore, the present methods do not rely upon inserting artificial devices into the body of patient. It is evident that the present methods represent a significant advancement over the state of the art, as the disclosed non-invasive procedure is able to alter the function of the vagus or other cranial nerve without artificial devices or surgery. The present methods are also economical and would therefore provide access to treatment to the vast majority of a population.

The presently disclosed embodiments of a method of blocking signal transduction upon the vagus nerve will now be further elaborated upon by reference to the following examples. In each of these examples, the disclosed method was able to successfully treat a human disease, or ailment, that was associated with a particular cranial nerve. That is, the conditions treated in the following example were able to be controlled to a clinically effective degree by the disclosed method of performing auricular anesthesia on the vagus or other cranial nerve, *i.e.* the "Crews Maneuver."

EXAMPLES

Example 1: Treatment of Post-Tonsillectomy Pharyngeal or Oropharyngeal Pain

A. Protocol

A test of a preferred embodiment of the present method was conducted to evaluate the efficacy of the method for treating patients suffering from post-tonsillectomy pharyngeal, or oropharyngeal pain.

500 patients that had previously undergone a tonsillectomy were instructed to utilize six drops of a pharmaceutical composition comprising antipyrine (≈54.0 mg) and benzocaine (≈14.0 mg), in each ear three times per day, for a duration of ten days after the tonsillectomy.

B. Results

Out of the 500 patients treated, 495 patients reported significant reduction in pharyngeal and/or oropharyngeal pain.

Example 2: Treatment of Post-Adenoidectomy Pharyngeal or Oropharyngeal Pain

A. Protocol

A test of a preferred embodiment of the present method was conducted to evaluate the efficacy of the method for treating patients suffering from post-adenoidectomy pharyngeal, or oropharyngeal pain.

200 patients that had previously undergone an adenoidectomy were instructed to utilize six drops of a pharmaceutical composition comprising antipyrine (≈54.0 mg) and benzocaine (≈14.0 mg), in each ear two times per day, for a duration of seven days after the adenoidectomy.

B. Results

Out of the 200 patients treated, 200 patients reported significant reduction in pharyngeal and/or oropharyngeal pain.

Example 3: Treatment of Asthma

A. Protocol

A test of a preferred embodiment of the present method was conducted to evaluate the efficacy of the method for treating patients suffering from chronic asthma and acute asthmatic attack.

10 patients with asthma were instructed to utilize six drops of a pharmaceutical composition comprising antipyrine (≈54.0 mg) and benzocaine (≈14.0 mg), in each ear in the morning, for two months.

A patient suffering from a severe acute asthma attack was also treated by immediately filling the patient's ear canal with the aforementioned pharmaceutical composition.

B. Results

Out of the 10 patients treated, 10 patients reported significant reduction in asthmatic attacks.

Further, the patient suffering from the severe asthma attack experienced a dramatic increase in the amount of oxygen reaching his lungs within 60 minutes of the treatment.

Example 4: Treatment of Obesity (*i.e.* a method of appetite suppression)

A. Protocol

A test of a preferred embodiment of the present method was conducted to evaluate the efficacy of the method for treating patients suffering from obesity.

5 overweight patients were instructed to utilize six drops of a pharmaceutical composition comprising antipyrine (≈54.0 mg) and benzocaine (≈14.0 mg), in each ear in the morning, for an indefinite period of time.

B. Results

Out of the 5 patients treated, all 5 patients reported significant reduction in appetite while utilizing the treatment. The significant reduction in appetite led to weight loss.

Example 5: Treatment of Neurogenic Cough

A. Protocol

A test of a preferred embodiment of the present method was conducted to evaluate the efficacy of the method for treating patients suffering from neurogenic cough.

4 patients suffering from neurogenic cough were instructed to utilize six drops of a pharmaceutical composition comprising antipyrine (≈54.0 mg) and benzocaine (≈14.0 mg), in each ear two times per day, for a duration of seven days and then only as needed.

