FEASIBILITY ANALYSIS OF A NEUROSTIMULATION BASED POST-AMPUTATION PAIN RELIEF DEVICE

by

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Submitted in partial fulfillment of the requirements for the degree of

Master of Science

Department of Biology

CASE WESTERN RESERVE UNIVERSITY

May, 2011
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*we also certify that written approval has been obtained for any proprietary material contained therein.
Dedicated to my parents!
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Acknowledgements

I am extremely grateful to my advisor Prof. Christopher Cullis, Chair of the Department of Biology, Case Western Reserve University, for his excellent supervision, guidance, and constant encouragement throughout the thesis work.

Words fall short to acknowledge the untiring, whole hearted support and encouragement provided by Dr. Joseph Boggs, Director of Research, NDI Medical, Cleveland, OH. I am sincerely thankful to him for making this work a great learning experience for me, without whose help I couldn’t have completed this work.

I am highly obliged and indebted to Prof. James Zull, Department of Biology, Case Western Reserve University, for his efforts, extraordinary guidance and timely suggestions rendered to me during my study.

I am extremely thankful to Dr. Mark Willis, Department of Biology, Case Western Reserve University, for being the Chair of my thesis committee.

I extend my special thanks and deepest gratitude to Ms. Juliana Elstad, ex-VP of Business Development, NDI Medical for providing me the opportunity and showing her belief in me to carry out this project.

I am immensely thankful to all my friends who were always available for me while doing this study and for making necessary arrangements at every step of this work. Without their cooperation and help, this work would not have reached its desired ends.

A special word of regards to my Parents and my fiancé Sunayana Mann whose constant love, affection and blessings help me proceed with courage in every task I do.

There may be many unsung heroes without whom it would not been possible for me to finish my thesis. If I forget to name somebody, I humbly request them to forgive me.

Raghav Dutta
Feasibility Analysis of a Neuro-stimulation based Post-Amputation Pain Relief Device

Abstract

by

RAGHAV DUTTA

Around 1.7 million people in United States are living with limb loss and annually 185,000 more undergo amputation. 70% to 80% of the limb loss patients experience chronic post-amputation pain for which present methods of treatment are ineffective in providing pain relief. Evidence has been gathering that electric stimulation of peripheral nerves can effectively treat neuropathic pain conditions like occipital neuralgia, postherpetic neuralgia, CRPS etc. A peripheral nerve stimulation device to treat post-amputation pain is being studied by NDI Medical, LLC and its commercial feasibility was evaluated via market research that involved assessing present treatment methods, estimating market potential and physician interviews etc. In spite of a big market potential ($15B), a need for an effective therapy and a demand from physicians, certain factors like inapplicability in diabetic patients, etc. work against this device’s commercial feasibility.
1 INTRODUCTION

The years from 2000 through 2010 were declared as the Decade of Pain Control and Research and yet pain continues to be a leading public health problem in United States (Nelson 2003). One out of every five American is affected by pain and seeks medical attention each day. According to an estimate, pain is responsible for every 1 in 6 visits to a healthcare provider. Around 70 million physician visits occur as a result of pain and the treatment costs associated with it have been estimated to be more than $100 billion. Uncontrolled pain has been identified to be of epidemic proportions with a population of 50 million affected by chronic pain and another 25 million experiencing acute pain due to trauma or surgical procedures (Renn and Dorsey 2005). Apart from pain, the patients and their families often have to experience associated issues such as decreased quality of life; depression and interpersonal stresses. Not only is pain a societal and economic burden, the impact of increased healthcare utilization and lost productivity is also far reaching. Of the total population experiencing chronic pain, two-thirds have had it since 5 years or more, significantly affecting their daily activities. Estimates suggest that due to pain, 36 million people in the US have missed 4 billion days at work resulting in economic losses of $65 billion annually (Gentry 1999).

Of particular importance is the occurrence of chronic neuropathic pain as a result of amputation and commonly known as post-amputation pain. An estimated 1.7 million individuals in United States were living with a limb loss in 2007 and a significant majority (95%) of the population experienced post-amputation pain. Post-amputation pain also results in significant decrease of the quality of life, inability to perform daily activities, unemployment and has been correlated with increased incidence of depression
The economic burden of management of amputee pain has been estimated at $13 billion in US.

Over years, several neuropathic pain indications have been treated using the approach of peripheral nerve stimulation. NDI Medical, LLC of Cleveland OH, is a medical device manufacturer that is testing their proprietary implantable neuro-stimulation device to provide relief from post-amputation pain. The objective of this study was to assess the commercial feasibility of a potential neuro-stimulation device to relieve post-amputation pain. Based on the analysis, it seems that this device will not be commercially feasible as the actual market size is very small according to literature data and physicians’ experiences and is inapplicable in diabetic patients. However, it is further discussed that if the use of device is expanded (to increase market size) to include other neuropathic pain conditions like carpal tunnel syndrome, cervical radiculopathy, etc., and appropriate surgical protocols are followed in diabetic patients, the device can be commercially viable.
2 BACKGROUND OF PAIN

2.1 Definition of Pain

Pain is an unpleasant perception/sensation that arises due to actual or potential tissue damage that may occur because of a chemical, thermal or mechanical injury etc. It is both a personal emotional experience as well as the result of complex physiological adaptations of molecular and biological function. In contrast, a number of people report pain in the absence of any physiological pathology, which is believed to occur due to psychological reasons. Such an experience is regarded as pain if it is reported as similar to pain caused by tissue damage or injury. Pain serves an important protective function by warning of an injury that should be avoided and causes an individual to react and remove the pain stimulus (Guyton 2006, Kandel 2000).

2.2 Physiology of Pain Processing

Although classification of pain has been done depending on its duration (acute vs. chronic), its location (bone/joint, muscle, superficial or deep etc.) or its cause or type (inflammatory, neuropathic, cancer), the general mechanism underlying pain activation and its experience is similar, regardless of how it is categorized. Central to the pain mechanism is the process called nociception which is defined as the activation of sensory transduction in nerves due to a noxious stimulus imposed on specialized nerve endings. A noxious stimulus occurs by thermal, mechanical or chemical insult and has the capacity to
activate particular receptors called the nociceptors that respond to and convey the information about tissue damage to the central nervous system (Fig 1). Nociceptors are sensory neurons, present with varying degree of innervations in skin, muscle, joints, and viscera, and when activated or active contribute to the experience of pain. These sensory neurons have a cell body with a central process terminating in central nervous system (CNS) and a peripheral process terminating in a peripheral target as in the skin and other tissues (Gebhart and Gold 2010). The sensory neurons that respond to pain inducing noxious stimuli have free or unencapsulated nerve endings while those (low threshold afferents) responsive to non-noxious stimuli (Aα & Aβ fibers), such as touch or pressure, end up in specialized structures called Ruffini endings or Merkel discs (Mearow and Diamond 1988, Johnson 2001). The sensory neurons can either be myelinated (Aα, Aβ and Aδ) fibers or non-myelinated C-fibers. For a nociceptor to transmit information to the central nervous system about a noxious stimulus on any peripheral tissue requires four distinct steps. First, the transduction of stimulus (mechanical, thermal or chemical) as an electric signal occurs resulting in the formation of a generator potential (2.4.1 Stimulus Transduction). Second, the generator potential transforms into an action potential, which constitutes the basic unit of electrical activity in the nervous system (2.4.2 Action Potential Generation). Third, the action potential must be successfully propagated from
the peripheral terminal to the central nervous system (2.4.3 Action Potential Propagation). And fourth, the propagated action potential should enable the release of neurotransmitters to initiate the whole process once again in the second order neurons (2.4.4 Transmitter Release) (Fig 2). The afferent neurons may terminate directly on the second order projection neurons or indirectly through the interneurons to transmit pain signal to the central nervous system via different ascending pathways.

2.2.1 Stimulus Transduction

Nociceptive afferents are not dependent on other cell types for transduction of a noxious stimulus as the proteins responsible for the process are intrinsic to the nociceptor. Isolated sensory neurons respond to thermal [both hot (Cesare and McNaughton 1997) and cold (Reid and Flonta 2001)], mechanical (McCarter 1999) and a range of chemical stimuli, including endogenous (Bevan and Yeats 1991) and exogenous compounds (Bautista, et al. 2006) (Table 1). Nociceptor proteins like Transient Receptor Potential (TRP) channels and Acid Sensing Ion Channels (ASICs) are activated by all kinds of stimuli in contrast to chemotransducers that specifically respond to chemical stimulus only. Proteins like Transient Receptor Potential Vanilloid type 4 (TRPV4) (Alessandri-Haber, et al. 2005), ASIC-3, and the low voltage-gated calcium channel (VGCC) CaV3.2 (Shin, et al. 2003) respond to mechano-transduction of a stimulus. Transduction of noxious stimulus because of temperature changes occurs through diverse classes of receptors like TRPA1, ankyrin type 1 for cold (Story, et al. 2003), TRPV4 for warm (Guler, et al. 2002) and TRPV1, vanilloid type 1 for hot (Caterina, et al. 1997). A number of chemoreceptor proteins function in response to tissue acidosis (TRPV1 and ASIC-3), noxious organic compounds e.g. aldehydes (TRPA1) (Kwan, et al. 2006) and endogenous chemicals e.g.
ATP (P2X3) (Burnstock 2006) (Fig 3). Alterations in the nociceptive terminals after tissue insult results in increased sensitivity towards noxious stimuli and the depolarization of membrane. Due to the secretion of inflammatory mediators such as ATP, prostaglandin E2, NGF and TNF-α, the density of transducers increases which brings about the depolarization of nociceptive terminals and posttranslational modifications through secondary messenger pathways. Therapeutic strategies (Table 2) employed in drugs currently under development or in use, try to attenuate experience of pain by targeting receptors for pro-inflammatory mediators like ATP(Xu 2008) or responsible chemoreceptors on nociceptive afferents (Burnstock 2006).

Figure 3 Pain signal transduction due to tissue insult (Gebhart and Gold 2010)
Table 1 Ion channels and the type of noxious stimuli to which they respond

<table>
<thead>
<tr>
<th>Channels</th>
<th>Stimulus type</th>
</tr>
</thead>
</table>
| TRPV4        | 1. Mechanical  
               2. Warm             |
| ASIC 3       | 1. Mechanical  
               2. Chemical          |
| VGCC CaV3.2  | Mechanical                   |
| TRPA 1       | 1. Cold                    
               2. Chemical          |
| TRPM 8       | Cool                        |
| TRPV 1       | 1. Hot                     
               2. Chemical          |
| P2X3         | Chemical (endogenous)       |

Table 2 Type for drugs that are used to suppress the molecules involved in pain receptor binding

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2X3 Antagonist</td>
<td>ATP</td>
</tr>
<tr>
<td>Cox Inhibitor</td>
<td>PGE 2</td>
</tr>
<tr>
<td>Anti-NGF</td>
<td>Nerve Growth Factor</td>
</tr>
<tr>
<td>Anti-TNFα</td>
<td>Tumor Necrosis Factor</td>
</tr>
</tbody>
</table>

2.2.2 Action Potential Generation

Generator potential becomes weak over a certain distance due to factors like membrane resistance, membrane capacitance and internal resistance of the nerve terminal and requires it to be converted into an action potential in order to propagate it beyond the terminal ending. As the action potential initiation does not occur at the site of stimulus transduction, the magnitude of the generator potential must be greater than or equal to the action potential threshold. Studies have demonstrated a number of ion channels that are involved in determining the spike
initiation threshold and upstroke of the spike. A number of K⁺ channels play a crucial role in regulating the action potential threshold via voltage-gated K⁺ channels (Kᵥ), inward rectifying K⁺ channels (Kᵢᵦ), 2-pore K⁺ channels (K₂P), large-conductance calcium modulated K⁺ channels (BK), and small conductance K⁺ channels (SK) (Gebhart and Gold 2010). A similar role is played in determining the action potential threshold by the nonselective inward rectifying cation channel (HCN) (Dunlop, et al. 2009). The low-threshold calcium channel (CaV3.2) and voltage-gated sodium channel (VGSC) NaV1.9 may also play a part in establishing the action potential threshold (Coste, Crest and Delmas 2007). However, the VGSCs NaV1.7 and NaV1.8 (Fig 4) work in concert with each other (Rush, et al. 2006) and play crucial roles in initiating the upstroke of the action potential (Djouhri, et al. 2003). In contrast to other VGSCs, NaV1.8 works at low temperatures (4°C) and is responsible for pain sensation associated with cold stimuli (Zimmerman, et al. 2007). Recently, low-voltage activated, or T-type, calcium channels have been demonstrated to contribute to spike initiation of subsequent action potentials as channels underlie a sustained depolarization after a single action potential (Zamponi, et al. 2009) (Table 3).

