

INTERVENTIONAL PAIN MANAGEMENT

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INTRODUCTION:

The costs of unrelieved, chronic pain continues to be a major socioeconomic problem. Chronic, unrelieved pain is not only a major drain on scarce healthcare resources, but it is the cause of needless suffering of millions of people worldwide. Approximately 30 percent of the general population of the US suffers from chronic pain.ⁱ In a recent study of the general population of the state of Michigan, **The Michigan Pain Study**, it was found that one in five adults, or about 1.2 million people in Michigan suffer from some form of chronic, ongoing or recurring pain.ⁱⁱ The direct palpable costs to these patients and their families include loss of job, loss of income, loss of savings and security, loss of insurance, and loss of self esteem. Of the 1.2 million people in Michigan who suffer from chronic pain, 42 % say pain has affected their relationships with spouses, family members and fellow workers. 48% experience depression, 18 % have overdosed on pain medication and 10%, about 120,000 people, have contemplated suicide. Looking for relief from their pain has lead to 5%of the chronic pain sufferers in this population (representing approximately 60,000 adults) to drink alcohol, including 18%who admit to overdosing on their medications. Indeed, these figures paint a gloomy and compelling picture of the true costs of chronic, unrelieved pain to our society.

Clearly the consequences of intractable pain, in respect to both its impact our society is staggering; finding a solution should be a high priority for governmental agencies, healthcare intermediaries, and healthcare workers. Abandoning patients when less costly and less invasive interventions do not work to relieve pain and suffering is unethical and extremely costly to patients and their families; it just makes no sence. Interventional pain medicine is appropriate for patients suffering from chronic unrelieved pain and, based on efficacy reports in the literature, is justifiable, when less costly and less invasive therapies fail to relieve pain.

THE USE OF A PAIN TREATMENT CONTINUUM:

Pain of Terminal Illness:

These tools of the pain practitioner include all of the modalities and therapies, either conservative or invasive, that are used for treating chronic pain syndromes. These tools can be broadly organized as non-invasive and invasive therapies. **See figure #1** Non-invasive therapies include cognitive and behavioral therapies, rehabilitational pain therapies such as physical and occupational therapies, and alternative pain relieving therapies such acupuncture, acupressure, meditation/relaxation, Qui-gong, etc. Interventional pain therapies includes pharmacologic therapy, nerve blocking techniques, surgical interventions, neuromodulatory interventions (spinal cord stimulation, peripheral nerve stimulation, deep brain stimulation, and intrathecal therapies) and neurodestructive interventions.

In the early 1970's the World Health Organization (WHO), after much debate, provided guidelines for managing the pain of dying patients. These guidelines were an attempt to obey a recognized medical management principle, the KISS principle ("keep it sweet and simple"), simplifying pain management for cancer patients by suggesting the use of less invasive interventions that could be used by technologically advanced as well as technologically deprived societies. **See figure #2.** These guidelines in the form of a three step ladder, group cancer related pain syndromes by severity and intensity into mild, moderate, and severe pain and suggest "tailoring" strength and potency of pain medications to the severity of the pain syndrome. According to some, 80-90 percent of patients dying of cancer should have their pain well controlled using these guidelines.ⁱⁱⁱ

However, in certain populations, only 50% of patients receive benefit of the WHO guidelines.^{iv} Because this WHO pharmacologic tailoring approach provides adequate pain management 50-80 percent of patients suffering from pain of terminal illness, and because interventional approaches do work, some propose the addition of interventional strategies to the WHO guidelines as a

“fourth rung” of this ladder. **See figure 3.** Strategies that do not work should be abandoned for strategies that have not been tried. If at all possible, care givers should not give up on the goal of pain control and comfort care when less invasive therapies fail to provide adequate analgesia.

Pain of Non-terminal Illness:

Because there are also multiple noninvasive and invasive modality choices for the treatment of chronic nonmalignant pain, it is suggested that these patients be treated using an algorithmic treatment continuum such as the one suggested by the WHO for cancer patients. Obeying the time honored medical principle of utilizing simple, least invasive, and least costly interventions before using more invasive, highly technological, and more costly interventions (the KISS principle), it is suggest that an algorithm of treatment, **a pain treatment continuum**, that lists available pain therapies by increasing order of both invasiveness and cost be used for the treatment of patients with chronic pain. **See figure 4.**

Referral to a pain specialist who performs interventional techniques should be made either for diagnostic purposes to locate the “pain generator” or when the referring physician acknowledges that all of his or her good intentions have failed to provide adequate analgesia to the patient with chronic pain. Pain management is multifactorial and requires interdisciplinary expertise. A pain specialist using interventional strategies should do so in the context of an interdisciplinary practice. Referral to pain specialists who do not provide interdisciplinary pain medicine, but only perform blocks or implantation of implantable devices is, in the estimation of this author, doomed to fail. The following paragraphs are intended to introduce the reader to only some and not all of the interventions that interventional pain managemt physicians may be able to offer the patient who has failed more conservative attempts to provide adequate analgesia.

NERVE BLOCKS IN THE MANAGEMENT OF PAIN

Nerve blocks with local anesthetic or neurolytic agents are helpful to manage intractable pain. Nerve blocks for pain may be used diagnostically to determine the pain generator, prognostically as outcome indicators of neurolytic procedures, therapeutically for peripheral or central blockade, analgetically for painful procedures or surgery, and to preempt the propagation of chronicity of pain. Nerve blocks that are used in cancer and non cancer include head and neck blocks, blocks of the cervical, thoracic, and lumbar spinal axis, peripheral nerve blocks, and blocks of thoracic, abdominal and pelvic visceral nerves.

Nerve Blocking of the Head and Neck:

Local anesthetic blocks of the nerves of the head include blocks of the gasserian ganglion, the ganglion of the trigeminal nervous system which lies within meckel's cave, just inside the foramen ovale of the skull, blocks of the peripheral trigeminal nervous system including blocks of the maxillary, ophthalmic and mandibular branches of the trigeminal system, blocks of the sphenopalatine ganglion, and blocks of the glossopharyngeal and hypoglossal nerves. These blocks may be, as stated above, for diagnostic purposes or therapeutic purposes to evanescently relieve patients of pain and suffering.

Blocks of the neck include blocking of the cervical plexus, a plexus of anterior primary divisions of the upper four cervical nerves, blocks of the brachial plexus, blocks of nerve roots, blocks of the facet joints and epidural analgesia.