B. Results

Out of the 4 patients treated, all 4 patients reported significant reduction in cough.

Example 6: Treatment of Globus Hystericus

A. Protocol

A test of a preferred embodiment of the present method was conducted to evaluate the efficacy of the method for treating patients suffering from globus hystericus.

2 patients suffering from globus hystericus were instructed to utilize six drops of a pharmaceutical composition comprising antipyrine (≈54.0 mg) and benzocaine (≈14.0 mg), in each ear one time per day, for an indefinite period of time as needed.

B. Results

Out of the 2 patients treated, all 2 patients reported significant reduction in throat tightness.

Example 7: Treatment of Spasmodic Dysphonia

A. Protocol

A test of a preferred embodiment of the present method was conducted to evaluate the efficacy of the method for treating patients suffering from spasmodic dysphonia.

1 patient suffering from spasmodic dysphonia was instructed to utilize six drops of a pharmaceutical composition comprising antipyrine (≈54.0 mg) and benzocaine (≈14.0 mg), in each ear one time per day, for an indefinite period of time as needed.

B. Results

The patient reported significant reduction in throat hoarseness and vocal cord spasms almost immediately upon using the treatment.

Example 8: Treatment of Laryngeal Pain

A. Protocol

A test of a preferred embodiment of the present method was conducted to evaluate the efficacy of the method for treating patients suffering from laryngeal pain.

2 patients suffering from laryngeal pain were instructed to utilize six drops of a pharmaceutical composition comprising antipyrine (≈54.0 mg) and benzocaine (≈14.0 mg), in each ear one time per day, for an indefinite period of time as needed.

B. Results

Out of the 2 patients treated, all patients reported significant reduction in laryngeal pain.

Example 9: Treatment of Gastroesophageal Reflux Disease

A. Protocol

A test of a preferred embodiment of the present method was conducted to evaluate the efficacy of the method for treating patients suffering from Gastroesophageal Reflux Disease (GERD).

2 patients suffering from GERD were instructed to utilize six drops of a pharmaceutical composition comprising antipyrine (≈54.0 mg) and benzocaine (≈14.0 mg), in each ear one time per day, for an indefinite period of time as needed.

B. Results

Out of the 2 patients treated, all 2 patients reported significant reduction in acid reflux and heartburn.

The results from the aforementioned clinical experiments can be found below in Table 1.

10 **Table 1**

Disease Treated	Number of Subjects Treated	Treatment Protocol (1mL ≈ 15-20 drops)	Amount of Time Treated	Number of Subjects Exhibiting Clinical Improvement in Symptoms	% of Subjects Exhibiting Clinical Improvement in Symptoms
Post-Tonsillectomy Pharyngeal or Oropharyngeal Pain	500	6 drops per ear 3 times per day	For 10 days post operation	495	99%
Post-Adenoidectomy Pharyngeal or Oropharyngeal Pain	200	6 drops per ear 2 times per day	For 7 days post operation	200	100%
Asthma	10	6 drops per ear in the morning	For 2 months	10	100%
Obesity *via* Appetite Suppression	5	6 drops per ear in the morning	Daily	5	100%
Neurogenic Cough	4	6 drops per ear 2 times per day	7 days and then as needed	4	100%
Globus Hystericus	2	6 drops per ear once a day	As needed	2	100%
Spasmodic Dysphonia	1	6 drops per ear once a day	As needed	1	100%
Laryngeal Pain	2	6 drops per ear once a day	As needed	2	100%

Gastroesophageal Reflux Disease (GERD)	2	6 drops per ear once a day	As needed	2	100%

The diseases that are treatable by the disclosed methodology are numerous. Any disease that is associated with an organ or bodily tissue that is innervated by the particular nerve could potentially be treated by the present methods. Particular mention of the following diseases treatable by the present methods is made: asthma, neurogenic cough, globus hystericus, spasmodic dysphonia, gastroesophageal reflux disease, and obesity. The present methods are also suitable for treating post-tonsillectomy or post-adenoidectomy pharyngeal pain, or oropharyngeal pain.