<table>
<thead>
<tr>
<th>Channels</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺ channels</td>
<td>↓</td>
</tr>
<tr>
<td>NaV 1.7, 1.8, 1.9</td>
<td>↑</td>
</tr>
<tr>
<td>HCN</td>
<td>↑</td>
</tr>
<tr>
<td>CaV 3.2</td>
<td>↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retigabine</td>
<td>K⁺ ch. opener</td>
</tr>
<tr>
<td>Local Anesthetics</td>
<td>Na⁺ ch. blockers</td>
</tr>
<tr>
<td>Antidepressants TCAs</td>
<td>Na⁺ Ch. blockers</td>
</tr>
<tr>
<td>Cox Inhibitors</td>
<td>Cyclooxygenase-2</td>
</tr>
</tbody>
</table>
2.2.3 Action Potential Propagation

The propagation of action potential into the central nervous system takes place through a voltage-gate sodium channel (VGSC) NaV1.6 as NaV1.7 and NaV1.8 can only extend the potential through a distance of 5-10mm. NaV1.6 channels are located in both the myelinated (clustered at Node of Ranvier) and non-myelinated (spread through the axon) of nociceptive and non-nociceptive afferents (Wittmack, et al. 2004) (Fig 5). Since the propagation of action potential is VGSC dependent a number therapeutic approaches (Table 5) utilize sodium channel blocking compounds such as local anesthetics, TCAs, tetrodotoxin (TTX) and some Cox inhibitors.

Table 5 Therapeutic modalities used to target different ion channels involved in Action Potential Propagation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Anesthetics</td>
<td>Na⁺ channels</td>
</tr>
<tr>
<td>TCAs</td>
<td>Na⁺ Channels</td>
</tr>
<tr>
<td>Cox inhibitors</td>
<td>Cyclooxygenase-2 enzyme</td>
</tr>
</tbody>
</table>
2.2.4 Transmitter Release

To transmit information to the central nervous system it is essential that the transmitters are released at the central terminals of the nociceptive afferents. It is facilitated by the voltage-gated calcium channels (VGCCs) through the initial influx of calcium, necessary for the process of neurotransmitter release to initiate. VGCCs are classified into different subtypes: the low-threshold activating T-type (CaV 3.1-3.3) and high-threshold activating L-type (CaV 1.1-1.4), N-type (CaV2.2), P/Q type channels (CaV2.1) and the R-type channels (CaV2.3), all present in the nociceptors (Catterall 2005) (Table 6). Majority of the channels are N-type VGCC and play a dominant role in transmitter release. The VGCCs are often blocked through intrathecal opioid receptor and alpha adrenergic receptor agonists mediated activation of inhibitory GPCRs (Ikeda 1996). Transmitters are stored in nociceptive afferents as vesicles called as small clear vesicles which contain excitatory amino acid glutamate, neuropeptides such as substance P and calcitonin gene-related peptide (CGRP). Calcium has an important role in the fusion of vesicles to the cell membrane, necessary for transmitter release, and this mechanism requires 4-5 calcium ions to be triggered (Schneggenburger and Neher 2005). The α2δ1-subunit complex required for transferring channels to the membrane has been put into use as a target binding site for drugs gabapentin and pregablin (Li, et al. 2006).
Table 6 Channels involved in neurotransmitters release and the type of effect they induce

<table>
<thead>
<tr>
<th>Channels</th>
<th>Transmitter Release</th>
<th>Drug</th>
<th>Drug Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Excitatory</td>
<td>Inhibitory</td>
<td></td>
</tr>
<tr>
<td>GABA-A</td>
<td></td>
<td>x</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Receptor Agonist</td>
</tr>
<tr>
<td>Excitatory GPCRs</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(EP and B1.2 receptors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2X</td>
<td>x</td>
<td></td>
<td>P2X Antagonist</td>
</tr>
<tr>
<td>TRPV1</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CaV 2.2, 2.1, 1.3</td>
<td>x</td>
<td></td>
<td>Antiepileptics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ca(^{2+}) ch. blockers</td>
</tr>
<tr>
<td>K(^{+}) ch. (K(_V) and BK)</td>
<td></td>
<td>x</td>
<td>Retigabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>K(^{+}) ch. openers</td>
</tr>
<tr>
<td>Inhibitory GPCRs</td>
<td>x</td>
<td>1.OR Agonists</td>
<td>1. Opioid Receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.AR Agonists</td>
<td>2. Adrenergic Receptor</td>
</tr>
<tr>
<td>NaV 1.8</td>
<td>x</td>
<td>1.Gabapentin</td>
<td>Na(^{+}) ch. blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.Pregablin</td>
<td></td>
</tr>
</tbody>
</table>

2.2.4.1 Neurotransmitters from Primary Afferents

Nociceptive primary afferents predominately terminate in the dorsal horn of the spinal cord for synaptic transmission of information to the second order neurons, for CNS processing. Neurotransmission between first order afferents and second order neurons chiefly occurs through the release of transmitters - Excitatory Amino Acids (EAAs) such as glutamate and aspartate from the primary afferent neurons. EAAs generate excitatory postsynaptic potentials (EPSPs) by binding to three ligand-activated ion channels, namely \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors; N-methyl-
D-aspartate (NMDA) receptors; and kainite (KA) receptors (Randich 2010). EAAs also induce second messenger systems via three groups of eight different metabotropic glutamate receptors. Group I (mGluR1 and mGluR5) and Group II (mGluR2 and mGluR3) have been implicated to play roles in nociception while Group III (mGluR6, mGluR7, and mGluR8) have not yet had a clear link to nociception (Gerber, Gee and Benquet 2007). Substance P acts by binding to the NK1 receptor on the second order neurons and bringing about intracellular G-protein related phosphorylation processes to promote nociceptive transmission through membrane depolarization (Harrison and Geppetti 2001). Different studies on Calcitonin gene-related peptide (CGRP) studies limit its role in nociceptive processing while peripheral vasodilation in headaches remains to be its most important effect. CGRP receptor antagonists have been reported to be effective in migraine pain relief and indicate that it may be vital for peripheral effects of nociceptive activation (Edvinsson 2007). Cholecystokinin (CCK) is a neuropeptide which increases in content and its receptors following a nerve injury. CCK receptor antagonists may promote opioid analgesia and exhibit analgesic effects in neuropathic pain (Wiesenfeld-Hallin, Xu and Hökfelt 2002). Adenosine Triphosphate (ATP), when functioning as a neurotransmitter, acts via both ligand-gated ion channels and metabotropic purinergic receptors (Table 7). Breakdown products of ATP are also known to act as agonists to purinergic receptors located on the second order neurons (Gu and MacDermott 1997).

2.2.4.2 Neurotransmitters from Interneurons

While majority of the transmitters secreted from the primary afferents are excitatory, the predominant effect exerted by interneuron-released neurotransmitters is inhibitory. γ-
aminobutyric acid (GABA) and glycine are two main inhibitory amino acids of the CNS (Table 7). GABA binds to fast ligand-activated ion channel called the GABA$_A$ receptor and functions in supraspinal regions while glycine acts through strychnine-sensitive and strychnine-insensitive receptors. The strychnine-sensitive receptor is a ligand-gated anion channel with similarity to the GABA$_A$ receptor complex. Inhibitory neuropeptides like enkephalins, dynorphin, and β-endorphin form part of the endogenous opioids that act in the dorsal horn region. They bind to G-protein-related receptor complexes divided into three classes: the μ opioid receptors (MOR), the κ opioid receptors (KOR) and the δ opioid receptors (DOR) (Randich 2010).

2.2.4.3 Neurotransmitters from Supraspinal Sources

Neurotransmitters from Supraspinal sources modulate the transduction and experience of pain and; spinal transection has been associated with depletion of neurotransmitter content in the dorsal horn of the spinal cord. Serotonin is known to bind 5-HT3 receptors to produce an increase in the perception of pain by excitation of signals (Table 7). In contrast, binding to the 5-HT2 receptor is associated with anti-nociceptive properties. The transmitter noradrenalin has two subtypes: α1 and α2 with excitatory and inhibitory properties, respectively. The subtypes bind at different sites of action that include the presynaptic terminal of primary afferent terminal (α2 inhibitory), second order neuron (α2 inhibitory) and interneurons (α1 excitatory).
Table 7 Site of Neurotransmitter origin and the type of nociceptive effect it exerts

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Primary Afferent</th>
<th>Second order neuron</th>
<th>Interneuron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate/Aspartate</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>AMPA</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NMDA</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>KA</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GABA-A</td>
<td>-</td>
<td>-</td>
<td>x/-</td>
</tr>
<tr>
<td>GABA-B</td>
<td>-</td>
<td>-</td>
<td>x/-</td>
</tr>
<tr>
<td>Glycine</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Substance P</td>
<td>x</td>
<td>+</td>
<td>x</td>
</tr>
<tr>
<td>CGRP</td>
<td>x</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>ATP</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
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<td>Adenosine</td>
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<td>Acetylcholine</td>
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<tr>
<td>Cholecystokinin</td>
<td>x/+</td>
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x = origin of neurotransmitter
+ = pain inducing nociceptive effect
- = anti-nociceptive effect
2.3 Targets of Primary Afferent Input

The primary afferent nociceptive fibers form synaptic connections with second order neurons, either directly or indirectly (via interneurons), in the dorsal horn region of the gray matter (Traub and Mendell 1988). According to Rexed’s classification system, the cross sectional spinal gray matter is divided into 10 laminae numbered I to X from dorsal to ventral direction comprising the dorsal horn region (laminae I to VI) and ventral horn (VII to X) (Fig 6). The marginal layer (lamina I) and the substantia gelatinosa (lamina II) of the superficial dorsal horn consist majorly of nociceptive neurons that receive direct synaptic input from Aδ and C-fibers. Lamina I neurons predominantly respond to noxious stimulation while some neurons are capable of responding to both noxious and non-noxious insults. Lamina II majorly comprises of both excitatory and inhibitory interneurons, of which a few are stimulated only by the nociceptive signals and others by the non-noxious stimuli too. The Aβ fibers form monosynaptic contact with neurons of the lamina III and IV that predominantly transmit non-noxious signals to the higher brain centers. The neurons of the lamina V receive pain signals from both Aβ and Aδ fibers and project to the brain stem and to the regions of thalamus. The C-fibers also transmit pain input to lamina V neurons either directly through its dendrites or indirectly via excitatory interneurons. The inputs received by the neurons of lamina VI are non-noxious in nature and transmitted through large diameter afferents (Aα and Aβ fibers) from muscles and joints. The ventral horn neurons of lamina...
VII and VIII contribute to the sensation of diffuse pain as it receives polysynaptic nociceptive inputs and in contrast to the dorsal horn neurons, inputs from either side of the body are received. The lamina X neurons surround the central canal of the spinal cord and receive pain input from both myelinated and unmyelinated afferents with axonal projections reaching medullary targets.

