NSS: An Adjunct for Treatment of Cancer Pain and Chemically Induced Nausea and Vomiting (CINV)

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Introduction
Non-traditional methods of controlling cancer pain have gained popularity and are a major growth industry in both Europe and the United States. One such nontraditional method is Complimentary Alternative Medicine (CAM). Patients choose CAM to maximize their chances of survival or to improve their quality of life both during and after conventional treatment, seeking help to manage unpleasant symptoms such as pain and chemically induced nausea and vomiting (CINV). Patients often seek these options from outside resources, other than their primary cancer treatment center, due to feeling uncomfortable discussing such avenues of treatment with their treating physician. (1) (2) As the incidence of cancer increases and the survival time lengthens the population seeking access to CAM is likely to increase. (3)

The Cancer Treatment Centers of America have built their reputation upon being inclusive, accepting, and even offering adjunctive CAM approaches. These centers address unpleasant symptomology in conjunction with conventional cancer care putting the patient at ease while emphasizing a patient centered approach of scientific care, comfort, and well being.

**History of IHS and the NSS**

The Innovative Health Solution’s (IHS) development team, with a varied background in: engineering; research; involvement in national pain management organizations; primary patient care; and multi-disciplinary traditional and non-traditional treatment approaches toward pain management, looked to the empirical scientific evidence centering on reproducible evidence-based results when developing the NeuroStim System (NSS). Measurable results of multiple treatments and its commonality were analyzed. The NSS, based on neuro-vascular anatomy, bio-thermodynamics, and fractal geometric principles, is the culmination of a progressive evolution in the field of peripheral nerve field stimulation.

The NSS after over nine years of development received FDA clearance in 2015 and was assigned its federal FSS number in August 2015.

IHS is actively involved with the Department of Defense conducting a randomized double blind study measuring the effect of the NSS on opioid consumption, pain reduction, and sleep improvement in the wounded warrior population. IHS is also involved in a randomized double blind clinical trial at The Wisconsin Children’s Hospital measuring the effect of the NSS on Cyclical Vomiting Syndrome and abdominal pain in children. (4) IHS is also in the developmental stage with several other universities and Veteran’s Administration Hospitals to study the effects of the NSS on autonomic dysfunctions relating to cancer and non-cancer pain.

**Identifying and Defining Pain**
The first step is to objectify and define pain. Pain is both a subjective and objective experience each with clinical observable, empirical evidence. All pain is co-factored with emotion, learned behavior, and individual responses. Acute pain may have little emotional components but chronic pain almost always does.

Pain in and of itself is a good thing. It is nature's warning system that harm is being done to the organism. It is what causes a person to take their hand off a hot stove. It is reflexive, reactive, and purposeful.

When pain outlives its purpose and becomes its own entity then there is a problem. Pain becomes its own separate entity, a disease of sorts, causing harm to rather than warning the individual.

The human organism is adaptive to pain. The body is built for survival so when a continual pain stimulus is present the body will adapt neurologically, physiological, and emotional to “live with the pain.” As a result, pain, over time, rather than being reflective of an underlying or extraneous noxious stimulate, takes on its own life form harming the “host.” Pain can no longer be a result of noxious stimuli but rather becomes the noxious stimuli.

Nausea is always associated with autonomic responses. If the situation is acute than the autonomic responses are acute, quickly repositioning the host into a state of quiescence. This encompasses not only physical assaults but chemical, bacterial, viral, and emotional. The response however is usually self-limiting.

When the aspects of time and emotion are added, the result is a chaotic adaptation of neuroplasticity involving all aspects of the autonomic nervous system and the tissues to which and from which they convey information.

The conditions most commonly recognized as involving noxious stimuli over extended periods of time and maladaptive autonomic neuroplasticity are Central Sensitization Syndrome (CSS), Post Traumatic Stress Disorder (PTSD), and fibromyalgia (5) Cancer with all of its physical, emotional, and financial stressors certainly fits this paradigm.

**Beyond Philosophy**

The next step in the NSS development was looking beyond philosophical and treatment dogmas that concentrate on empirical evidence defining the commonalities of various multi-disciplinary treatments. All chronic pain management techniques, from traditional to CAM, work some of the time but none works all of the time. Some techniques work best in singular fashion and others as adjunctive therapy.
Autonomic physiological conditions found in many different disease states are reactions and adaptations which are consistent, common, and predictable. Addressing these underlying autonomic reactions often result in a reduction of symptoms allowing a return to homeostasis. That was the common thread IHS discovered which lead to the development of the NSS co-joined with the use of the transillumination technique for optimal visualization of the auricular neurovascular bundles.

The NeuroStim System (NSS)

The NSS is a disposable convenience kit consisting of a battery powered pre-programmed neuro-modulating generator, an array of four electrode/needle arrays, connected by a wire harness, tape, skin disinfectant, application instructions, and a disposable light.