In yet other embodiments, the diseases treatable by the disclosed methodology include, but are not limited to: cardiac diseases, paroxysmal (lone) (vagal) atrial fibrillation, reflex systolic syncope, postural orthostatic tachycardia syndrome (POTS), excessive gag reflex, esophageal dysphagia, vomiting, nausea, odynophagia, esophageal pain, esophageal neuralgia, gastritis, dyspepsia, gall bladder disease, colecistitis pain, abdominal pain, esophageal motility disorder or esophageal dysmotility, spastic colon, pancreatic pain or spasms, pediatric colic, rectal spasms and pain, bladder spasm (overactive bladder), interstitial cystitis, dysmenorrhea, premature labor, pelvic pain, chronic pelvic pain, chronic prostatitis pain, eclampsia, preeclampsia, HELLP syndrome, cystitis pain, irritable bowel syndrome, Cohn's disease, ulcerative colitis, reflux disease, gastritis, gastroenteritis symptoms, hyperemesis gravidarum, pediatric colic, hepato-renal syndrome, appetite suppression, gall bladder pain, inflammation of the esophagus, inflammation of the stomach, inflammation of the colon, kidney pain (from stone, infection, or tumor), enuresis, dysuria, dyspareunia, encopresis, heavy flow periods, frequent urination, prolonged vaginal bleeding, inhibit erections, prevention of premature ejaculation, inhibit excessive sweating, ureteral spasms, menstrual cramps, uterine spasms, ovarian pain and spasms, fallopian tube pain and spasms, pediatric asthma, adult asthma, chronic obstructive pulmonary disease (COPD), bronchial mucus, acute bronchitis, asthmatic bronchitis, chronic bronchitis, bronchospasm, cystic fibrosis, inflammation of the lung, emphysema, pleuritic chest pain, intercostal muscle pain, nerve pain, bronchospasm secondary to intubation and extubation, angina pectoris, cardiac vagal blockage, vasovagal reflex blockage, bradycardia, hypotension, orthostatic hypotension, hypertension, diabetes, shock, septic shock, reduction of

blood sugar, inflammation of the pancreas, syncope secondary to vagal or cardiac reasons, vasovagal syncope, bradyarrhythmias, vasodilation of the skin, neuralgia, laryngospasm, acute laryngitis, laryngeal pain, chronic laryngitis, post extubation and intubation laryngospasms, palatal myoclonus, post-tonsillectomy pain, snoring, allergic rhinitis, vasomotor rhinitis, inflammatory polyposis (nasal), chronic sinusitis, chronic nasal congestion, allergic conjunctivitis, sneezing, hiccups, rhinitis, tinnitus, dysphagia, croup, chronic fatigue syndrome, fibromyalgia (chronic), epilepsy, obsessive compulsive disorder, panic attacks, post-traumatic stress disorder, Tourette's syndrome, focal dystonia, tic doloreaux, bulimia, anxiety, depression, restless leg syndrome, dysautonomia, familial intentional tremor, migraines, autism spectrum, anxiety headaches, insomnia, multiple sclerosis, modulation of the reticular activating system, peripheral neuropathy, apraxia, neck and shoulder pain, and Parkinson's disease.