Depending on the kind of stimuli, second order neurons have been classified into Class 1 if excited by innocuous stimuli such as hair movement or vibration, Class 2 if excited by both noxious stimuli and innocuous stimuli and Class 3 if excited by noxious stimuli only (Table 8). This classification is also described as low-threshold for Class 1 (receive input from Aα and Aβ fibers), wide-dynamic range (WDR) or convergent for Class 2 neurons (receive input from C and myelinated A fibers) and high-threshold or nociceptive-specific neurons for the Class 3 (receive input from Aδ and C fibers) (Mendell 1965, Baron 2006).

<table>
<thead>
<tr>
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<th>Class 1</th>
<th>Class 2</th>
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<tr>
<td>Aα &amp; Aβ fibers</td>
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<td>C fibers</td>
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<td>Aδ fibers</td>
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The primary afferent nerve fibers enter the spinal cord from the dorsal root into the dorsolateral region of the grey matter and bifurcate into a “T” pattern. The fibers then travel 2-3 segments within the Lissauer’s tract in the rostral (toward the nose) and caudal
(toward the tail) directions. While travelling in the grey matter, the fibers transmit pain signal via collateral projections over a broader area which is significant in the wake of a pathophysiology, such as a lesion, which could get obstruct if signal is transmitted to a discrete site. The axonal projections of second order neurons receiving the signal extend toward the rostral and caudal sites of termination such as supraspinal structures like thalamus, hypothalamus, midbrain, pons, medulla and various limbic structures. The axonal projections mainly travel in the white matter of the spinal cord through different ascending pathways to reach these termination sites (Renn and Dorsey 2005).

2.3.1 Spinothalamic Tract Pathway

The Spinothalamic tract (STT) is the most prominent and well understood pathway located in the ventrolateral white matter of the spinal cord that projects second order neurons to the thalamus. In primates, the STT neurons predominantly originate in the laminae I, II and V of the spinal dorsal horn but are also highly present in the laminae IV, VI, IX, and X with additional representation in the III, VII and VIII laminae (Apkarian and Hodge 1989). Around 20% of the STT neurons are also known to respond to nonnoxious light touch sensations. The tract comprises – the neospinothalamic tract (nSTT) which relays information to the ventrobasal group of the thalamus and the paleospinothalamic tract (pSTT) where the axonal bifurcations end in synaptic contact with medullary, pontine, midbrain and medial thalamic structures (Fig 7). The activation of numerous limbic structures occurs due to pSTT excitation and is linked to the motivational aspects of the pain. The transmission of information through nSTT activates ventrobasal and posterior thalamus which is important to localize the pain-related
sensation and its intensity (Randich 2010). Pain is experienced if the spinothalamic tract is electrically stimulated but if lesions are induced through anterolateral cordotomy, pain sensation is markedly relieved (Basbaum 2000).

![Diagram](image_url)

**Figure 7** Three major ascending pathways that transmit nociceptive information from spinal cord to higher centers in brain (Willis 1995)

### 2.3.2 Spinoreticular Tract Pathway

Another important pathway that exists is called the Spinoreticular tract (SRT) which terminates in the reticular formation of the medulla as a target and sometimes also in the other areas of brainstem as collateral projections. The neurons are majorly localized in the deeper laminae (VII and VIII) and tend to have signal-receptive qualities of nociceptive specific (NS) and WDR type STT neurons (Fig 7). The SRT tract is chiefly involved in activating targets that are involved in nociceptive systems and autonomic regulation.
2.3.3 Spinomesencephalic Tract Pathway

A third pathway called the Spinomesencephalic tract (SMT) has similar localization and functional characteristics as that of STT neurons. The SMT neurons originate in the laminae I, II and V of the spinal dorsal horn and travel to the mesencephalon, also known as the midbrain. The SMT neurons are majorly NS type and their target synaptic targets include periaqueductal gray (PAG), an important center of nociceptive regulation, and collicular and cuneiformis nuclei (Fig 7) (Wiberg, Westman and Blomqvist 1987). A number of axonal projections of this tract project into dorsal part of lateral funiculus instead of entering the anterolateral quadrant and if not removed during pain relief surgical procedures such as anterolateral cordotomy, can cause persistence of pain (Basbaum 2000).

2.3.4 Other Ascending Pathways

Apart from the three important pathways discussed above, there exist other ascending pathways as well. The spinocervicothalamic tract does not occur in humans but has been found to have important function in species of lower mammals (Nógrádi and Vrbová n.d.). Pathways ending in hypothalamus, amygdala and cerebellum with roles in autonomic regulation, emotional modulation and motor coordination, respectively, have also been found (Bernard, Bester and Besson 1996). Pathways carrying information from visceral and deep tissues are carried by vagal afferents directly to the brainstem without interruption from spinal pathways. Primary afferents carrying information from visceral and peripheral travel through sympathetic chain and penetrate spinal cord at higher levels and bypassing spinal lesions. Such pathways play an important role in conditions of spinal injury.
3 POST-AMPUTATION PAIN

Individuals undergoing limb amputation experience postoperative chronic pain and non-painful sensations that arise as result of tissue trauma, nerve injury and various other factors. The chronic pain associated with amputation is a secondary condition commonly referred as the post-amputation pain. It is slowly being recognized as multifactorial and the existence of pre-amputation pain has been acknowledged as a risk factor in the development of Amputee Pain (Hagberg and Brånemark 2001). Post-amputation pain results in the development of two different types of pain – the Phantom pain and the Residual limb pain also called the Stump Pain. Phantom pain is often described as the pain occurring in the missing part of the body and experienced as stabbing, throbbing, burning or cramping kind of pain. Phantom pain may get exacerbated due to physical factors, such as weather change, pressure etc. or psychological factors like emotional stress (Flor 2002). Post-operatively “phantom limb” is said to have the same size and shape as that of the amputated limb. It has been seen that with passage of time the phantom size gradually decreases and gets restricted to the residual limb such that only the foot, hand or digits are left on the stump, a phenomena defined as telescoping (Hill, Phantom limb pain: a review of the literature on attributes and potential mechanisms 1999). In comparison, the Residual limb pain occurs in the body part that still exists and experienced in the distal residual portion. Sometimes patients may also encounter itching, tingling or cramping along with the pain.
3.1 Post-amputation Pain Mechanism

Post-amputation pain is thought to occur as a result of interaction between the brain, spinal cord and the peripheral nervous system and the mechanisms underlying its cause seem to be complex and incompletely understood.

3.1.1 Physiological Mechanisms

It is known that upon amputation of limbs, the nerve fiber axons are damaged and regenerate into a scrambled nodule called a neuroma, in the residual limb. The neuromas consist of enlarged and disorganized nerve endings of nociceptive C-fibers and demyelinated Aδ fibers that show increased rate of spontaneous activity (Argoff and Smith 2010). Though about 30% of the times, neuromas may act as “pain generators” (Flor 2002), the abnormal discharges are known to cause post-amputation pain (Gutnick and Wall 1974). The neuromas are not usually spontaneously painful (Burchiel and Russell 1987) but a mechanical (e.g. pressure) or chemical stimulation may increase the rate of ectopic discharges from them by upregulating the expression of sodium channels (Devor, Govrin-Lippmann and Angelides 1993, Devor, Jänig and Michaelis 1994). The discharges from neuroma can get aggravated even by innocuous stimuli like pressure or temperature change and may be perceived as painful. It is further corroborated by the observation that application of a local anesthetic injection into a stump neuroma can temporarily reduce both phantom and stump pain in some if not all patients (Argoff and Smith 2010).
Due to abnormal increase in the excitatory input at the dorsal horn as a result of nerve injury, apoptosis of GABA and glycine expressing interneurons occur because of which inhibition on the nociceptive pain signals is removed (Argoff and Smith 2010, Flor 2002) leading to experience of post-amputation pain. After the nerves are damaged because of amputation, significant augmentation of ectopic discharge originating from the dorsal root ganglion (DRG) neurons occur which majorly causes chronic pain (Zhang, Li and Brull 2000, Kajander 1992). Switching of inhibitory interneurons into excitatory nociceptive interneurons occurs by the action of brain derived neurotrophic factor (BDNF) released from DRG neurons because of nerve injury and promotes the release of pain signal promoting neurotransmitters like glutamate (Argoff and Smith 2010).
4 NEED ASSESSMENT

Chronic pain as a result of amputation is a problem that needs to be addressed. Despite the presence of a variety of treatment options, amputee pain patients often experience chronic pain which is difficult to treat. Phantom and stump pain are often treated with pharmacological and electric stimulation methods which are not often successful in significantly providing pain relief. The present treatment methods are unsatisfactory, have side-effects and carry the risk of addiction. Not only does the pain seriously affect a limb loss patient’s life, there are several factors like unemployment, disability, anger, frustration, depression etc. that come into play and degrade their quality of life. There is a huge unmet need for effective therapies to successfully manage post-amputation pain that remains to be filled. Such issues make it all the more important to develop bring to market newer technologies and products that can deliver fulfill the unmet need in this area.

4.1 Present Treatments

A number of treatment options are available for alleviating post-amputation pain but none seems to be specific and effective. A multimodal approach is followed while treating this pain condition and options available include antidepressants, anticonvulsants, opioids and non-opioid analgesics, NMDA blockers, neural blockade, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS) and behavioral studies. Although some clinical studies support particular treatment interventions other have found them to be ineffective in providing any significant pain relief.
4.1.1 Antidepressants

Although tricyclic antidepressants (TCA) are the first line of treatment (Finnoff 2001) while treating post-amputation pain, only a few controlled trials show their efficacy (Wilder-Smith, Hill and Laurent 2005, Kuiken, Schechtman and Harden 2005). TCAs are also preferred because of the associated antidepressant effects that may be beneficial as a number (35%-50%) of amputees suffer from depression even though the dose for pain relief (100mg/day) is below the antidepressant dose (Kashani, et al. 1983, Peterson 2010). Tolerance of secondary amine TCAs like desipramine, nortriptyline is better than tertiary amine TCAs like amitriptyline with equal effectiveness but nonetheless, they could also be intolerable by many patients (Max, et al. 1992, Rowbotham 2005). Dose-dependent adverse effects like urinary retention, sedation, dry mouth and constipation are often associated with these medications. As number of amputees run a risk of developing coronary diseases or have had peripheral arterial disease in the past, TCAs are not recommended due to increased risk of sudden cardiac death (Dworkin, et al. 2007). To prove the efficacy of TCAs, more trials are required as too few controlled studies have been done and failure of a trial did not find any use of antidepressants in treatment of post-amputation pain (Robinson, et al. 2004).