Sympathetic Blocks

The paravertebral sympathetic chain consists of sympathetic neural tissue from several sympathetic plexuses that run along the paravertebral region of the body. These axial sympathetic chains include the cervical, thoracic and lumbar sympathetic ganglia. The sympathetic system receives afferent nociceptive impulses from visceral fibers of the head and

neck and upper extremities (stellate ganglion), from the cardiothoracic viscera (thoracic sympathetic ganglia), from the abdominal viscera (celiac plexus), from the uro-genital system and lower extremities (lumbar sympathetic ganglia), and finally from the pelvic viscera (superior hypogastric plexus and ganglion of impar).. Pain information from the sympathetic nervous system can be controlled by either anesthetic nerve blocking or by neurolysis of these ganglia using chemical, surgical, or radiofrequency thermal lesioning or cryoneurolysis.

The **stellate ganglion** is formed by fusion of the inferior cervical and first thoracic sympathetic ganglia. The stellate ganglion, lying over the neck of the first rib, controls sympathetic outflow to the head, neck and upper extremity. Stellate ganglion block is indicated for the treatment of sympathetically mediated pain of the head, neck, and upper extremities. This block is also used to increase perfusion of the upper extremities, to decrease excessive perspiration of the head, neck, or upper extremities, as in hyperhidrosis, or used for patients suffering from cluster headache.

Blocking of the stellate ganglion can be performed “blindly” from an anterior approach utilizing anatomic surface landmarks, however, performance of this block under fluoroscopic guidance may ensure diagnostic specificity when using the block to establish a diagnosis of sympathetically mediated pain. Serious complications associated with the stellate ganglion block include pneumothorax, damage to the recurrent laryngeal nerve, local anesthetic induced seizures from inadvertent injection into the vertebral artery and/or intradural or subarachnoid injections resulting in high spinal anesthesia, respiratory depression and even death.

Pre-ganglionic neurons from the intermediolateral horn of T5-T12 exit the spinal cord to join the white rami communicans. Instead of synapsing in the sympathetic chain and pre-vertebral sympathetic ganglia, they pass through the chain to synapse at the **celiac plexus**. The celiac plexus lies anterior to the aorta at the level of the L-1 vertebral body and anterior to the crura of

the diaphragm. The celiac plexus receives afferent nociceptive impulses from all abdominal viscera except the transverse colon, the descending colon, the sigmoid colon and the rectum. Intractable pain originating from the structures enervated by the celiac plexus can be blocked by local anesthetic injection or by neurolysis of the celiac plexus with alcohol or phenol. Celiac plexus block may be performed under fluoroscopic or CT guidance.^{v, vi}

The lumbar sympathetic ganglia are located anterolateral to and along the L2 and L4 vertebral bodies bilaterally between the vertebral bodies and anterior and medial to the psoas major muscle. Indications for **lumbar sympathetic blockade** include sympathetically mediated pain relating to radiation lumbosacral plexitis, phantom limb pain, herpes zoster, neuropathic pain of the lower extremity, vascular insufficiency secondary to malignancy, spread of tumor to involve sympathetic neural structures, complex regional pain syndromes (reflex sympathetic dystrophy or causalgia), vasospastic disorders of the lower extremities, and peripheral vascular disease. This block should be performed using fluoroscopy to prevent some of its inherent complications including bleeding, infection, profound hypotension, inadvertent epidural or intrathecal injection, intraneural injection, and inadvertent intravascular injection. Chemical neurolysis with alcohol may be associated with rare damage to the genitofemoral nerve resulting in groin and flank pain^{vii} or damage to the artery of Adamkiewicz resulting in flaccid paraplegia and spinal sensory dissociation.^{viii}

The **superior hypogastric plexus** is located bilaterally at the lower one third of the fifth lumbar vertebral body and upper one third of S-1 vertebral body in proximity to the bifurcation of the common iliac vessels. The pelvic splanchnic nerves arise from the second, third, and fourth sacral nerves. Sympathetic afferents from the distal end of the transverse colon, left colic flexure, the descending colon, the sigmoid colon, and finally the rectum, and parasympathetic afferents from the sacrum ascend to the superior hypogastric plexus via the hypogastric nerves. Pelvic visceral pain can be alleviated by blocking the superior hypogastric plexus.^{ix} Complications of this block are similar to those of lumbar sympathetic blocks. Because this

block is performed at a lower vertebral level than the block performed for lumbar sympathetic nerve block, the risk of damage to the artery of Adamkiewicz is minimal. Spreading of the solution laterally from the anterolateral border of the bodies could result in damage to the genitofemoral nerve. Since the superior hypogastric plexus carries both sympathetic and parasympathetic efferent and afferent fibers involved in the control of micturition, bowel motility, and sexual function, alcohol neurolysis of this plexus could conceivably impact negatively on these vital and important functions.

Epidural Steroid Injections

The placement of steroid around inflamed epidural tissues, though controversial, has been shown to be efficacious in certain individuals. Much has been written about the efficacy of epidural steroid injection in the low back pain population. Epidural steroid injections are used as an alternative to surgery as more conservative efforts should be exhausted prior to an invasive surgical procedure. However, there remains debate as to whether epidural steroid injections in the low back pain patient, including diagnosis of herniated nucleus pulposus and spinal stenosis, are helpful in relieving back and leg pain. Several investigations have been carried which show conflicting results. Some studies support the use of epidural steroid injection in decreasing low back pain,^{x, xi} while others state that no conclusion can, as yet, be made regarding the efficacy of epidural steroid injection in low back pain.^{xii, xiii} Explanations for this discrepancy lay in the methodological design of patients studied. Patients with low back pain secondary to spinal stenosis do not appear to respond to epidural steroid injections as well as those patients with herniated discs. Additionally, the long-term benefits of epidural steroid injections appear to be greater in patients with disc herniations.^{xiv} Epidural steroid injections, however, have been proven to be safe. There are few published reports of consistent complications as a result of an epidural injection procedure. The most common complications are headache (non-positional) 3.1%, incidence of a minor complication is reported at 9.6%.^{xv, xvi} Additionally, randomized case controlled studies are needed to validate the use of epidural steroid injections in chronic low back pain.

Continuous Epidural Analgesia:

Local anesthetics are commonly used for the relief of pain in both acute and chronic states. However, in certain circumstances, single bolus administration of a local anesthetic may not be sufficient in controlling pain. The use of continuous epidural infusions for the control of both acute and chronic pain have been well established.^{xvii,xviii,xix} Pain states in which continuous epidural infusions may be indicated include uncontrolled neuropathic pain processes, failed neck and back surgery syndrome, brachial and lumbosachrial plexopathies and cancer pain. Pain states which require a sustained sympathetic blockade such as in complex regional pain syndromes type I and II, and limb ischemia would benefit as epidural analgesia does result in a chemical sympathectomy. In addition to continuous analgesia, tighter control of drug dosages delivered to the epidural space can be achieved. In cases where pain cannot be controlled with oral or epidural therapies, the amount of oral medication required for pain relief results in intolerable side effects. In this setting, epidural analgesia would be indicated as lower concentrations of medication can be used to achieve pain relief.