The generator is affixed to the skin behind the ear with supplied adhesive and the electrode/needle arrays are percuncateously implanted into the peri-auricular region as guided by transillumination to visualize and isolate the neurovascular anatomy of the external ear.
Once activated, the NSS is designed to produce a neuro-modulating signal running for 120 hours with a 2 (two) hour on and off cycle to help avoid attenuation of the neurovascular bundles and allow proper signal transmission for the life of the device.

The Results of NSS Stimulation

The NSS neurostimulator achieves a rapid onset of analgesia and is a safe, additive, non-addictive, non-pharmaceutical approach to pain management in a clinical setting. Electrode implantation into the skin of the ear allows for direct access to branches of Cranial Nerves V, VII, IX, X as well as branches of the occipital nerves. (6) Direct access to the arterial branches of the head and neck are accessible (7) and reduction of sympathetic stimulation results in an increase of vascular flow rate, reduction of vascular resistance, and increase of perfusion (8) (9) The arterial branches of the superficial temporal artery (STA) and the posterior auricular artery (PAA) form a rich interconnecting complex network the terminal branches of which anastomose throughout the ear.

The NSS neurostimulator may also alleviate other symptoms commonly associated with CSS (central sensitization syndrome) which involves “hyper-excitability” of the CNS resulting in headaches, body pain, confusion, sleep disturbances, and chronic fatigue. (10) Direct access by the NSS neurostimulator into the spinal cord via the lesser and greater occipital nerves, cranial nerves, and sympathetic reduction along
with endogenous endorphin production, may account for the reduction of these symptoms. Electro-analgesia is thought also to be mediated by three types of CNS opioid receptor sites: mu, sigma, and kappa (11) producing a more regionalized analgesia effect indicated by the use of the NSS neurostimulator.

In addition, the NSS, as a result of addressing the autonomic nervous system, alters the transmission information into the central nervous system by the reduction of the neuropeptide Substance P which is associated with inflammation, pain, and nausea. (12)

**Why the Ear?**

The external ear has been traditionally used in auricular acupuncture addressing reflex points, energy flows (Chi), or hot/cold energy flow. (13) (14)

However separate publications by Peuker and Filler (15) and Wiseman (16) indicate distinct peri-auricular neurovascular anatomy which can be tracked directly to the nucleus tractus solitarius, the hypothalamus, the thalamus, the hippocampus, the medulla, and the gray matter of the spine. Subsequent studies substantiate CNS activity as a direct result of peri-auricular neurovascular stimulation. (17)(18)(19)

The introduction of neurovascular transillumination, a technique patented by IHS, allows for accurate percutaneous implantation of the needle/electrode arrays based upon neuro-anatomy allowing for isolation and targeting of specific peri-auricular neurovascular bundles.
**Cancer Pain**

When people are injured, sick (cancer or non-cancer), or undergoing chemotherapy, the neuro-matrix is overloaded by nociceptive stimulation. The brain interprets the stimuli as pain, discomfort, nausea or a combination of the above. Pain/nausea are interpreted in the same neuro-matrix of the brain. The responses are mediated by the autonomic nervous system through a complex neurological/biochemical/vascular/cellular feed-back loop.

Central acting opioids are widely used for pain control in patients with cancer. While often effective they have many unwanted side effects negatively effecting the patient’s quality of life. (20)(21)

The concept of treating primary and metastatic cancer pain with Percutaneous Electrical Nerve Stimulation (PENS) is not a new concept. Publications supporting the efficacy of PENS for significant cancer pain control and reduction of opioid consumption have long been reported. (22)(23)

The NSS however is the only neuro-modulating PENS-type device used in conjunction with auricular transillumination that directly addresses the cranial neurovascular bundles providing stimulation directly to the central nervous system, is physician applied ambulatory treatment, lasting 120 hours per device. This allows the treating clinician to titrate needed medications against a base line of NSS autonomic nervous system stimulation according to the individual patient’s needs helping control pain and nausea in a multi-modal fashion. The use of the NSS allows for effective treatment of cancer pain and improvement in the patient’s quality of life not only by the pathways previously described but also by the lowering of the use of base line and break-through central acting opioids and minimizing their unwanted side effects.

**Chemically Induced Nausea and Vomiting (CINV)**

CINV is one of the most common side effects of both chemotherapy and narcotic use resulting in prolonged hospitalizations, change in activities, and depression. (24) Overall over 61% (sixty-one percent) of patients receiving chemotherapy for cancer treatment suffer from this unpleasant side effect and reported lower Functional Living Index-Emesis (FLIE) scores for quality of life despite prophylaxis. (25) CINV is ranked as one of the major complaints which can alter the patient’s compliance with chemotherapy. (26) In those with uncontrolled CINV the overall mean additional costs often exceed $ 5,000.00/ episode. (27)

While CINV is a complex entity originating from multiple etiologies, it is predominately controlled by the vomiting center (VC) of the brain. The VC is a complex of neurons composed of and interconnected to the thalamus,
hypothalamus, the amygdala, and the medulla oblongata. Cells in the intestine called the Enterochromaffin (EC) cells often contribute to CINV and act as chemo and mechano-receptors which are innervated by the vagus nerve and thought to be a major contributor interconnecting the various cellular structures involved in nausea and vomiting.