4.1.2 Antiepileptic drugs

Usage of anticonvulsants like Gabapentin has been found to be ineffective in substantially reducing both phantom pain and residual limb pain (Nikolajsen, Finnerup, et al. 2006, Fassoulaki, et al. 2002) or even provide any significant improvement in depression, life satisfaction or functionality. Even in cases where gabapentin is effective
in alleviating pain, no significant differences in mood, sleep interference or daily activity is present (Bone, Critchley and Buggy 2002). Orally delivered carbamazepine is effective in alleviating shock-like pain but does not reduce other qualities of post-amputation pain (Patterson 1988).

4.1.3 Opioids


4.1.4 NMDA Receptor antagonist

Though promising in animal studies, oral NMDA receptor antagonists have proven ineffective in clinical trials (Peterson 2010). Studies with intravenously delivered Ketamine have shown some effectiveness in reducing amputation pain immediately post-operatively but the results from controlled trials are inconsistent (Hayes 2004, Nikolajsen 1996, Stannard and Porter 1993). Elevation of pressure-pain thresholds is known to occur with ketamine treatment but no affect has been seen on the thermal sensitivity (Eide, et al. 1994, Felsby, et al. 1996). Treatment with Calcitonin may provide pain relief post-
operatively (Jaeger, Maier and Wawersik 1988) but is ineffective in chronic post-amputation pain conditions (Eichenberger, et al. 2008). Attempts to treat phantom limb pain with Memantine, a NMDA receptor antagonist, also failed to provide effective pain relief (Maier, et al. 2003, Nikloajsen 2000).

4.1.5 Neural Blockade

Different types neural blockades like sympathetic blocks, stump injections, peripheral nerve blocks, epidural and subarachnoid blocks have been used for the treatment of post-amputation pain but result in a significant temporary change only in a few patients (14%) and even lesser significant prolonged change (5% patients) (Sherman and Sherman, Prevalence and characteristics of chronic phantom limb pain among american veterans: results of a trial survey 1983). Neural blockades may be helpful if used immediately post-operatively but no fixed inclusion criteria for their use are present (Blankenbaker 1977, Halbert 2002).

4.1.6 Surgical Intervention

Treatment of post-amputation pain with surgical intervention is difficult and involves the postsurgical resection/removal of neuromas that develop at the severed ends of peripheral nerves. Surgical management may alleviate pain to some extent but does not completely relieve an amputee from pain (Prantl, et al. 2006). Even upon removing the neuroma, the cut nerve ends grow back again to form new neuroma and instigate the pain again (Sturm, Kröger and Penzholz 1975). Techniques like anterolateral cordotomy and dorsal root entry zone (DREZ) to induce lesions (to block pain signal) have been tried to reduce
phantom limb pain and will require large multicenter studies to support any significance as they also carry risks of high morbidity and some mortality (Argoff and Smith 2010).

4.1.7 Miscellaneous Treatments

Mirror-box therapy that involves placing the amputee’s intact limb in front of a mirror to create an image that amputated limb in still present, has been found to completely relieve pain (Ramachandran, Rogers-Ramachandran and Cobb 1995, MacLachlan, McDonald and Waloch 2004). However, more robust clinical trials and experimental investigations are required as controlled data are lacking (Moseley, Gallace and Spence 2008). Adjusting the prosthesis may be helpful, but only if the pain is due to poor prosthetic fit. Extensive and regular use of myoelectric prosthesis may help in reducing phantom limb pain but more investigation is required to determine its effectiveness (Lotze, et al. 1999). Botulinum toxins A (botox) and B have shown effective phantom and stump pain relief in preliminary studies but require further investigations and controlled trials in larger number of patients before this therapy’s efficacy can be determined (Kern, et al. 2004).

4.1.8 Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is a portable device that is inexpensive and safe; and generates electric currents that passes through skin and activates underlying nerves. TENS has been in use since several years for reducing pain emanating from neuropathic conditions. However, no randomized controlled trials have been performed that could prove the effectiveness of TENS use in phantom and stump pain relief. The trials conducted so far to show TENS use in treating amputee pain lack methodological rigour and are thus insufficient in
judging its effectiveness (Halbert, Crotty and Cameron, Evidence for the optimal management of acute and chronic phantom pain: a systematic review 2002, Mulvey 2010). The long-term effectiveness of TENS for relief of chronic pain is unknown and there is a need to conduct multicenter RCTs to conclude the effectiveness of TENS for or against chronic pain treatment (Nnoaham 2008). Due to its external system, cables and interference with daily activities, patients often discontinue its use in the long run.

4.1.9 Spinal Cord Stimulation (SCS)

Treatment of phantom pain with Spinal Cord Stimulation has been effective in reducing 50% or more pain in 51% of the patients but its long term efficacy is a problem (Seigfried and Zimmerman 1981). A common problem (in 45-88% cases) often faced is lead migration due to which the active contacts move farther from their target nerves and the effectiveness decreases (North, Ewend, et al. 1991, Andersen 1997, Spincemaille, Technical data and complications of spinal cord stimulation: Data from a randomized trial on a critical limb ischemia 2000, Sharan, Evolving patterns of spinal cord stimulation in patients implanted for intractable low back and leg pain 2002). Although multiple-contact leads are being used to maintain contact in case of migration, original parasthesia coverage and pain relief are hard to achieve. Reprogramming the contacts may help regain efficacy in 30% of the cases, frequent reprogramming and revision surgery may still be required in 11-23% of the cases (North, Ewend, et al. 1991, Andersen 1997, Sharan, Evolving patterns of spinal cord stimulation in patients implanted for intractable low back and leg pain 2002, Cameron 2004). SCS is still considered to be an invasive procedure by physiatrists in amputee pain patients with low
long term success rate (23-32%) which does not justify the risks and complication (displaced or fractured electrode, infection, hardware failure, cerebrospinal fluid leak, etc.) involved with it (Krainick and Thoden 1981, Kumar, Toth, et al. 1998, Katayama, et al. 2001).

4.1.10  Electrical stimulation of the brain

Reduction in post-amputation pain by at least 50% has been shown to occur as a result of treatment with Deep brain stimulation (DBS) and motor cortex stimulation (MCS) but the data is based on studies performed on small number (3-11) of patients (Carroll, et al. 2000, Bittar, et al. 2005, Yamamoto, et al. 2006). Presently, it is difficult to predict which patients will benefit from this treatment as further study is still needed to test its effectiveness under double-blind conditions (Carroll, et al. 2000, Bittar, et al. 2005).

4.2  Affect on patient’s Quality of life

Amputee pain can be functionally limiting and affects a patient physically as well as psychosocially. Clinical depression is known to occur at 3 to 5 times in amputees when compared to general population and depressed mood and depression following amputation has 35% to 51.4% prevalence rate (Kashani, et al. 1983). Limited activity, age and time since amputation have been predicted to cause poor adjustment in psychological health following limb loss in such individuals. In amputees with moderate to severe post-amputation pain, it is frequently the pain following amputation rather than the loss of a limb that most impacts the activities of daily living, prevents completion of simple tasks, and correlates most negatively with return to employment (Millstein, Bain
and Hunter 1985, Whyte and Carroll 2002, Rudy, et al. 2003). Amputees who experience chronic pain have been reported to be more disabled than amputees without pain (Marshall, Helmes and Deathe 1992).

4.3 Economic Burden on Society

For a person with post-amputation pain, the median cost for pain and depression medications can exceed $3,000 per year and the median cost for a treatment regimen provided by a pain management center is over $6,000 per year. The total average annual cost in the United States to manage severe phantom and stump pain is estimated to be over $1.4 billion for medications and over $2.7 billion for pain center treatment programs. When the overall costs of all care associated with pain management, such as physician and emergency department visits, hospitalizations, radiology, nerve blocks, and other surgical procedures are included, the total cost can exceed $30,000 per year per patient leading to a cost of over $13 billion to treat amputees in the US with severe pain (Ephraim, et al. 2005, Mekhail, Aeschbach and Stanton-Hicks 2004).
5 POST-AMPUTATION PAIN RELIEF THERAPY

5.1 Peripheral Nerve Stimulation

Peripheral Nerve Stimulation (PNS) has been in use as a treatment option for neuropathic pain relief since 40 years when it was tested to treat pain conditions like mononeuropathies, sciatica, metastatic disease, reflex sympathetic dystrophy and occipital neuralgia. Initial implants of PNS devices occurred in 1960s but the most significant development was the successful treatment of a neuropathic pain syndrome called the occipital neuralgia. (Weiner 1999). An electrode was percutaneously inserted to electrically stimulate the region around occipital nerve to provide pain relief. Following years have seen both open and percutaneous PNS technique being applied to treat trigeminal pain, inguinal pain, abdominal pain and low back pain (Slavin, Use of long-term nerve stimulation with implanted electrodes in the treatment of intractable craniofacial pain 2000, Rauchwerger, et al. 2008, Paicius 2007). PNS is reserved for alleviating severe, chronic type of pain that has not been treated by medications, nerve blocks, TENS or surgical intervention. Other than pain relief electrical stimulation of peripheral nerves is used in a number of medical applications that include, it’s most common use in neuromuscular conduction testing during anesthesia, pacing of phrenic nerve in paralysis and vagal nerve stimulation in epilepsy and depression treatment.

PNS may reduce pain at high success rates (up to 80%) in case studies, and it has been positively correlated with chronic pain patients’ ability to return to work, resume daily activities, sleep pattern, relief from depression and reduce dependency on opiate analgesics (Strege, et al. 1994, Campbell and Long 1976, Racz 1990). In patients
implanted with nerve stimulators in upper and lower extremities, a majority of them (50% – 80%) experienced successful pain relief and a significant number (50%) returned to work (Nashold, et al. 1982, Strege, et al. 1994, Novak and Mackinnon 2000). In long term studies (2-10 years), 65% to 80% of patients receiving PNS implants reported good to excellent results and no difference was seen between upper and lower extremity implants which was earlier thought to provide better pain relief in upper extremity (Eisenberg, Waisbrod and Gerbershagen 2004, Novak and Mackinnon 2000). Such an observation may be attributed to structural improvements in the stimulator design (Belzberg and Dorsi 2010). In addition to pain relief, complete elimination or significant reduction of pain medication was also reported (Nashold, et al. 1982, Racz 1990, Strege, et al. 1994). Even though peripheral nerve stimulator can provide significant pain relief, the major limitation faced is the lack of electrodes that can be placed quickly and easily and do not migrate.

If patient selection is done carefully, the success rate of PNS for chronic neuropathic pain relief increases. The PNS treatment is considered effective if pain is reduced by at least 50%. However, sometimes, a less than 50% improvement coupled with patient satisfaction also justifies the effectiveness or success of an implant (Slavin, Peripheral Nerve Stimulation for Neuropathic Pain 2008). Generally, patient selection criteria includes: 1) pain localized to one nerve 2) pain relief following nerve block with local anesthetic 3) absence of surgically correctable lesions and 4) a satisfactory mental health status.
5.2 PNS Mechanism

The mechanism through which peripheral nerve stimulation of nerves provides pain relief is not well understood. But it is said to work on the principle of Gate Control Theory according to which the perception of pain occurs through a balance between the activity of nociceptive Aδ & C-fibers and non-nociceptive Aβ fibers (also called large fibers because of greater degree of myelination). Inputs from both nociceptive Aδ & C-fibers and non-nociceptive Aβ fibers converge with the projections neurons of Lamina V and possibly with Lamina I too (Fig 8). The inhibitory interneurons in the lamina II are activated by Aβ fibers that inhibit the lamina V projections neurons thereby blocking the nociceptive signals. During a noxious stimulus, the intensity of pain signal travelling in the Aδ & C-fibers inhibits the firing of inhibitory interneurons in lamina II. In a way, non-nociceptive afferents “close” the gate to pain signal transmission while the nociceptive afferents “open” the gate for central transmission of pain input (Melzack and Wall 1965, Basbaum 2000).