Various medications have been used in continuous epidural analgesia including local anesthetics, opioids, and alpha-2 agonists.^{xx} The major complications of epidural anesthesia are infection, dural penetration, spinal cord damage, and respiratory depression. One major drawback to the use of continuous epidural analgesia is that it is not as useful in conditions involving multiple pain states, as the epidural catheter is in a fixed position in the epidural space. Raj, et al, suggest that medications delivered into the epidural space provides analgesia for 5-7 continuous dermatomes.

Intrapleural Analgesia:

Intrapleural analgesia has been used in a variety of painful conditions including metastatic bronchogenic carcinoma^{xxi}, breast surgery^{xxii}, minimally invasive direct coronary artery bypass grafting^{xxiii}, open cholecystectomy^{xxiv}, pancreatic carcinoma^{xxv}, and post thoracotomy syndrome.^{xxvi} Intrapleural analgesia can also be used to produce an upper extremity

sympathectomy. It also has clear indications in both acute and chronic pain syndromes. However, actual efficacy depends on the drug and for which condition the drug is being administered. In those conditions in which intrapleural analgesia helps to decrease pain, several mechanisms of actions have been postulated. As the drug or drugs diffuse through the pleura, a block of the thoracic sympathetic chain and the splanchnic nerves may occur. Additionally, multiple intercostal nerve blocks may occur. Upper extremity analgesia is thought to occur through diffusion of the medication to the brachial plexus.^{xxvii}

An important consideration regarding the use of intrapleural analgesia is that bilateral analgesia should not be attempted secondary to risks of bilateral pneumothorax, and that patients that have pleural adhesions would be at further risks of pneumothorax. Moreover, patients with emphysema and empyema, pleural effusions, or pulmonary fibrosis should be carefully considered for intrapleural analgesia secondary to differential absorption of local anesthetic, technical difficulties, and additional risk of pneumothorax.

Neurolytic techniques

Neurolysis, or destruction of neural tissue may be performed surgically, chemically, thermally with radio frequency, or by freezing by cryoneurolysis. A careful selection of patients and a thorough understanding of the pathophysiology of the specific disease process may help determine the appropriate modality for neurolysis. Several chemical neurolytic agents may be used including commercially available preparations of absolute ethyl alcohol, phenol, or glycerol.

Absolute, 100 percent alcohol is available in the United States. It acts by precipitation of the proteins in neural tissue and extraction of phospholipids and cholesterol resulting in neural degeneration. Alcohol may be used for neurolysis of the trigeminal, glossopharyngeal, celiac, lumbar and superior hypogastric sympathetic ganglia. If used intrathecally, alcohol is relatively hypobaric and therefore rises in the cerebrospinal fluid (CSF) after injection. Because alcohol

rises in CSF, correct positioning of a patient undergoing alcohol subarachnoid neurolysis cannot be over emphasized. Alcohol neurolysis is extremely painful and is usually, except when used in the subarachnoid space, preceded by injection of local anesthetic to block the area before the injection of the alcohol.

Phenol, in lower concentrations, acts as a local anesthetic, but at higher concentrations is neurodestructive. Phenol therefore lacks the local algesic properties of alcohol. Commonly used phenol concentrations vary between 6 and 10 percent. Unlike alcohol which is hypobaric relative to CSF, phenol is hyperbaric relative to the CSF. Both phenol and alcohol have been used for neurolysis of peripheral nerves, but both might cause peripheral neuritis. The incidence of peripheral neuritis is greater when alcohol is used.^{xxviii, xxix}

Thermal destruction of neural tissue is performed using a radiofrequency generator system. Electrical currents generated by the radiofrequency generator heat tissue surrounding the non-insulated radiofrequency needle tip which raises the temperature of the electrode tip which produces the thermal lesion. Radiofrequency thermocoagulation is indicated where neurodestruction of central neural tissues is indicated and when the tissue to be destroyed is accessible to placement of the radiofrequency probe or needle. Radiofrequency thermocoagulation has been used for thermal lesioning of the Gasserian trigeminal ganglion,^{xxx,xxxii} neural enervation of cervical, thoracic and lumbar facet joints,^{xxxii,xxxiii,xxxiv,xxxv} sacroiliac joints,^{xxxvi} the cervical and thoracic sympathetic chain,^{xxxvii} the lumbar sympathetic chain,^{xxxviii,xxxix} and cervical, thoracic, lumbar, and sacral dorsal root ganglia.^{xl}

Cryoneurolysis, unlike radiofrequency thermal neurolysis, may be used for neurolysis of peripheral nerves. To perform cryoneurolysis, a cryoprobe consisting of an inner and an outer cannula is placed on or in very close proximity to the nerve being frozen. High pressure N₂O or CO₂ is passed via the outer cannula to a cooling chamber and returns via the inner cannula. This process expands the gas and rapidly cools the tip of the probe to -70° centigrade. Like

radiofrequency thermal neuroablation, cryoneurolysis has been used for temporary cryodestruction of several spinal pain generators such as those arising from the spinal facet joints, neuromas of the ilioinguinal and iliohypogastric nerves, and the coccygeal nerve for coccydynia. Pain emanating from the branches of the trigeminal nerve can be relieved with cryoneurolysis of these branches.¹¹ Patients may experience pain relief after undergoing cryotherapy for 3-6 months but actual pain relief may vary in individual cases.^{xli,xlii,xliii}

IMPLANTABLE TECHNOLOGY FOR THE CONTROL OF PAIN:

In the above paragraphs we have laid the foundation for the appropriate use of implantable technologies. As seen above, there are multiple therapies for the treatment of chronic pain, and implantable technologies, by nature of it being invasive and costly, should be used when less invasive and less costly therapies, including the non-invasive therapies and invasive therapies discussed above, fail to work. In the following sections of this chapter I will discuss implantable devices for the control of pain., but limit this discussion to spinal cord stimulation SCS and intrathecal therapies.

SPINAL CORD STIMULATION:

Spinal cord stimulation, for the clinical control of pain, was first introduced in 1967 by Norman Shealy, M.D.^{xliv} and colleagues in response to the publication of the gate control theory of pain by Melzack and Wall, in 1965.^{xlv} The gate control theory, as first published, without benefit of later refinements, stated that painful “electro-chemical” nociceptive information in the periphery is transmitted to the spinal cord in small diameter, unmyelinated c-fibers, and lightly myelinated A-delta fibers. These fibers would also, in turn, terminate at the substantia gelatinosa of the dorsal horn, “the gate,” of the spinal cord. At the same time, other sensory information such as touch or vibration, carried in large myelinated A-beta fibers, would also converge and terminate at this gate of the spinal cord. The basic premise of this theory is that reception of large-fiber information, such as touch or vibration would turn off or close the gate to reception of small-

fiber information. These authors theorized that the clinical end result of this gate closure would be analgesia.