In particular, improvement was reported in over half of the patients treated in accordance with the above methods, where there were minimum of 5 patients treated for symptoms or conditions associated with the following diseases or disorders, vasovagal reflex blockage, chronic bronchitis, asthmatic bronchitis, hypotension, hypertension, diabetes, bladder spasm, dysmenorrhea, pelvic pain, cystitis pain, enuresis, dysuria, dyspareunia, heavy menstrual flow periods, frequent urination, spasmodic dysphonia, snoring, allergic rhinitis, vasomotor rhinitis, chronic sinusitis, chronic nasal congestion, allergic conjunctivitis, sneezing, hiccups, rhinitis, dysphagia, irritable bowel syndrome, gastritis, appetite suppression, chronic fatigue syndrome, fibromyalgia, anxiety, depression, restless leg syndrome, familial intentional tremor, migraines, autism spectrum, anxiety headaches, insomnia, sleep disorders, apraxia, and neck and shoulder pain. Similar positive results (i.e., positive results reported for all or more than half of all patients treated) also were seen with the other listed diseases or closely-related diseases.

While the methods for treating various diseases associated with the vagus and other cranial nerves have been described in the application in connection with various embodiments, the scope of the methods is not intended to be limited to the particular embodiments so disclosed. But on the contrary, the methods are intended to cover such alternatives, modifications, and equivalents, as may be included within the scope and spirit of the below claims.

CLAIMS

What is claimed is:

1. A method for treating a disease associated with a particular cranial nerve, comprising:

administering to an ear canal of a subject in need of such treatment a pharmaceutical composition, comprising: (i) an analgesic and (ii) an anesthetic;

wherein said pharmaceutical composition is administered to the ear canal of the subject in a concentration sufficient to physiologically alter the activity of the subject's particular cranial nerve compared to the physiological activity of that particular cranial nerve in a subject not administered the pharmaceutical composition.

2. The method according to claim 1, wherein the particular cranial nerve is the trigeminal nerve, the facial nerve, the glossopharyngeal nerve, or the vagus nerve.

3. The method according to claim 1, wherein the disease is at least one selected from the group consisting of: asthma, neurogenic cough, globus hystericus, spasmodic dysphonia, gastroesophageal reflux disease, and obesity.

4. The method according to claim 1, wherein the disease is at least one selected from the group consisting of: vasovagal reflex blockage, chronic bronchitis, asthmatic bronchitis, hypotension, hypertension, diabetes, bladder spasm, dysmenorrhea, pelvic pain, cystitis pain, enuresis, dysuria, dyspareunia, heavy menstrual flow periods, frequent urination, spasmodic dysphonia, snoring, allergic rhinitis, vasomotor rhinitis, chronic sinusitis, chronic nasal congestion, allergic conjunctivitis, sneezing, hiccups, rhinitis, dysphagia, irritable bowel syndrome, gastritis, appetite suppression, chronic fatigue syndrome, fibromyalgia, anxiety, depression, restless leg syndrome, familial intentional tremor, migraines, autism spectrum, anxiety headaches, insomnia, sleep disorders, apraxia, and neck and shoulder pain.

5. The method according to claim 1, wherein the analgesic is at least one pyrazolone derivative selected from the group consisting of ampyrone, dipyrone, antipyrine, aminopyrine, and propyphenazone.

6. The method according to claim 1, wherein the analgesic is antipyrine.

7. The method according to claim 1, wherein the anesthetic is at least one selected from the group consisting benzocaine, chloroprocaine, cocaine, cyclomethycaine, dimethocaine, larocaine, piperocaine, propoxycaine, procaine, novocaine, proparacaine, tetracaine, amethocaine, articaine, bupivacaine, cinchocaine, dibucaine, etidocaine, levobupivacaine, lidocaine, lignocaine, mepivacaine, prilocaine, ropivacaine, trimecaine, and pharmaceutically acceptable derivatives thereof.

8. The method according to claim 1, wherein the anesthetic is benzocaine.

9. The method according to claim 1, wherein the subject does not have an ear infection.

10. The method according to claim 1, wherein the pharmaceutical composition further comprises one of more of an antibiotic, a vasoconstrictor, glycerin, or acetic acid.

11. The method according to claim 1, wherein the pharmaceutical composition is administered in a solution.

12. The method according to claim 1, wherein the pharmaceutical composition is administered in a foam.

13. The method according to claim 1, wherein the analgesic is present in the pharmaceutical composition in a concentration of from 50 to 60 mg per mL and the anesthetic is present in the pharmaceutical composition in a concentration of from 10 to 20 mg per mL.