The Gate Control theory is involves the interplay of four kinds of neurons present in the spinal cord’s dorsal horn region and includes: 1. Projection neurons 2. Nociceptive Aδ & C-fibers 3. Aβ-fibers and 4. Inhibitory interneurons (Fig 9). The inhibitory interneuron normally remains active and inhibits the projection neuron, thereby blocking the transmission of the pain signal from nociceptive fibers. Under a noxious stimulus, the intensity of the pain signal travelling through the nociceptive fibers reduces the interneuron’s inhibition on the projection neuron thus letting the experience of pain to occur. When non-nociceptive fibers are stimulated, the interneurons start to inhibit the projection neurons from transmitting the pain signal to the brain. Simply put, if
someone’s head is hit, rubbing or massaging it provides pain relief through activation of non-nociceptive large fibers (Aβ) that inhibit the conduction of pain signals in the nociceptive Aδ & C-fibers.

Figure 8 Schema of the Gate Control Theory (Willis 1995)

Figure 9 Termination of nociceptive and non-nociceptive afferents occurs on projections neurons in the dorsal horn (Fields 1987)
5.3 PNS Application for Post-Amputation Pain

NDI Medical, LLC based in Cleveland is testing its proprietary neuro-stimulation device for the treatment of both stump and phantom pain. The device consists of an implantable pulse generator (IPG) which is implanted into a patient and delivers electrical impulses through implantable leads to the target affected peripheral nerves to provide pain relief (Fig 10). The approach is intended to be tested first in lower-limb amputees and if found successful, will be applied to upper-extremity amputees as well. The placement of the IPG and leads includes a two-phase procedure: During the first phase, the target nerve is identified and electrically stimulated using an external pulse generator (EPG) through temporary percutaneous leads. The patient is asked to use the system for 1-2 weeks and determination of generation of a tingling sensation (paresthesia) and pain relief is done during this period. If the pain is reduced to satisfactory levels, the temporary leads are removed and the patient is implanted with implantable leads and an IPG for long term pain relief.

Currently as part of the phase 1 of the study, the sciatic and femoral nerves that innervate the lower limb regions will be electrically stimulated with temporary percutaneous intramuscular leads using an EPG (Fig 12 & Fig 14). The placement of temporary leads in intended to be done in an in-office setting with a <10 min procedure. The phase 1 study aims to demonstrate the generation of tingling sensation (paresthesia) in the area of pain, and 50% reduction in stump and phantom pain. If the aims of the study are
successfully met, the patient will be implanted with the patented device and permanent implantable leads (Fig 11).

Figure 11: Temporary coiled fine wire leads for the phase 1 study

As discussed, careful patient selection is necessary for the device’s success and key eligibility criteria for the study include:

**Key Inclusion Criteria**

1. Adults (at least 21 years old)
2. Healed amputation and healthy stump
3. Stump and phantom pain scores $\geq 4$ on a scale of 0-10 Numeric Rating Scale of Brief Pain Inventory (BPI)
4. Patient has a score of $\leq 20$ on the Beck Depression Inventory (Beck Depression Index)

**Key Exclusion Criteria**

1. Sepsis, infection, or condition that places the patient at increased risk in the opinion of the investigator.
2. Cardiac pacemaker (as electrical stimulator may interfere with pacemaker’s firing)
3. Pregnancy (as risks to pregnant women and fetuses are unknown)
5.4 Treatment Protocol

Prior to stimulation, the patient’s stump and phantom pain baseline scores will be determined on the 0-10 numeric rating scale of the BPI. Nerve block approach of regional anesthesia administration will be utilized in placing the leads such that percutaneous leads will exit the skin and anesthesia will not be applied to the target nerve. Under aseptic conditions, the relevant leg portion will be cleansed and general anesthesia administered prior to lead implantation in patients with lower extremity amputation. Likewise, to place temporary percutaneous leads in the upper extremity amputees, brachial plexus nerve block approach will be utilized. Target nerves will be electrically stimulated with EMG needles at various places to determine the location of percutaneous lead placement. Ultrasound and muscle response to electric stimulation will help in properly placing the leads along with patient’s response to stimulus-evoked sensations (paresthesias) in their stump and/or phantom limb (Fig 13 & Fig 15). To provide comfortable parasthesias and pain relief, stimulation parameters will be optimized. Since, tissue mass can vary across different patients, targeting the nerve of interest will require modification to technique.
A current-regulated external pulse generator (EPG) will be connected to the temporary percutaneous leads which will monopolarly stimulate via the distal contact (on the tip of the lead) at 4 mA, 100 μs, 100 Hz, and an on-off duty cycle of 0.25 sec. The introducer will be slowly advanced until the subject reports the first evoked sensation in the stump or phantom hand. Until sensation is evoked at 1mA, the introducer will be slowly advanced and stimulus amplitude progressively reduced. Afterwards, the introducer will be stopped and stimulation-evoked parasthesia will be achieved over stump and phantom.
pain areas by increasing amplitude gradually by 0.1mA each time. Once the parasthesia is expanded to the stump and phantom pain regions the introducer will be withdrawn, leaving the percutaneous lead in proximity to the target nerves. This procedure is expected to be performed in less than 10 minutes.

The subjects who maintain a significant improvement (of at least 50%) in their pain over 1-2 week will have their trial stage system replaced with an implantable system. The safety, efficacy, and resistance to lead migration of the fully implanted system will be evaluated over a 12-month period by assessing paresthesia coverage, pain scores, thresholds of stimulus intensity, medications taken for pain, x-rays of the lead and surrounding landmarks, and adverse events at implantation and at follow-up intervals of 1, 3, 6, and 12 months after implantation. Subjects with insignificant improvement after the 1-2 week of home trial (stage 1) will have their trial stage lead removed.
MARKET ANALYSIS OF POST-AMPUTATION PAIN

Generally, before the process of bringing a product to market or even to initiate its development it is important to critically assess whether it will be commercially feasible or not. A number of factors play an important role in such an assessment and include target market size, market demand, competition (similar products or alternative means to meet the demand), exclusivity or patentability, reimbursement (restricted to the healthcare market), etc. As part of this study, primary and secondary market research was conducted to assess the market size and understand the market demand of the product. Secondary market research included finding the epidemiology data of both phantom pain and residual limb stump pain. Research and analysis of published data was performed using Pubmed to determine the prevalence and incidence rates of the post-amputation pain and calculate the US market size for it. Primary research included one-on-one interviews with physicians from various faculties like Anesthesiology, Orthopedic Surgery, Physical Medicine and Rehabilitation who consult amputee pain patients. Based on the market research done, conclusions were to be drawn and commercial feasibility of neurostimulation-based post-amputation pain therapy ascertained.

6.1 Prevalence and Incidence Data

According to the Amputee Coalition of America, prevalence rate of limb loss in the year 2007 was estimated at 1.7 million amputees in the US which is expected to reach around 1.8 million in 2010 and 2.2 million amputees in the year 2020. A 1996 National Health Interview Survey’s incidence estimates show that one out of every 200 persons in US has undergone an amputation while a recent study suggests the incidence rate to be 185,000

A survey conducted on 590 war veterans found that phantom limb pain was experienced in 85% by the amputees (Sherman and Sherman 1983). In another study, post-amputation pain was experience by 95% of the 914 limb loss patients interviewed. Of all the patients, 80% experienced phantom pain while residual limb pain was found to occur in approx. 70% amputees. Of the patients experiencing phantom pain, 65% reported their pain to be of moderate to severe intensity while a similar percentage (60%) of residual limb pain patients reported moderate to severe intensity of pain. A range of 73% to 82% phantom pain prevalence was seen in patients who underwent amputation within the last 2 years and those with more than 10 years of amputation. In residual limb pain amputees the range was 65% to 75% for the same duration since amputation. Also, the pain experience was irrespective of the amputee’s age or gender (Ephraim, et al. 2005).

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Subjects</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanley, MA et al. 2009</td>
<td>USA</td>
<td>104</td>
<td>79%</td>
</tr>
<tr>
<td>Ephraim PL et al. 2005</td>
<td>USA</td>
<td>914</td>
<td>80%</td>
</tr>
<tr>
<td>Ehde DM et al. 2000</td>
<td>USA</td>
<td>255</td>
<td>72%</td>
</tr>
<tr>
<td>Wartan et al. 1997</td>
<td>UK</td>
<td>590</td>
<td>55%</td>
</tr>
<tr>
<td>A D Houghton 1994</td>
<td>UK</td>
<td>176</td>
<td>78%</td>
</tr>
<tr>
<td>Jensen et al. 1985</td>
<td>Denmark</td>
<td>58</td>
<td>59%</td>
</tr>
</tbody>
</table>

In a study done on amputees with upper-limb amputation, pain was accounted in 90% of those surveyed and 76% reporting more than just one type of pain. Of all the studied,
phantom pain and residual limb pain were experienced by 79% and 71% of the amputees, respectively. Pain intensity was found to be moderate to severe in 45% of phantom limb pain amputees while 35% of the residual limb pain amputees reported moderate to severe pain (Hanley, et al. 2009). In a study conducted in lower-limb amputation patients, 79% amputees had phantom sensations while phantom pain was reported by 72% amputees and residual limb pain by 74% of those surveyed. Around 30% of phantom pain patients described it to be of severe intensity while 38% of those with residual limb pain found it to be severe in intensity (Ehde, et al. 2000).

Similar prevalence rates of phantom pain and residual stump pain have been seen irrespective of geographical location as evident from certain studies conducted outside US. In a study conducted in UK, of the 176 amputees assessed, phantom pain was experienced by 78% of the amputees while 82% of those had reported phantom sensations. In a 107 lower-limb amputee sample study done in Ireland, residual limb pain was reported by 60% of the patients.

Phantom limb pain is known to initiate in an amputee as early as 1 week after amputation or even 40 years after amputation (Ribera 2001). Certain studies have however reported a lower prevalence rate of phantom pain - a study done in Denmark on 58 patients undergoing amputation reported a decrease in prevalence rate of phantom pain from 72% to 59% at 2 years post-amputation (Jensen, Krebs, et al. 1985). In another survey conducted on 590 British veterans with long-standing amputations, 55% reported phantom pain while residual limb pain was reported by 56% of the respondents (Wartan, Phantom pain and sensation among British veteran amputees 1997). Of particular
mention is the residual limb pain as its prevalence can vary from 10% to 13% after 2 years from amputation to 55% to 76% after several years post-amputation (Ephraim, et al. 2005). In one of the studies mentioned above, just 21% of the amputees reported residual limb pain (Jensen, Krebs, et al. 1985).