Shealy, et al. theorized that the electrical stimulation of large A-beta fibers of the dorsal columns would antidromically inhibit reception of painful small-fiber information at that stimulated spinal segment and all other information “downstream” from the area of stimulation. They called this electrical stimulation of the spinal cord dorsal column stimulation. Since it is now known that this electrical stimulation inhibition of pain occurs, not only at the dorsal columns, but also at the dorsal root entry zones and other regions of the spinal cord, the term dorsal column stimulation is now supplanted by the more accurate term of spinal cord stimulation (SCS).

Spinal Cord Stimulation: What Is It?

Spinal cord stimulation for pain control is therapy based on producing an electrical field over the spinal cord, that, blocks pain of neuropathic origin, **not** pain of nociceptive origin.. The electric field is propagated by either an external neuropulse generator which transmits an electrical pulse, via cable, to an externally worn antennae that is radio-coupled to an implanted receiving device (RENEW®, Advanced Neuromodulation Systems, Plano, Texas) **See figure #3**

Figure 1 PLACE FIGURE #3 HERE: RENEW SYSTEM OF ANS

or by an implanted, programmable neuropulse generator (ITREL-3® or SYNERGY® Medtronic, Minneapolis, Minnesota or GENESIS®, Advanced Neuromodulation Systems, Plano, Texas) that contains a battery pack, an antenna and a computer module that allows for programming externally. **See figure 4, and 5**

Figure 2 **PLACE FIGURE #4 HERE: SYNERGY SYSTEM OF MEDTRONIC**

Figure 3 **PLACE FIGURE #5 HERE: GENESIS OF ANS**

After generation, the electrical pulse is transmitted to its intended target, the spinal cord, via an implanted electrical cable connected to a surgically (mini-laminotomy electrodes) or percutaneously implanted array of electrodes. These electrodes are placed directly into the epidural space either over the spinal cord segment processing the patients pain or from a retrograde direction over the nerve roots conducting the patients pain. **See figure #6**

Figure4 **PLACE FIGURES #6 HERE: DIFFERING ELECTRODES FROM MEDTRONIC**

Very early on in the development of this therapy intrathecally placed monopolar or non-programmable bipolar SCS leads were placed, but after the development of early problems and therapy limiting complications, these intrathecal leads were supplanted by quadropolar and octopolar leads that were only able to be programmed at the time of the initial surgery. Still later on, due to advances in technology, multichannel quadropolar and octopolar leads, implanted epidurally and utilizing bipolar or multipolar stimulation were introduced and were found to be superior to single channel devices. Prior to the early 1990's most, if not almost all, electrode arrays were single quadropolar or single octopolar electrodes. Today, multiple electrode arrays with multiple contacts, placed either percutaneously into the epidural space through an appropriate needle or directly through a laminotomy incision have been developed. These electrode arrays allow for, at least, bipolar stimulation and allows for the external reprogramming of these devices. These four-contact quatropoles and eight-contact octropoles provide the ability to change the cathode-anode combinations to better locate affected painful areas, as well as accommodate for electrode migration. It has been calculated that with a longitudinal lead of four contacts, 65 different anode-cathode combinations can be programmed and in a lead with eight contacts, 6000 combinations are possible. Advances in programming technology also allow for the independent programming of multiple (up to 24) differing programs. This complex, advanced programming is facilitated by the use of a computer program. **See figure #7**

Figure 5 **PLACE FIGURE #7 HERE: PAIN DOC FROM ANS**

Mechanism Of Action Of SCS

As stated above, SCS, for the clinical control of pain, was first introduced in 1967 by Norman Shealy, M.D and colleagues in response to the gate control theory of Melzack and Wall. Shealy, et al., theorized that the electrical stimulation of large A-beta fibers of the dorsal columns would antidromically inhibit reception of painful small-fiber information at that stimulated spinal segment.

Foreman, et al., investigating the effects of “dorsal column stimulation” (SCS) on spinothalamic tract cells in anesthetized monkeys,^{xlvi} theorized that SCS segmentally turned off lamina V cells of the gray matter of the spinal cord. Their theory was confirmed by their experiments where SCS was applied to mid-thoracic or cervical dorsal white matter of the spinal cord, while responses of spinothalamic cells to von-frey hair activation of the sural nerves were examined. These authors found that dorsal column stimulation depressed the activity of spinothalamic tract cells for about 150 ms. and the best points for stimulation producing inhibition were over the ipsilateral dorsal columns. Lesioning of the dorsal columns eliminated this depression of activity by SCS stimulation below the lesion. Lesioning the lateral columns in this model had no effect.

Another theory supporting the notion that spinal cord stimulation works segmentally is that stimulation blocks actual transmission of electrochemical information anywhere in the spinothalamic tracts. In a study published in 1974, SJ Larson, et al, using averaged somatosensory recordings from scalp electrodes in 18 patients with cancer and intractable pain, before, during, and after application of current, found in 11/18 patients, that there was decreased perception of touch and joint rotation and pain below the level of stimulation.^{xlvii} All neurological changes returned to baseline one hour after cessation of this current. SCS was also applied to 15 monkeys over the lower, middle, and upper thoracic spinal cord, in nucleus ventralis posterior lateralis, and over the sensory motor cortex. Results of these studies suggested that applied currents blocked neuronal transmission by producing local changes in the

cord. The authors suggest that this alteration of cerebral evoked potentials and relief of pain could also, alternatively, be secondary to changes in supraspinal neurons.

Alternatively, as suggested by Larson, et al, stimulation of the dorsal columns or stimulation of the spinal cord could produce changes in supraspinal neurons effecting either pain transmission or pain modulation. Saade, et al, studying this possible effect of stimulation on supraspinal centers utilized a rat model of antinociception for two types of pain tests, the tail immersion test and the formalin test representing two different putative neurophysiological mechanisms of “phasic” and “tonic” pain respectively.^{xlvi} Dorsal column nuclei were stimulated through chronically placed electrodes rostral to bilateral dorsal column lesions. Effects of dorsal column nuclei stimulation and dorsal column stimulation were then observed for the above tests of antinociception. The results showed a clear antinociceptive effect of dorsal column nuclei stimulation on both experimental models of phasic and tonic pain in the awake animals studied. The authors concluded that these effects could be attributed to the activation of supraspinal pain modulating centers since antidromic activation of dorsal column stimulation was prevented by dorsal column cuts caudal to the stimulating electrodes.