14. The method according to claim 1, wherein the analgesic is present in the pharmaceutical composition in a concentration of from 50 to 55 mg per mL and the anesthetic is present in the pharmaceutical composition in a concentration of from 10 to 15 mg per mL.

15. A method for treating post-tonsillectomy pharyngeal pain, comprising:

administering to an ear canal of a subject in need of such treatment a pharmaceutical composition, comprising: (i) antipyrine and (ii) benzocaine,

wherein said subject has had a tonsillectomy within the preceding 168 hours prior to administering said pharmaceutical composition, and

wherein said pharmaceutical composition is administered to the ear canal of the subject in a concentration sufficient to physiologically alter the activity of the subject's vagus nerve compared to the physiological activity of a vagus nerve in a subject not administered the pharmaceutical composition.

16. The method according to claim 15, wherein the subject has had a tonsillectomy within the preceding 48 hours prior to administering said pharmaceutical composition.

17. The method according to claim 15, wherein the pharmaceutical composition is administered to the ear canal of the subject within 4 hours of the subject undergoing a tonsillectomy.

18. A method for treating post-adenoidectomy pharyngeal pain, comprising:

administering to an ear canal of a subject in need of such treatment a pharmaceutical composition, comprising: (i) antipyrine and (ii) benzocaine,

wherein said subject has had an adenoidectomy within the preceding 168 hours prior to administering said pharmaceutical composition, and

wherein said pharmaceutical composition is administered to the ear canal of the subject in a concentration sufficient to physiologically alter the activity of the subject's vagus nerve compared to the physiological activity of a vagus nerve in a subject not administered the pharmaceutical composition.

19. The method according to claim 18, wherein the subject has had an adenoidectomy within the preceding 48 hours prior to administering said pharmaceutical composition.

20. The method according to claim 18, wherein the pharmaceutical composition is administered to the ear canal of the subject within 4 hours of the subject undergoing an adenoidectomy.

21. A method for treating asthma, comprising:

administering to an ear canal of a subject in need of such treatment a pharmaceutical composition, comprising: (i) antipyrine and (ii) benzocaine,

wherein said subject has asthma, and

wherein said pharmaceutical composition is administered to the ear canal of the subject in a concentration sufficient to physiologically alter the activity of the subject's vagus nerve compared to the physiological activity of a vagus nerve in a subject not administered the pharmaceutical composition.

22. The method according to claim 21, wherein the subject has suffered an asthma attack within the preceding 48 hours.

23. The method according to claim 21, wherein the subject has suffered an asthma attack within the preceding 60 minutes.

24. The method according to claim 21, further comprising:

monitoring the subject after the administration of the pharmaceutical composition and providing a second administration of the pharmaceutical composition upon indication that the subject is suffering from another asthma attack.

25. A method for suppressing appetite, comprising:

administering to an ear canal of a subject in need of such treatment a pharmaceutical composition, comprising: (i) antipyrine and (ii) benzocaine,

wherein said administering occurs at least once during a 24 hour period, and

wherein said pharmaceutical composition is administered to the ear canal of the subject in a concentration sufficient to physiologically alter the activity of the subject's vagus nerve compared to the physiological activity of a vagus nerve in a subject not administered the pharmaceutical composition.

26. The method according to claim 25, wherein the administering occurs at least 3 times during a 24 hour period.

27. The method according to claim 25, wherein the pharmaceutical composition is administered to the ear canal of the subject immediately upon the subject feeling hungry.

28. The method according to claim 25, wherein the pharmaceutical composition is administered to the ear canal of the subject from about 20 minutes to about 60 minutes prior to a food being consumed by said subject.

29. The method according to claim 25, wherein the pharmaceutical composition is administered to the ear canal of the subject concurrently with the consumption of a food.