Table 10 Prevalence of Stump Pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Subjects</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanley MA et al. 2009</td>
<td>USA</td>
<td>104</td>
<td>71%</td>
</tr>
<tr>
<td>Smith E et al 2007</td>
<td>Ireland</td>
<td>107</td>
<td>60%</td>
</tr>
<tr>
<td>Ephraim PL et al. 2005</td>
<td>USA</td>
<td>914</td>
<td>67%</td>
</tr>
<tr>
<td>Ehde DM et al. 2000</td>
<td>USA</td>
<td>255</td>
<td>70%</td>
</tr>
<tr>
<td>Jensen et al. 1985</td>
<td>Denmark</td>
<td>58</td>
<td>21%</td>
</tr>
</tbody>
</table>

6.2 Market Potential of Post-amputation Pain

6.2.1 Calculation of Market Size of Phantom Pain

The prevalence of phantom pain ranges from 55% to 80% and to calculate the market size the prevalence rate was taken as 80% (most common). Since the target market would consist of patients experiencing moderate to severe pain, it comprises 65% of the phantom pain patients. Therefore, the target phantom pain population will consist of 884,000 patients with an annual growth of 96,000 patients (Table 11).
### Table 11 Epidemiology Studies of Phantom Pain Experienced in Limb Loss Patients

<table>
<thead>
<tr>
<th>% of Total</th>
<th>Prevalence ('000)</th>
<th>Incidence ('000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1700</td>
<td>185</td>
</tr>
<tr>
<td>Patients with Phantom Pain</td>
<td>80%</td>
<td>1,360</td>
</tr>
<tr>
<td>Mod. to Sev Phantom Pain Patients</td>
<td>65%</td>
<td>884</td>
</tr>
</tbody>
</table>

**Assuming the price of the device per patient to be $15k, Market Potential is $13B with Annual Growth Potential (new patients) of $1.5B**

6.2.2  Calculation of Market Size for Residual limb Pain

As mentioned above, prevalence of residual limb pain ranges as low as 13% to 70% but to calculate the market size the prevalence rate was taken as 70% (most common). Since the target market would consist of patients experiencing moderate to severe pain, it comprises 60% of the phantom pain patients. Therefore, the target phantom pain population will consist of 714,000 patients with an annual growth of 78,000 patients (Table 12)

### Table 12 Epidemiology Studies of Stump Pain Experienced in Limb Loss Patients

<table>
<thead>
<tr>
<th>% of Total</th>
<th>Prevalence ('000)</th>
<th>Incidence ('000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,700</td>
<td>185</td>
</tr>
<tr>
<td>Patients with Stump Pain</td>
<td>70%</td>
<td>1,190</td>
</tr>
<tr>
<td>Mod. to Severe Stump pain patients</td>
<td>60%</td>
<td>714</td>
</tr>
</tbody>
</table>

**Assuming the price of the device per patient to be $15k, Market Potential is $11B with Annual Growth Potential (new patients) of $1.1B**
6.2.3 Total Market Size of Amputee Pain

From the calculations above, the total market size of the neuro-modulation amputee pain therapy would appear to be $24B and the annual growth potential would appear to be $2.6B. But there are many patients who experience both kind of pain and hence the market size above is not adjusted. A study showed that 58% of all patients experiencing phantom pain also experience residual limb pain and vice versa (Ephraim, et al. 2005). Therefore, the market size was adjusted as follows:

Patients experiencing both pain \[= 0.58 \times (884 \times 10^6) = 512,000 \text{ pts.}\]

Pts. experiencing Phantom pain only \[= (884 - 512) \times 10^3 = 372,000 \text{ pts.}\]

Patients experiencing Stump pain only \[= (714 - 512) \times 10^3 = 202,000 \text{ pts.}\]

Total Amputee Pain patients in US \[= 1,086,000 \text{ pts.}\]

Hence, the adjusted total Market Potential of Amputee pain is $15B, assuming the device price to be $15k and Annual Growth Potential of $960M.
7 PHYSICIAN INTERVIEWS

As part of the study, five physicians were interviewed from different specialties like Anesthesiology, Orthopedic Surgery, Physical Medicine & Rehabilitation and Pain Medicine. The interviews were 30-60 minute phone discussions and the objectives of this study were to:

1. Get a first-hand experience of physicians at consulting the amputee pain patients,
2. Better understand the patient care pathway,
3. Identify the targeted physician specialty for AP therapy,
4. Explore physicians’ reaction to our proposed device/therapy,
5. Solicit additional indications for the therapy

7.1 Physician Questionnaire

Given below is the questionnaire based on which the physician interviews were conducted and the responses analyzed and conclusions drawn.

**Post-amputation Pain Questionnaire**

This questionnaire is designed for 30 min in-depth one-on-one interviews with physicians who manage Amputee Pain patients. The targeted audience is physicians who consult amputee pain patients.

**Patients care pathways, referring and managing physicians ( 10 min)**

1. What different disease backgrounds do the candidates for amputation come from?
2. What physician(s) perform a limb amputation surgery?
3. What physicians typically see patients who complain of limb pain, immediately
post-amputation? Is it the amputation performing surgeon?

4. After an amputee patient is discharged from the hospital, who does typically see patients with amputee pain? How long? How often?
   a. Is it the primary physician?
      i. If No, then who?
      ii. If yes, to what physician does, in the first place, the patient gets referred to in case the pain treatment does not work?

5. Which are the primary physicians managing patients 6 months and 2 years after amputation?

6. Do you refer your amputee pain patients to other physicians for treatments? What type of physicians you refer them to? What procedures?

**Physicians’ practice and patients (5 min)**

1. How many amputations/amputees do you see each year?

2. How many amputees complain post-amputation pain?

3. How many days post-amputation, a patient typically starts complaining amputee pain?

4. What are the top health problems that your amputee patients struggle with? If not mentioned, ask:
   a. How important is the treatment of amputee pain and why? (i.e., what impact does it have on the patient and their rehab?)

5. How many have severe amputee pain? Moderate?

6. How long does the follow-up period go?
Final product of this discussion:

<table>
<thead>
<tr>
<th>Physician</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputee pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputee pain pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phantom pain – severe pain pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate pain pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stump pain – severe pain pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate pain pts</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Current treatments for amputee pain and their effectiveness (5 min)

1. How do you treat the amputee pain presently?
2. What is the first line of treatment? Is it always the same
3. Is it dependent on any factors? E.g. age, pain intensity, type of amputation
4. What other treatment options are available that you practice?
5. How do your colleagues treat amputee pain patients?
6. How many patients (%) improve as a result of each treatment option?
7. What % of pts becomes pain free?
8. What % of pts improves but still have moderate to severe pain?

Reaction to Amputee Pain therapy (10 min)

1. What do you think about implantable stimulation device for amputee pain therapy?
2. Would you offer implantable stimulation device therapy to your patients with amputee pain? What kind of patients would you offer it to? If so, at what point in the care continuum would you prescribe this therapy?
3. Compared to other treatments, what are the key benefits of amputee pain therapy to you? To your patients?

4. What do you think will be the key challenges for amputee pain therapy to penetrate the market?

5. Assuming amputee pain therapy got FDA approval, out of the patients you treated last year, how many do you think you would treat with amputee pain trial therapy and amputee pain therapy?

6. Considering amputation to be itself a big operation; in your opinion, would a patient be willing to undergo another invasive procedure?

7. Do you think your colleagues would use amputee pain therapy? How would they think about it and use it?

*Final product of this discussion:*

<table>
<thead>
<tr>
<th>Physician</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acceptance of Amputee Pain therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of pts to be treated with amputee pain therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. What kinds of physicians are positioned best to perform the device implant procedure to manage amputee pain patients? Why?

9. What kind of physicians are the best to manage patients once device is implanted? Why?

10. What pain indications other than amputee pain should NDI investigate? Why?
7.2 **Interview Summary with Dr. A** (Professor of Anesthesiology and a Pain Management Specialist)

**Patient Care Pathways**

Most patients that Dr. A manages are immediately after amputation. According to him, majority of amputations are done by vascular surgeons (may be 75%) and the rest by orthopedic surgeons at his hospital.

Dr. A acknowledges the uncertainty and complexity of referral pathways and the lack of medical specialty that is dedicated to amputee pain patients. He suggested that the best way to find amputee pain patients is at the VA rehabilitation facility where they are treated by Physical Medicine & Rehabilitation Doctors (physiatrists). 100% of amputees go through some form of rehab therapy. He mentioned two major hospitals managing amputee pain patients in Cleveland.

**Pain Prevalence**

Dr. A sees 1-2 amputee pain patients per year. According to him, based on publications and experience of his colleagues, 90% amputees have phantom limb sensation and a significant proportion have pain. 10-20% amputees have severe pain, 70% have moderate pain and a very small proportion have moderate to none intensity of pain.

**Treatments and their effectiveness**

Most treatments for amputee pain are based on conservative pain management. Treatments include various medications like epileptic drugs, antidepressants, steroids, NMDA blockers. And they are effective only sometimes.
Spinal Cord Stimulation has been tried for amputee pain but is not impressive, less than 20% of patients improve. Also, brain stimulation is used occasionally especially for phantom pain but has not been studied well. Patients report that the improvement is only 20-30% with brain stimulation. With medication, 50% improvement occurs in about 5% patients.

**Reaction to Implantable Therapy for Post-amputation Pain**

Dr. A would like to see the effectiveness of implantable nerve stimulation therapy for amputee pain. After amputation the central nervous system (CNS) undergoes changes and whether Peripheral Nerve Stimulation or Spinal Cord Stimulation would be effective is a question.

Dr. A believes that the therapy will be appropriate for severe pain patients, not moderate or mild. The therapy is still invasive and patients and physicians will be reluctant to undergo another invasive procedure if the pain is not severe.

Dr. A believes that diabetic patients should be contra-indicated for the therapy because of the risk of infection. Even low infection rate will be devastating for diabetes patients and might result in another amputation. Thus, this is a risk that is too high and physicians won’t prescribe Peripheral Nerve Stimulation (PNS) for diabetes pts who just went through amputation.

The advantages of PNS for amputee pain that he sees are its less invasive nature and easier application. The issues of concern are that the therapy should not cause more of problem by damaging the nerves. Also, the life expectancy of diabetes patients after
amputation is not too long. Probably going after the post-traumatic patients would be the best option.

Additional indications where this therapy might find application would be:

1. Tarsal Tunnel Syndrome
2. Peripheral Focal Neuropathies

If PNS is found as effective as Spinal Cord Stimulation and considering it to be less invasive it would be good to add it as a way to manage pain.

Dr. A shared his experience with implantable subcutaneous field stimulation where a patient had fracture in both hands and had pain. A test implant was done at home on one hand and the therapy worked well. On patient’s request the device was implanted in the other hand too but the improvement was better in one hand only.

7.3 **Interview Summary with Dr. B** (Professor of Anesthesiology and a Pain Management Specialist)

**Patient Care Pathways**

Major physicians performing amputations include the trauma, vascular and orthopedic surgeons. A vascular surgeon would be involved in amputations resulting from ischemic disease (diabetes) and a trauma and orthopedic surgeon would do an amputation resulting from an accident or an injury.

Most of the patients after leaving the hospital end up at nursing homes or rehabilitation centers. A major problem that is faced is locating the patients because their phones
change. Sometimes, patients are poor or have past history of alcohol or drug abuse. Nursing homes also refuse to practice any experimental or innovative treatments that represent additional issues with market penetration.

Post-amputation, post-op follow-up is done for 8 weeks. If amputee pain occurs, the physiatrist at the rehabilitation center manages the pain if the intensity is low. The patient is referred to a pain management specialist if the pain intensity is high.