Since vasodilatation is a consistent post-stimulation finding in animal models and humans alike, a fourth mechanistic theory for SCS is that SCS activates central inhibitory mechanisms influencing sympathetic efferent neurons. These vasodilatory effects might only be secondary to the pain relieving effect of SCS, might be secondary to antidromic effects on small afferent fibers, and might also be secondary to direct effects of SCS on central neurophysiological mechanisms controlling sympathetic efferent outflow from the spinal cord. According to Linderoth, et al, the theory that SCS antidromically activates primary afferent fibers including unmyelinated, small diameter fibers leading to the vasodilatory effects of SCS, based on the work of Bayliss^{xlix} from experiments performed at the turn of the century, is unlikely since this mechanism of action would require the recruitment of high threshold, unmyelinated fibers not usually activated by SCS in clinical situations. In a study, testing this hypothesis of antidromic

activation of small diameter fibers, Linderoth and his co-authors observed that vasodilation, as measured by laser doppler flowmetry, was present after SCS and stimulation of the proximal ends of cut dorsal roots innervating the hind limb, but not after stimulating the distal end of these same cut nerve roots.¹ The conclusion of this study was that SCS antidromically activates a central “loop” and not small afferent fibers for post- stimulation vasodilatation to occur. Another possible mechanism for this vasodilatory response to SCS is that stimulation releases vasoactive substances such as vasoactive peptide (VIP), substance P, or calcitonin gene related peptide (CGRP). Most recently, Croom and Foreman have shown that peripheral vasodilatation at high rates of stimulation do, in fact, antidromically activate c-fibers in the dorsal roots causing release of CGRP in the periphery leading to stimulation induced vasodilation.^{li}

Linderoth and colleagues from the Karolinska institute in Sweden, more than any other group, have helped elucidate the autonomic effects of stimulation induced vasodilatation. In his studies with the rat model, Linderoth has shown that high spinalization of rats prior to SCS, in of itself, causes vasodilatation which further increases after SCS, presumptive evidence that SCS induced vasodilatation is not secondary to supraspinal autonomic centers.^{lii} Also, in these same rat studies, sectioning of the ventral roots, alpha adrenergic blockade, and bilateral lumbar sympathectomy were found to abolish SCS induced vasodilatation.

Since it was known that SCS causes vasodilatation in animal studies, clinicians have used this modality for the treatment of clinical pain due to peripheral vascular disease in humans. LE Augustinsson, et al., from the department of Neurosurgery at the University of Goteborg, Sweden, published a paper in 1985 which showed significant pain relief and healing of painful ischemic ulcers in patients with both vaso-occlusive and vaso-spastic disease.^{liii} In this study of 34 patients with severe limb ischemia with resting pain and ischemic ulcers in most, 26 had arteriosclerotic peripheral vascular disease, 1 had Buerger’s disease, and 7 had severe vasospastic disease. 94% percent of patients in the entire group experienced pain relief and 50% experienced healing of their ulcers. Of note is that only 38% of the stimulated group underwent

subsequent amputation compared to 90% of a comparative control non-stimulated group over a mean follow-up period of 16 months.

A fifth and final theory for mechanism of action of spinal cord stimulation, based on the clinical observation in patients that pain relief often outlasts actual electrical stimulation of the spinal cord by minutes, hours, or even days, is that stimulation might release putative neuromodulators, effecting this prolonged pain relief. This theory has been tested by numerous investigators with often confusing and conflicting results. Levin, et al, in 1980, found an increase in epinephrine in the CSF after SCS^{liv} and Meyerson, et al., found an increase in substance P like immunoreactivity in the CSF after spinal cord stimulation.^{lv} Naloxone, while reversing the antinociceptive effects of deep-brain periaqueductal or periventricular stimulation, does not reverse the pain relieving effects of SCS.^{lvi} Tonelli, et al., observed increases in B-endorphin and B-lipotrophin in the CSF of some patients after SCS.^{lvii} Broggi, et al, in spinal tissue of rats, and Richardson and Dempsey, in the cerebrospinal fluid of humans, found elevations in serotonin and 5-HIAA, the metabolite of serotonin, after spinal cord stimulation.^{lviii,lix} Likewise, in cats, Linderoth, et al, using high-performance liquid chromatography for serotonin and radioimmunoassay for substance P, observed elevations of serotonin, but not 5- HIAA, after SCS applied to the thoracic spinal cord.^{lx} These authors also found that substance P like immunoreactivity did not increase in the dorsal horns after SCS in decerebrated animals, but significantly increased after SCS in normal animals. The clinical significance of these studies is yet to be elucidated.

Most recently, Cui, et al., have looked at the role of both alanine and GABA on the effects of SCS.^{lxi, lxii} They have found that, using dorsal horn microdialysis probes, in neuropathic pain rat models, there is a decrease in GABA in the dorsal horn. After SCS, there is an increase in the release of GABA in these rats. Psychophysiologic pain studies show an improvement in pain behavior after SCS. In a separate study, in a group of rats that do not receive analgesic benefit of

SCS who do not release GABA after SCS, the addition of Baclofen, a GABA-b agonist, leads to an increased release of GABA and a return to anti-nociception.^{lxiii}

Efficacy Of SCS:

In the field of spinal cord stimulation there are numerous retrospective studies that tout the efficacy of spinal cord stimulation. These studies or reports usually lump patients together that have varied and differing pain syndromes. The take home message of most of these reports is that there appears to be approximately a 60% efficacy rate that lasts approximately 2 years. After 2 years, for whatever reason, there appears to be a fall off of efficacy in some patients. As stated above, spinal cord stimulation, not only has efficacy in neuropathic pain of appendicular origin, but has known efficacy in patients with back pain secondary to failed back surgery syndrome, degenerative disk disease, and chronic arachnoiditis, CRPS, peripheral vascular disease, and in patients with intractable angina.

Failed back surgery syndrome (FBSS) is a commonly recognized indication for spinal cord stimulation.^{lxiv} Some authors have suggested that mixed neuropathic and nociceptive processes associated with failed back surgery syndrome is the most common indication for this modality.^{lxv, lxvi} The incidence of failed back surgery syndrome has been reported to be between 20-40%^{lxvii}. Using the most common criteria for "success" after spinal cord stimulation implantation, which is greater than or equal to 50% pain relief, pain relief has been experienced in 11-70% of patients with FBSS.^{lxviii} An explanation for this wide range of success rates may have to do with the difficulty in alleviating the back pain which is often associated with leg pain in the FBSS patient. In fact this back pain after back surgery may be due to nociceptive processes and not to neuropathic processes. As we have seen, SCS does not relieve pain of nociceptive origin. Some authors have suggested that dual SCS electrodes on both sides of the midline can relieve axial low back pain.^{lxix} However, a follow up study by North, et al, demonstrated no difference with regard to decreasing back and leg pain when using either single or dual spinal cord stimulating electrodes.^{lxx} While the issue of concurrently treating low back

pain associated with limb pain with single or dual electrodes persists, most practitioners continue to favor dual electrodes in those patients with bilateral lower extremity pain. In general, a decrease in the need for oral pain medications and an improvement in function can be attained in a successful trial of spinal cord stimulation.