Neuromodulating stimulation from the percutaneous auricular placement of the NSS directly affects cranial nerve X a vital information pathway for autonomic pain and CINV.

**Vagus nerve**

The vagus nerve is an integral source of stimuli to the chemoreceptor Trigger Zone (CTZ) within the postrema region of the fourth ventricle of the brain affecting the CTZ and the VC with regard to emetogenisis. The vagus nerve is the primary afferent nerve of the GI tract and mediates messages to the brain to the Nucleus Tractus Solitarius (NTS) and receives sensory information from abdominal organs and the GI tract.

**Nucleus Tractus Solitarius**

The Nucleus Tractus Solitarius (NTS) is considered the main site for the termination of vagal afferents from the gut. The Dorsal Motor Nucleus of the vagus nerve (DMV) is the part of the brain where motor efferent signals to the gut originate. Several experiments with direct electrical stimulation to several cerebral locations have demonstrated emetogenic potentials. (28)

NSS auricular vagal (X) stimulation causes a decrease in the activity of the hypothalamus and hippocampus and an increase in activity of the Nucleaus Tractus Solitarius (NTS). The result is a reduction of sympathetic activity and an increase in parasympathetic activity, blocking of efferent signals to the brain and afferent signals to the gray matter of the spine through the medulla oblongata via cranial V. This stimulation is thought to reduce the co-morbidity of nausea and vomiting as well as autonomic components of pain affecting both the brain and intestinal receptors by similar pathways.
Summary

Great advances have been made in the treatment of cancer and its symptoms. Pain management is an essential adjunct to the treatment of cancer. Narcotics, while of utmost importance in the control of cancer pain, have their limitations and unwanted consequences. CINV is an unpleasant, costly, and unwanted side effect of chemotherapy and opioid use sometimes altering the ability of the patient to tolerate life saving treatment.

Pain/nausea are interpreted in the same neuro-matrix of the brain. The responses are mediated by the autonomic nervous system through a complex neurological, biochemical, vascular, and cellular feed-back loop. The percutaneous implantation of the NSS needle/electrode arrays directly stimulates peripheral branches of cranial nerves V, VII, IX, X; the peripheral branches of the lesser and greater occipital nerves; and the neurovascular bundles of the superior temporal and posterior auricular arteries resulting in an increase in parasympathetic activity, a decrease in the sympathetic activity, and an increase in endorphin and melatonin production. The neuro-modulating electrical stimulation of the NSS also interrupts the nociceptive stimuli reducing Substance P, altering corticosteroid levels, and allowing the body to return to homeostasis. The result is a centrally mediated reduction of pain, nausea, inflammation, anxiety/depression, and an increase in sleep.

The use of peri-auricular percutaneous electrical nerve field stimulation by the NSS in conjunction with visual transillumination of the neurovascular bundles of cranial nerves V, VII, and X is a promising adjunct to traditional methodology reducing the noxious autonomic components of cancer pain and associated CINV along with the potential reduction of central acting opioid consumption.
Biography

1. Christopher Brown DDS, MPS is head of scientific research and development for IHS. His degrees include a Bachelors (BS) from U Indy, Doctor of Dental Surgery (DDS) from Indiana University School of Dentistry, and a Masters of Professional Studies (MPS) from Lynn University. Proceeding Dental school Dr. Brown worked for The American Arthritis Society in research Immunology and while in dental school at IU Oral Health Research Institute. He is currently assisting with research development with several Universities, the Henry Jackson Foundation and the Defense and Veteran’s Center for Integrative Pain Management (DVCIPM). He served on the Board of Directors of The American Academy of Pain Management for 15 years and a term as the President.

Dr. Brown has authored many articles and textbook chapters regarding the diagnosis and treatment of acute and chronic pain and the bio-mechanics of physical trauma. His most recent publications (2014) are regarding the diagnosis and treatment of chronic fibrosing osteomyelitis (CFO) and the multi-disciplinary and multi-modality approach to chronic pain. In addition to the American Dental Association, Dr. Brown retains membership in The American Academy of Pain Management, The Society of Automobile Engineers, and the North American Neuromuscular Society. In addition to his role at Innovative Health Solutions Dr. Brown continues in private practice in Indiana with a concentration in head, neck, and facial pain and advancing clinical applications of peri-auricular percutaneous electrical nerve field stimulation (PENFS).

2. John Sacco, MD graduated from The Medical College of Virginia in 1982. He completed internships in Internal Medicine at Morristown Memorial Hospital in 1985, radiation oncology at New York University in 1988. His professional activities include faculty and clinical instructor of integrative medicine at The University of Cincinnati Medical Center and served previously as a clinical instructor at Stanford University. Dr. Sacco currently works at Oncology Hematology Care, Inc. in Cincinnati, Ohio serving both as a radiation oncologist and pain management.
Footnotes

4. clinicaltrials.gov