**Pain Prevalence**

According to him, his hospital does 120 amputations per year of patients suffering from ischemic diseases like diabetes and around 30 amputations per year of trauma patients. Since his hospital is primarily not a trauma center, larger numbers of trauma amputations are done at another hospital dealing with trauma cases. A smaller number of amputation cases involve people suffering from various tumors like sarcomas, cancers, etc.

Diabetes-related amputees are a declining patient population. With the advances in the medical technologies more and more amputations are avoided, by-pass procedures to allow blood flow and preserve the limb become more frequent. Diabetes-related amputees in his experience tend to have a high rate of drug abuse, alcoholism and poor health insurance plan.

Post-trauma amputees are a much better patient population: younger, otherwise healthy.

He indentified three kinds of problems that occur post-amputation:

**Phantom limb pain:** this is a centralized pain
**Neuroma:** As a result of amputation a bunch of nerve cells is formed at the nerve ending. Due to movement it causes severe shooting pain.

**Reflex Sympathetic Dystrophy of Stump:** this presents as a cold, grey to red, shiny limb. It forms severe oedema. It is also known as Chronic Regional Pain Syndrome (CRPS). The population suffering from this problem is smaller than the neuroma amputee pain patients.

**Treatments and their effectiveness**

Dr. B mentioned that he has tried anesthetic medication to prevent pain and continue it for 6 months to 1 year but the problem of patient follow-up is faced. He has tried neuromodulation in ischemic patients but the results were disappointing. According to his experience, not too many patients improve as a result of Spinal Cord Stimulation approach. In his opinion, he would be more comfortable treating other neuropathic pains than phantom pain as he believes the majority of patients would fail to improve with spinal cord stimulation or peripheral nerve stimulation.

According to him, the effectiveness of Deep brain stimulation is better for treating centralized pain than SCS or PNS. But a problem with DBS and SCS is lead migration which results in lowering in effectiveness over time.

He also mentioned that neuromas that result in amputee pain are treated through excision, freezing it, anesthetic injections or burning with radio frequency.

**Reaction to Implantable Therapy for Post-amputation Pain**

Dr. B expresses some concerns about the implantable therapy:
• Patient selection: It will be difficult to tell for which patient the therapy will work and he believes it won’t work for everyone. This therapy would be contraindicated in case of CRPS patients.

• Migration and breakage of the leads. He wasn’t familiar with intramuscular leads and reflected on other experience with PNS where lead migration was an issue.

Dr. B describes his experience with PNS. Two leads are put as a sandwich around the nerve to get efficacy but leads eventually break because of the movement. Anything around the large joint can possibly migrate or break. Even if a lead is put next to the nerve with Ultra Sound guidance it will still migrate. He described a procedure with On-point lead (Medtronic) which might help to reduce the problem of lead migration and a study performed at Mayo Clinic. Needles were used to place the leads near the nerve with ultra sound guidance and once the leads “catch stimulation” they were left at their place. However, out of the 5 patients who were implanted by this procedure a few lost stimulation effect. When skin and muscle move, it might cause lead migration even if IPG is placed in the proximity to the stimulation location (on the stump or elsewhere on the leg)

Neurosurgeons and Orthopedic surgeons together need to perform implant procedure. Ortho surgeon will perform the dissection as they are more familiar and experience with leg anatomy and this kind of surgery. Neurosurgeon will place the electrode and IPG as well as program it initially as they are more familiar with these devices.

Percutaneous placement can be done at the rehab center but dissection needs to be done at the hospital.
Other indications for PNS that Dr. B recommended include:

1. Occipital Nerve Stimulation for Migraine
2. Posterior Tibial Nerve Neuralgia (also Tarsal Tunnel Syndrome)
3. Femoral Cutaneous Neuralgia
4. Supra Orbital Neuralgia
5. Hernia repairs pain

Dr. B also mentioned a physician at Mayo Clinic as an expert who also recently had a publication on Amputee Pain at AAPM.

7.4 Interview Summary with Dr. C (PM&R Specialist)

Patient Care Pathways

According to Dr. C, civilian trauma patients are stabilized and sent to vascular surgeons, orthopedic surgeons, sometimes plastic surgeons and rarely to neurosurgeons. Prolonged attempts to resuscitate damaged parts are time consuming and extensive. For military trauma injuries, patients are transported to hospitals far off.

The diabetic population work for a long term on their disease with an internal medicine doctor or a diabetic specialist. Under circumstances of amputation, they end up with a vascular surgeon either to save the limb or undergo amputation.
After amputation, the patients are psychologically prepared and referred to rehab centers. At the rehab centers the patient is looked after by prosthetists, physiatrists and psychologists. Most amputees would first go to the primary physician for pain treatment but if it gets complicated they are referred to a pain specialist or regional anesthesiologist.

Pain prevalence

Dr. C says that the epidemiology is not good as the published articles are old and the data are from European studies. He believes that Amputee Pain is a small market. Dr. C suggested NDI should go for a bigger indication. After several minutes of brainstorming he recommended single-nerve painful peripheral neuropathy as the indication to pursue.

Treatment and their effectiveness

In most cases, the primary doctor tries to manage the amputee pain. They know about treating neuropathic pain through anti-convulsants, anti-depressants, opioids. However, he mentioned opioids are not effective in reducing pain post-operation.

Reaction to Implantable Therapy for Post-amputation Pain

Target physicians: When it comes to usage of this technology, Dr. C advised against the primary care physicians, neurologists, neurosurgeons. Neurologists and primary care physicians would be reluctant to use the invasive technology like this. Neurosurgeons might not be interested as it might be too simple for them and they don’t want to manage amputee patients. Anesthesiologists (especially the subgroup that he called “regional anesthesiologists”) are most likely to implement the technology and manage a lot of pain pts.
As a researcher, Dr. C is familiar with the technology and would like to go ahead with it if it can be developed well. Current challenges would be to prove it scientifically and get out the word that it is not only safe but it works too. He mentioned that he would have been reluctant to use an invasive procedure had it been 15 years ago but since now with the improvement in technology people are more comfortable with it.

He suggested that the device should be positioned between TENS and the Spinal Cord Stimulation and it is not difficult for a physician to differentiate between all three. The positioning should be that it’s more effective that TENS and less invasive than SCS. The technology needs to be portrayed as less invasive and as good as spinal cord stimulation.

Additional indications where the technology might find its use would be:

1. Carpal and tarsal tunnel syndromes
2. Radiculopathy – Since the invasiveness of the procedure would be as close as to the Spinal Cord Stimulation this challenge needs to be met
3. Trigeminal neuralgia – the challenge it presents is that it’s hard to place an invasive device on a patients face.
4. Mononeuritis multiplex – a common cause of this indication is Diabetes and the target nerve has to be highly specific in order for the device to work

Dr. C also said that market for amputee pain is not as big as compared to other neuropathies like the carpal tunnel syndrome and radiculopathy which present a larger patient population. However, he mentioned that this technology can be checked in amputee pain, carpal tunnel syndrome and postherpetic neuralgia. And if it works in majority of these indications and with FDA’s change of strategy at approvals, this
technology can be filed for approval to be used in other Mononeuropathic Pain indications.

7.5 Interview Summary with Dr. D (Orthopedic Surgeon)

Patient Care Pathways

Dr. D’s practice focuses on orthopedic surgery. His experience with amputation is majorly due to orthopedic related diseases like chronic osteomyelitis or cancers. The options they have are either above knee or below knee amputations. Also, his group tries to perform limb salvage procedures to save the limb. His hospital; has a prosthetics facility where the amputee patients end up after amputation for the prosthesis to be fitted and visit orthopedics alongside too. Also, patients from outside get referred to his hospital in case of amputee pain. He mentioned Dr. C (already interviewed) to be one of the consulting physicians on phantom pain to whom the patients get referred.

Pain Prevalence

According to Dr. D the volume of such patients is not high and in the last 5 years of practice, he has done amputations only on 5 patients. Dr. D believes that his experience is typical for most physicians. Orthopedic surgeons, vascular surgeons or pain management specialists do not focus on amputees and do 1-2 procedures a year. Dr. D estimates that there are only 10 physicians or so in U.S. who focus on amputation and have significant volume.
His experience with amputee patients has been the same at his earlier place of practice, the Metro Health Hospital. At his hospital, he has encountered sub acute pain problems although his major focus is on dealing with chronic pain.

**Treatments and their effectiveness**

Dr. D says that current treatments depend upon the symptoms. In case of neuromas, stump revision is done to deal with chronic stump pain. Also, anti-depressants and anti-convulsants are given to patients. Also, he pointed out that Dr. C was trying some pre-amputation methods to stop phantom pain.

Also, he mentioned about the pain due to prosthesis that patients wear and is often taken care by prosthetists.

**Reaction to Implantable Therapy for Post-amputation Pain**

When asked if he would use it for amputee pain, Dr. D had concerns about the battery life, its effectiveness and chances of causing infections due to implantable nature of the device. If these issues can be taken care of, he’ll be fine recommending its use. From the patient’s perspective, he said that there are such patients who are looking for some solutions because there isn’t much that can be offered to solve pain associated problems. He believes that patients’ resistance to invasive procedure would be minimal.

According to him, the device should be targeted at chronic pain management specialists with surgical basis and nerve stimulator implanters, most of which are anesthesiologists. Also, orthopedic surgeons with specialization in amputation are potential targets. Tumor
doctors can also be included as they too devote a part of their time in the practice of stump pain management.

He mentioned that his hospital targets patients and educate them about latest treatments through advertizing. However, most times, amputee patients are unemployed and can be low on priority of being advertized at, because of reimbursement issues.

7.6 **Interview Summary with Dr. E (PM&R Specialist)**

**Patient Care Pathways**

Post-amputation, the patients are referred to Dr. E’s clinic for evaluation and management for prosthesis, rehabilitation and pain. The amputations at Dr. E’s hospital are done majorly by vascular and orthopedic surgeons and post-amputation, all amputees get referred to the Physical Medicine and Rehabilitation Center. The pain management for amputee pain goes on for lifetime. Under the ideal patient referral pathway at his hospital, the patient is referred to the PM&R before amputation for consultation and for follow up after amputation. Then the rehabilitation of the patient is either done as an in-patient or out-patient. After rehab the patient is followed up for prosthesis, fitting and management.

Dr. E gets around a 50 patients every month including follow-ups and new amputee patients. Most of the patients (60-65%) that come to his clinic are referred by vascular surgeons due to diseases like diabetes and development of a non-healing foot ulcer. The rest (25-30%) are trauma related amputations due to accidents or work related injuries.
Dr. E acknowledged that he does not specialize in Amputee Pain management; however, he is an expert over this indication at his place of work. He also added that it is normal for most rehab centers to have specialization in amputee pain. Generally, 25 bed or more sized rehab center would have an amputee pain specialist and may not necessarily be an in-patient rehab center.

Pain Prevalence

According to Dr. E, “most if not all” patients have pain. Around 80-90% patients present phantom pain symptoms. Many of the patients also have stump pain which occurs due to pressure or neuromas in the nerve is related to the amputation site.

Treatment and their effectiveness

The pain management strategies aimed at amputee pain patients include 1) Medications and injections, 2) Modification to prosthesis 3) Meditation and psychology sessions 4) Surgery. Dr. E mentioned that methods like demyelination, nerve excision and cutting have also been tried but there is no long term relief to the pain.

Dr. E said that 100% pain relief never occurs in patients and the treatments are somewhat effective. 50% reduction of pain occurs in 50-60% patients with amputations. Out of his experience he says that some patients learn to live with the pain and some continue to complain of pain.