Success rates with spinal cord stimulation and angina pectoris have been reported. Linderoth, et al., have stated that "the most rewarding indication for spinal cord stimulation is angina pectoris" as up to 80% of patients with angina receive pain relief with spinal cord stimulation at one year follow up. At the five-year follow up mark, approximately 60% of patients continue to enjoy pain relief^{lxxi}. The pain associated with peripheral vascular disease is well documented. In addition to heaviness and a squeezing discomfort a burning sensation is also experienced in those patients suffering from peripheral vascular disease and claudication. Although studies have shown improvements in both blood flow and pain relief^{lxxii,lxxiii}, spinal cord stimulation for the use of peripheral vascular disease is not widely practiced. In Broseta's study, nearly 80% of patients with peripheral vascular disease who received a permanent spinal cord stimulating implant obtained good or excellent relief, and a significant improvement in function including improved walking distances, endurance, increased healing ulcer rates.

Studies have supported the use of spinal cord stimulation in treating the neuropathic components as well as the swelling components of complex regional pain syndrome (CRPS) Types I and II. In a 13 patient study by Kumar, et al, all with CRPS Type I, 100% of his patient population reported good or excellent pain relief at the 40 month follow up mark.^{lxxiv} Kemler et al, more recently, published the results of a randomized trial of two groups of patients, one group receiving physical therapy alone for their CRPS and the other group receiving physical therapy plus spinal cord stimulation for their pain. In an intention-to-treat analysis, the group assigned to physical therapy plus spinal cord stimulation had a mean reduction of 2.4 cm in the intensity of pain at six months, as compared with an increase of 0.2 cm in the group assigned to physical therapy alone. Also, this group found that the group randomized to SCS and physical therapy

had a global satisfaction scale much higher than the group with physical therapy alone.^{lxxv} Others, however, have shown variable results.^{lxxvi} In Barolat's study, 18 patients with CRPS were evaluated. 22% reported no pain relief, whereas 78% reported moderate to good relief in their pain. What are reported in successful outcomes are a decrease in hyperalgesia, allodynia, and chronology of the condition does not seem to change efficacy.^{lxxvii} Spinal cord stimulation remains a viable option in treating neuropathic as well as nociceptive pain.

INTRATHECAL THERAPIES

The discovery of opioid receptors and endogenous opioid compounds in the spinal cord^{lxxviii, lxxix, lxxx} provided rationale for early attempts to deliver opioid drugs intraspinally, first in experimental animals^{lxxxii, lxxxiii} and then in patients with chronic pain.^{lxxxiii, lxxxiv} This experience with “selective spinal analgesia”^{lxxxv} appeared to offer specific benefits to some patients and was followed by trials of continuous subarachnoid opioid infusions using implanted pumps with factory pre-set flow rates.^{lxxxvi, lxxxvii} This documented efficacy, however, is directly related to specific opioid-responsive or opioid-resistant pain syndromes.^{lxxxviii, lxxxix, xc}

Intraspinal Opioids: Selection Criteria For Pain Of The Terminally Ill

Selection criteria for the use of intraspinal opioid therapy in patients with cancer or AIDS related pain is relatively straightforward. In those cancer patients, in whom the systemic delivery of opioids is not working, because of either dose limiting toxic and intractable side-effects or because patients have developed opioid non-responsive pain syndromes, a trial of intraspinal opioids alone or in combination with non-opioids such as local anesthetics or the alpha-2 agonist, clonidine is indicated. Because these therapies are costly, it is also recommended by some authors that intraspinal, implantable opioid and non-opioid therapies be reserved for patients who have at least 3 months to live. Patients who do not have at least 3 months to live, who do not tolerate systemic delivery of opioids, who have successfully completed a trial of

intraspinal delivery of opioids, are candidates for the external delivery of spinal analgesics via an externalized catheter and external pump delivery system.^{xci}

Intraspinal Opioids: Selection Criteria For Non-Malignant Pain Syndromes

The selection criteria for patients with non-malignant pain is not so straight forward as with patients suffering pain from malignant disease. Because of the controversy surrounding the use of systemically administered opioids for the treatment of non-malignant pain, the use of intraspinal agents for non-malignant pain is also controversial. Clearly, as stated above, there is known efficacy for the use of intraspinal agents for cancer pain. There is also much support in the literature for its efficacy in chronic non-malignant pain.^{xcii,xciii,xciv} Until the opioid-for-non-malignant-pain controversy is settled, there will always be controversy surrounding their intraspinal use. This controversy, notwithstanding, the selection criteria for the intraspinal opioid use for patients with non-malignant pain is similar to the criteria for patients with pain of malignant origin. The glaring difference is that patients with non-malignant pain are not facing “end of life” due to their disease and may have long lives ahead of them. With the non-malignant pain population, the “3-month-to-th-end-of-life rule” does not exist. All non-cancer pain patients should, before undergoing a trial for intraspinal opioid and non-opioid delivery, have had benefit of sequential oral or transdermally administered opioids including all of the long-acting opioids available in the USA including methadone, levorphanol, long-acting morphine preparations, long-acting oxycodone preparations, and transdermal fentanyl. If patients have opioid non-responsive pain syndromes and do not respond to the systemic delivery of the above agents, they probably will not respond to the intraspinal delivery of opioids alone. The treating physician should contemplate a need for the intraspinal delivery of opioids and non-opioids alike.

Trial Of Intraspinal Analgesics

With failure of a sequential systemic opioid trial, the patient is a candidate for a trial of intraspinal analgesia. Any trial should, intuitively, rule in both analgesic and functional efficacy,

rule out toxicity of the agent being tried, and mitigate the non-specific or placebo effects of the drug. Trials for intraspinal opioids and non-opioids alike have been performed by single shot epidural or intrathecal placement of the drug or drugs intended, repeat single shot epidural or intrathecal placement of drug or drugs intended, and finally by continuous drug delivery via the epidural or intrathecal route using an external pump.

Because any analgesic intervention, and most importantly, last-resort interventions like intraspinal analgesia, carries with it very strong placebo responses in both non-cancer patients and cancer patients suffering from intractable pain, trials for efficacy must also mitigate these strong responses. The only way to mitigate a placebo response, **in any, one single patient**, is to extend the trial out as long as logistically possible.