He clearly pointed out that 5% of the patients still present with severe pain and don’t improve in response to current treatment methods. Either the medications or injections don’t work or they are unable to wear their prosthetics due to the pain.
Dr. E mentioned about the use of Intrathecal Baclofen Pump. The pump is placed by the neurosurgeons and after that it is managed by his center. His PM&R practice involves the management of wound, prosthesis, functionality and change of prosthesis. Addressing just the issue of pain would be a limit on the practice.

**Reaction to Implantable Therapy for Post-amputation Pain**

In Dr. E’s view, the implantable amputee pain therapy would be prescribed by PM&R specialists, Physiatrists and Ortho surgeons as they manage amputee pain patients. And he would like to see neurosurgeons, plastic surgeons to be the preferred implanters of the device. He mentioned that it would probably be recommended 1 year after amputation and when the conservative medications have failed.

He said that patients who have significant pain and don’t get better with medications and injections might be less reluctant to get an implantable therapy. Their reluctance will also depend on the place of implant and the reimbursement as many patients are dependent on Medicare due to age or inability to work.

Presently, this seems to be the most invasive method of amputee pain treatment but factors like cost effectiveness, functionality, comfort, benefits etc. would matter in its movement up on the chart of amputee pain treatment options from the physicians’ perspective.

Dr. E also mentioned that if patient follows up every six months with pain, injections are used and it is very difficult to tolerate for them. After a maximum of one or two injections the patient might say no and then an implantable device might be considered.
8 DISCUSSION

It is evident from interaction with physicians that all patients after amputation of a limb are referred to rehabilitation centers where post-amputation pain is managed by the Physical Medicine & Rehabilitation (PM&R) specialists. The rehab centers also consist of prosthetists for prosthesis fitting and sometimes psychologists who chiefly work on patient’s mental health. If the pain is not contained at the rehabilitation center, the amputees are referred to the pain management specialists.

Since all patients after limb amputation are managed at rehab centers, it is clear that the PM&R and pain management specialists will form the target customers to whom the sales forces will sell the product. It is important to know the specific target market so that a dedicated sales force can be trained and developed or the existing sales force already catering to these specialties can be trained. Managing a sales force for a company is resource intensive and therefore as one of the several key selection criteria, a device company looks for a new product which can be integrated into their product line with minimal resource utilization at their end. Two out of five physicians interviewed above supported that neurosurgeons should be the implanters of the device as they have experience with such devices. Similar, procedures like Deep Brain Stimulation or Spinal Cord Stimulation at hospitals like Cleveland Clinic Foundation or Case Medical School are being covered under the faculties of neurology or neurosurgery. Also, medical device giants like Medtronic have mentioned Neurosurgeons as part of the team that would perform such a procedure. PM&R with surgical skills can also be implanters of this device.
As discussed earlier (sections and subsections 4.1 to 4.3), the treatment modalities currently available are not helpful in significantly relieving post-amputation pain, hence, identifying a need of a new and effective treatment. All the physicians interviewed also confirmed the ineffectiveness of the current treatment modalities out of their experience, which is similar to published data in the literature. As patients experiencing post-amputation pain also face decreased quality of life (Millstein, Bain and Hunter 1985, Whyte and Carroll 2002, Rudy, et al. 2003) and get (35% to 51.4% of the amputees) predisposed to high risk (3 to 5 times of general population) of clinical depression (Kashani, et al. 1983), it can be suggested that reduction in pain with this device will also help in addressing such issues. It was expressed by every physician that they would be interested to use this device if it is found to be effective in providing pain relief. It is a positive indicator that the device, if effective, will be prescribed by the physicians consulting chronic post-amputation pain patients and will have an acceptance as a pain treatment method in the medical community.

However, there were certain issues raised by the physicians affect the commercial success of the product.

Two of the physicians (Dr. C and Dr. E) interviewed were not supportive of the fact that a peripheral nerve stimulation device be commercialized for post-amputation pain because in their view the market was not large enough, to make it commercially profitable. According to Dr. E’s comments, in his experience (as he sees the maximum number of amputees in comparison to other physicians) only 5% of the amputee pain patients have the kind of severe pain that does not improve and would be prescribed an
implantable neuro-stimulation based pain relief device. Above comments can be corroborated by the fact that only 0.5% to 5% of the amputees ever experience “severe” phantom limb pain (Melzack and Loeser 1978, Henderson and Smith 1948, Ewalt 1947, Wartan, Hamann, et al. 1997), in contrast to higher rates reported, so as to hinder the routine of a patient on “more than 6 days in a month” (Sherman, Sherman and Parker 1984). If in the view of physicians and published literature data, the actual patient population who would benefit from this device is small (0.5 to 5%), the market potential markedly decreases posing problems for its commercial success.

One of the indications important for application of peripheral nerve stimulation is that the pain has to be “severe” in intensity. Therefore, including patients suffering from moderate post-amputation pain may be an overestimation of market size. Hence, amputees with severe intensity of pain should only be included. As a result, only 40% of the patients experiencing phantom limb pain and 30% experiencing stump pain form part of the target patient population (Ephraim, et al. 2005). If the above two assumptions are taken into consideration the market size will reduce to 30,000 patients with a market revenue of $450M and an annual growth of $45M. Because now that the device will be applicable in lesser number of patients as compared to before, the market size is markedly decreased (Table 13).
The usage of this device in diabetic patient population was a concern that every physician expressed and discouraged its implantation in them. The diabetic patients who undergo amputation are an unhealthy set of population who have slow wound healing, a history of alcohol & drug abuse (not always) and a shorter life-expectancy. Diabetes is also a major reason of limb loss with approximately 60% of the lower limb amputation in US resulting
because of it (American Diabetes Association n.d.). Of the total amputee population about 6% to 30% undergo a second leg amputation within 1-3 years of initial leg amputation and ~28% - 51% of the diabetic amputees undergo a second leg amputation at 5 years (Ebskov and Josephsen 1980, Deerochanawong 1992, Stewart 1992). Five-year mortality rate for diabetics are estimated between 43% to 74% after amputation (Robbins, et al. 2008, Moulik, Mtonga and Gill 2003, Schofield, et al. 2006). It is fairly suggestive that physicians will not be willing to offer this therapy to the diabetic amputees because of the serious complications like high infection rates, slow wound healing, short life expectancy etc. Such a situation affects the number of patients that can be treated and hence decreases the chance of its commercial success.

As discussed above, a number of significant factors contribute toward suggesting the fact that the proposition of a neuro-stimulation device for post-amputation pain relief may not be commercially viable. But certain aspects like a need for an effective treatment for this pain condition, a demand from physicians for a new treatment modality make it important to study if through certain means the device could be introduced in the market.

In spite of physicians suggesting against the use of this device in diabetic patients, major surgeries and procedures such as cardiac implants like stents & defibrillators, renal transplant (Gaston, et al. 2004), dental implants etc. have been performed in diabetic patients. Any major surgical procedure in diabetics is often associated with increased risk of perioperative infection and postoperative cardiovascular morbidity and mortality (Lee, et al. 1999, Malone, et al. 2002). The goal in perioperative management of diabetes during a major surgery is to maintain glycemic control “through close monitoring,
adequate fluid and caloric repletion, and judicious use of insulin” (Dagogo-Jack 2002). Hyperglycemic states (>200mg/dl) can lead to impaired leukocyte function making a patient susceptible to infection, slow wound healing, dehydration & electrolyte imbalance, diabetic ketoacidosis, postoperative sepsis or cerebral ischemia (Marhoffer, et al. 1992, Rayfield, et al. 1982, McMurray 1984, Pulcinelli, et al. 1983, Walker, Marshall and Alberti 1989, Schade 1988). While hypoglycemic state (<40mg/dl) can result in arrhythmias, other cardiac events, or transient cognitive deficits (Nadia 2009). The perioperative “normoglycemic” values for major surgery should be maintained below 200mg/dl (Moghissi 2009, Canadian Diabetes Association 2008, American Diabetes Association 2001) and in the range of 120-180mg/dl(Dagogo-Jack 2002, Amiel and Alberti 2003). Along with blood glucose levels, the preoperative Hemoglobin A1C levels should be brought down to <7-8% to avoid postoperative infections (Nadia 2009, Dagogo-Jack 2002, Dronge, et al. 2006). For complex surgeries, including neurosurgical procedures, intravenous infusion (100ml/hr) of short-acting insulin with glucose and potassium (GIK) is the recommended standard therapy and considered better than subcutaneous delivery (Alberti and Gill 1997, Hirsch and McGill 1990). Close monitoring of glucose levels is necessary to avoid complications due to different metabolic profiles of each patient and GIK infusion should be administered depending on the feedback from glucose monitoring (Table 14).
Table 14 Regimen for Glucose-Insulin-Potassium (GIK) Combined Infusion (Amiel and Alberti 2003)

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dl)</th>
<th>Glucose-Insulin-Potassium Infusion Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5% Dextrose</td>
</tr>
<tr>
<td>&lt;80</td>
<td>↓5 units</td>
</tr>
<tr>
<td>&lt;120</td>
<td>↓3 units</td>
</tr>
<tr>
<td>120-180</td>
<td>No change</td>
</tr>
<tr>
<td>181-270</td>
<td>↑3 units</td>
</tr>
<tr>
<td>&gt;270</td>
<td>↑5 units</td>
</tr>
</tbody>
</table>

*Arrows indicate amount by which insulin in each 1,000-ml bag of infusate is to be decreased or increased

In order to increase the patient base to make the market size profitable, other neuropathic pain conditions can be added as potential targets where this device can be used. Several mononeuropathic pain conditions were addressed by the physicians during interview where they are looking for possible therapeutic solutions that can effectively reduce pain. If the device is successful in treating pain, it can find application in other neuropathic indications that have a larger patient population and thus a greater market potential. Two painful neuropathies, Carpal Tunnel Syndrome and Cervical Radiculopathy have large market potentials where the device can be targeted (Table 15). This way, the device can be projected as commercially viable with application in different indications and serves varied and large patient population and not just post-amputation pain patients.

Table 15 Other painful mono-neuropathies where a PNS device can be applied (Sadosky, et al. 2008)

<table>
<thead>
<tr>
<th>Neuropathic Pain condition</th>
<th>Incidence (per 100,000)</th>
<th>Growth Rate (pts/yr)</th>
<th>Annual market Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carpal Tunnel Syndrome</td>
<td>170</td>
<td>510,000</td>
<td>$7.65B</td>
</tr>
<tr>
<td>Cervical Radiculopathy</td>
<td>83</td>
<td>250,000</td>
<td>$3.75B</td>
</tr>
</tbody>
</table>
9  CONCLUSION

Based on analysis, it can be concluded that commercialization of a neurostimulation based device to treat post-amputation pain is not commercially feasible. Diabetic population would be a tough market to penetrate seeing the reluctance of physicians to perform an invasive surgery and other related issues as discussed above. This market potential again diminishes as according to physicians and published data only 5% of the patients are expected to ever opt for this pain relief therapy. The revised calculation of the market potential based on the above findings revealed that only 30,000 patients would undergo this treatment modality which reduces the market potential to just $450M with an annual growth rate of $45M. But if this device is to be introduced in the market, a larger market potential is needed to make it seem like a commercially viable plan. The application of this device can be expanded on to other neuropathic pain conditions so as to cover a large number of patients to increase the market potential. Certain diabetic surgery controls as discussed above can be implemented so as to include the diabetic amputee population to undergo neuro-stimulation device implant procedures.


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