A continuous intrathecal trial, extended out as long as logistically possible, is the one trial that allows for both sequential trialing of intrathecal agents and allows for extended trials to mitigate potent placebo responses. During the trial of the agent intended, a 50% reduction in pain intensity, an improvement in function, and a concomitant significant reduction in oral or systemic analgesics is usually indicative of analgesic effectiveness. The final evaluation of efficacy of a trial of intraspinal opioids must be individualized, weighed carefully against the risks of the procedure or changes to the lifestyle of the patient and/or burden of care on the family. Patient and family input is essential to deciding whether a trial of intraspinal analgesics is positive or not.

Intrathecal Pump Delivery Systems

As stated above, intraspinal drugs can be delivered externally through externalized epidural or intrathecal catheters or delivered internally through implanted pump systems. We focus our discussion in this article on implanted drug delivery systems.

The first drug delivery system approved for the delivery of intraspinal analgesics was the Infusaid, model #400 pump, a pump that is no longer in production. This pump was a factory, pre-set flow rate pump that delivered drug by utilizing vapor pressure against an expandable metal bellows which in turn, extruded drug through a rate reducing valve to an external nipple. Vapor pressure was provided by liquid freon, which at ambient temperature remained liquefied, but when implanted into body temperature, vaporized to a pressure of approximately 400 psi.

Today, there are other FDA approved factory pre-set, rate specific pumps including the Codman, model 400 pump See **figure #8**

Figure 6 PLACE FIGURE 8, CODMAN MODEL 400 PUMP HERE

and Medtronic's Isomed® pump. See **figure 9**.

Figure 7 PLACE MEDTRONIC'S ISOMED PUMP HERE

Codman's pump, like the Infusaid pump relies on the use of freon and a metal bellows. Medtronic's Isomed® pump relies on freon gas and a metal bellows for delivery of drug. Other pumps exist outside of the USA and include the Esox®, Archimedes®, Micromedes®, and the Anschutz pump, all of which are fixed rate pumps. Because rate is pre-set and non-programmable, dosing changes are made by changing concentrations of the drug.

Medtronic's Synchromed® system is the only totally programmable pump that is approved in the USA and Europe. This pump relies on a dual system for drug delivery. Like the rate specific pumps, this pump has a vapor pressure/bellows "assist" system which extrudes drug to a rotary pumping system which is battery controlled and externally programmable. Rate and therefore, dose of drug, are externally programmable. See **Figure 10**

Figure 8 PLACE MEDTRONIC SYNCHROMED SYSTEM PICTURE HERE

Besides increasing or decreasing the continuous rate of delivery of drug, the Synchronomed® system can be programmed to deliver a single bolus of drug, timed-specific boluses of drug, or a complex continuous delivery of drug to meet the timed-specific needs of the patient during the day.

All implantable pumps, today, come with a drug reservoir access port and a side port system to allow for direct injection of drug or other agents into the implanted catheter system which for the most part directly delivers drug or agent into the intrathecal space. Reservoir volumes are different for different pumps. The Synchronomed® pump volume is 20 cc's but the company (Medtronic, Minneapolis, MN) suggests that the pump only be filled to a maximum of 18cc's to prevent over-pressurization. Other pumps have differing volumes and can be ordered according to the clinical needs of the patient. Medtronic's Isomed® Pump is available in a variety of reservoir volumes including 20, 35, and 60 cc's, whereas Codman has fixed rate pumps with reservoir volumes of 16, 30, 50 cc's. Selection of the reservoir volume will depend on the needs of the patient.

Most pumps have their side port systems attached to the side of the pump, however the Codman, formally the Arrow system has a unique system allowing for "side port" injection of the catheter system through the central fill port. A special needle, when inserted correctly into the reservoir chamber allows for only "side port" injection and not refilling of the reservoir.

Pharmacologic Agents Used For Intrathecal Therapy:

Intrathecal Opioids

Morphine remains the "gold standard" of spinally administered opioid therapy because of its long duration of action and relative ease of use. In the US, only morphine has been approved for clinical intraspinal analgesia. However, based on the literature and sound clinical judgment, other opioids are used intraspinally when patients do not tolerate intrathecal morphine

administration. These agents include hydromorphone, meperidine, methadone, fentanyl, and sufentanil.

Time to onset of action of opioid given spinally, duration of action, uptake and distribution, availability to supraspinal centers, and CNS side effects are all governed by the opiate's lipid solubility and opiate receptor affinity.^{xcv} Opioids such as morphine, with low lipid solubility, enhanced hydrophilicity, and high receptor affinity, cross the dura and enter the lipid substance of the spinal cord slowly, but remain bound for prolonged periods of time. Hence, the onset of analgesic action for hydrophilic opioids is slow, but analgesia is generally prolonged. Because of this hydrophilicity, more drug remains in the CSF and therefore is available to ascend to supraspinal centers through bulk flow of CSF. Because of this hydrophilic property of drugs such as morphine, placement of a catheter for intrathecal infusion of the drug anywhere in the thecal sac ensures analgesia anywhere in the body. Risks of CSF side effects such as sedation, nausea and vomiting and respiratory depression are greater with this hydrophilic group of opioids than with those with higher lipid solubility and higher receptor affinity such as methadone, fentanyl or sufentanil.

As expected from their physical-chemical properties, lipophilic drugs such as fentanyl, methadone, and sufentanil have a rapid onset of action and a prolonged duration of action. Once receptors are saturated with these drugs, drug does become available for redistribution through spinal vessel uptake and CSF bulk flow. Over sedation then can become a problem. Because lipophilic agents enter the substance of the lipid containing spinal cord rapidly and are quickly eliminated from the CSF, catheter tip placement close to the spinal cord area processing the patient's pain is essential for optimal analgesia.

The appropriate dose of opioid for epidural or intrathecal use is highly individualized and depends on the patient's age, the patient's pain syndrome, and the systemic dose of the drug needed for analgesia before the decision to move to intraspinal delivery. As a general rule,

patients with neuropathic pain may require higher doses than those normally used for nociceptive pain; and the elderly usually require less drug than patients who are younger. However the dosing in all patients should be individualized.

Some patients do not tolerate morphine, but tolerate other hydrophilic though more lipophilic agents such as hydromorphone. Sometimes, we may want to use more lipophilic to decrease supraspinal effects such as severe nausea. Patients, however, though tolerating one drug well during the screening trial, may develop either intolerance to the drug at some time during ongoing intrathecal therapy, develop tolerance to the drug being infused, or may in fact develop opioid resistant pain syndromes. These problems that may arise can be categorized into side effects of and/or decreasing analgesic effects of the agent being infused. Should patients develop the known side-effects of therapy such as nausea and vomiting, urinary retention, generalized pruritus, constipation, over-sedation, or confusion, or develop other complications of intraspinal opioid therapy that have been reported such as polyarthralgia, amenorrhea, and peripheral edema, sexual dysfunction, etc.,^{xvii} an attempt should be made to manage these symptoms pharmacologically before switching to some other agent. If these side effects cannot be managed with symptom-specific pharmacologic agents, then switching to another spinal opioid is suggested. Because there is incomplete cross tolerance of one opioid agonist to other opioid agonists, patients who have side effects to one drug may not have the same effects with another drug at dose equivalencies.

Patients also may with time become tolerant to the agent being infused. Tolerance to one opioid analgesic, however, does not necessarily mean tolerance to all. Again, taking advantage of incomplete cross tolerance, analgesia can be restored by switching to a different opioid at a lower dose (usually one-half the expected equivalency).

Hydromorphone

Pain clinicians are sometimes faced with a dilemma when a patient no longer tolerates intrathecal morphine. Whether the patient has become tolerant to the morphine, is allergic or experiences significant side effects to the drug, an alternative drug is needed in the pump. Although not FDA approved in the United States for such use, many clinicians turn to hydromorphone. The Mu agonist, hydromorphone is 5-10 times more potent than morphine, and 8-10 times more lipid soluble.^{xcvii,xcviii} Because of its greater lipophilicity than morphine, one might expect a slightly quicker action of onset, shorter duration of action and more segmental spread. Also because of slightly less rostral CSF spread, one might expect less narcotic reaching the vomiting center in the brain, the *area postrema* or chemoreceptor trigger zone. When converting from intrathecal morphine to hydromorphone, the initial dose is approximately 50% of the equianalgesic dose of the new drug, because of incomplete cross tolerance.

Meperidine

Meperidine is a phenylpiperidine derivative with physical characteristics, molecular weight, and pk similar to local anesthetics. It is the only mu agonist opioid clinically available that is known to be efficacious as a sole subarachnoid anesthetic. Surgical procedures to the lower limbs, inguinal area, perineum, and even cesarean section can be performed under spinal meperidine alone.^{xcix, c} Subarachnoid administration of 0.5 mg/kg meperidine produces anesthesia with an onset of about 10 minutes, and post-operative analgesia for up to 6 hours or longer.^{ci,cii}

Meperidine is more lipid soluble than morphine or hydromorphone. It has a quicker onset and more segmental action than either morphine or hydromorphone. Greater than 1,035 patients reported in the literature have received intrathecal meperidine without any documented neurotoxic effect.^{ciii}

Fentanyl

Fentanyl is an opioid analgesic that preferentially binds to mu receptors which are found widely distributed throughout the brain and spinal cord. Fentanyl is lipophilic and has a fast onset of action, on the order of 4-5 minutes, with a peak effect of approximately 20 minutes when given epidurally.^{civ,cv} Its analgesic effect is mostly segmental owing to its lipophilicity and easy diffusability. Fentanyl has low cerebral spinal fluid spread and is equipotent when given either epidurally or intravenously.^{cvi} Fentanyl plasma levels are the same when given either epidurally or intravenously and thus studies are inconclusive as to which route provides greater analgesia.^{cvii,cviii} As fentanyl is 75-100 times more potent than morphine sulphate, lower doses are needed to produce similar analgesia. While scientific data on epidural and intrathecal fentanyl are evolving, there does appear to be a role for fentanyl in treating both acute and chronic pain processes.

Management of Non-Opioid Spinal Analgesia

Because many patients either develop tolerance to their opioid analgesics, have neuropathic, opioid less-responsive pain, or develop these pain syndromes during their intraspinal opioid therapy, it has become quite clear that intraspinal opioid therapy alone is not sufficient in providing adequate analgesia for many patients. This has led scientists and clinicians to look for other intra-spinal, pharmacologic solutions for these opioid resistant pain syndromes. The intraspinal use of other agents such as the alpha-2 adrenergic receptor drug, clonidine, opiate peptides such as DADLE or DPDPE, or other spinally active analgetic agents such as somatostatin or octreotide, NSAIDs, neuron specific Ca⁺⁺ channel blocking agents, NMDA receptor antagonists, etc. are all investigational and should only be used with investigational review board accepted protocols. The use of chronic intrathecal local anesthetics, though not investigational, should only be used with careful informed consent outlining the risks and possible consequences of their use.

Opioid-Local Anesthetic Combinations

Animal toxicity and human post-mortem studies suggest clinical safety with the long term infusion of intrathecal bupivacaine at the low doses used.^{cxix,cx} There are, however, other reports in both the animal and human clinical literature of potential neural toxicity of local anesthetic agents when used chronically. One study showed neurotoxicity after subarachnoid infusions of bupivacaine, lidocaine and 2-chloroprocaine in a chronic rat model.^{cxii} These neurotoxic effects, however, were both dose and duration related and bupivacaine appeared to have a lesser effect than either lidocaine or tetracaine.

Several recent clinical reports showing positive analgesic response with the use of local anesthetic-opioid intraspinal mixtures for the treatment of cancer and non-cancer related pain have been reported.^{cxii,cxiii}

Clonidine

Clonidine, an alpha-2 adrenergic receptor agonist, used intrathecally or epidurally in animal studies and in humans has been shown to provide potent analgesia whether used alone or in combination with intraspinal opioids. Clonidine is not approved for clinical use in the US and is experimental. Some authors have found that combining the alpha-2 adrenergic receptor drug, clonidine, with a mu receptor agent provides more profound analgesia at a dose lower than would be expected if either drug were given alone.^{cxiv,cxv, cxvi,cxvii} This phenomenon of one drug adding to the effect of another is called "synergy." Animal models of neuropathic pain have demonstrated antinociception with treatment by intrathecal clonidine and other alpha 2 agonists.^{cxviii} Clonidine may, in humans, be effective in neuropathic pain^{cxix,cxx} and sympathetically mediated pain syndromes.^{cxxi}

Studies in different animals and humans have demonstrated no neuropathology after intraspinal clonidine. The main side-effect of clonidine given intrathecally is hypotension. Humans may also experience decreases in heart rate. Electrolytes, glucose, and cortisol levels were found to

be stable in humans after infusion of clonidine.^{cxxii} Other side effects include dry mouth, drowsiness, dizziness, and constipation. Sudden withdrawal of clonidine can precipitate agitation and hypertension.

CONCLUSION:

Unrelieved chronic pain, as we have seen, is costly to patients and society. Non-invasive and less costly therapies should be used before more invasive and more costly therapies. Therapies for pain control should be used according to a **pain treatment continuum**. This pain treatment continuum lists available pain therapies by increasing order of invasiveness and cost. When less costly and less invasive therapies fail to provide adequate analgesia, more invasive and more technologically advanced therapies which have proven efficacy such as those presented in this discussion should be tried before informing the patient that there is nothing more that can be done. Nerve blocking techniques, neurolytic techniques, and implantable neuromodulatory technologies such as spinal cord stimulation and spinal delivery of analgesics are cost effective when less invasive therapies fail to provide adequate analgesia.

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