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Managing Chronic Pain Through Advancements in Transcranial Brain Stimulation Technology Currently Used for Depression

Ashley N. Skinner
University of South Dakota

MANAGING CHRONIC PAIN THROUGH ADVANCEMENTS IN TRANSCRANIAL BRAIN STIMULATION TECHNOLOGY CURRENTLY USED FOR DEPRESSION

by

Ashley N. Skinner

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The members of the Honors Thesis Committee appointed
to examine the thesis of Ashley N. Skinner
find it satisfactory and recommend that it be accepted

____

Dr. Debra Norris
Bachelor of Science in Social Work Program Director
Director of the Committee

____

Dr. Brian Burrell
Professor of Biomedical Sciences

____

Dr. Lisa McFadden
Assistance Professor of Biomedical Sciences

ABSTRACT

Managing Chronic Pain through Advancements in Transcranial Brain Stimulation Technology Currently Used for Depression

Ashley N Skinner

Director: Debra Norris, Ed. D

The purpose of this thesis is to bring attention to alternatives to using analgesics or painkillers and potentially addictive opioid analgesics. Transcranial Magnetic Stimulation (TMS) has been proven successful in treating medication-resistant depression. This literature review will look at the links between pain and depression and examine adaptations to TMS coils in hopes of being able to stimulate the regions of the brain that interpret pain. By looking at current advancements in TMS, we can work towards adapting TMS to stimulate deeper regions. The final section of this thesis will examine how making these alternatives more popular will impact pain management. The hope is that by bringing these non-surgical, non-medication alternatives to pain management into mainstream medical use rather than alternative medicine, we can work towards holistic care and move highly addictive opioid analgesics only available to those in critical care.

KEYWORDS: Transcranial Magnetic Stimulation, Pain, Opioid Use, Holistic Approach

TABLE OF CONTENTS

CHAPTER ONE

What is Pain?

Physical Pain

Before looking at how to utilize alternatives to managing chronic pain, one must first look at understanding the terminology and mechanics behind the topic of pain. Such as, what is the process for feeling pain, and what are the structures that allow us to feel pain. Being able to understand the terminology and processes the body and brain uses when gathering, interpreting, and signaling pain is vital in finding new ways to combat the traditional pill-based practices in modern medicine.

The process of feeling pain begins with nociceptive sensory nerves found throughout the body. These nerves send messages to the nerve cells in the brain called neurons. Neurons are cells that conduct electrical impulses which the brain then interprets as harmful or not harmful. Some of these neurons to interpret signals of pain and are called nociceptors, nociceptors respond by interpreting the pain signals as coming from actual or potentially damaging stimuli. There are two different types of nociceptors, categorized based on the conducting speed at which they send their messages and which phase of pain to which they are responding. The first is the faster conducting A-delta (Aδ) fibers; they respond to either dangerously intense mechanical or to mechano-thermal stimuli (Purves, 2012). They are also known as the first pain nociceptors since they react at a faster rate and due to more potentially damaging stimuli. The second type is the slower, unmyelinated C fibers; they respond to all three of the stimuli types, mechanical, thermal, and chemical. C fibers are more commonly associated with secondary or chronic pain (Purves, 2012). While there are many types of chronic pain, for this review, the focus will be on two kinds of chronic pain, hyperalgesia, and allodynia.

Hyperalgesia. Hyperalgesia otherwise described as being hyper-sensitive to pain from one of two different situations. The first situation is from an initial injury, and thus, the body is reacting in a way to help prevent further damage. Injury-based hyperalgesia subdivides further into primary and secondary categories. Primary injury-based hyperalgesia is when the pain sensitivity only occurs on the previously damaged tissues. Making damaged tissues more sensitive to pain is the body's initial reaction to keep the tissues from either becoming more damaged or preventing a repeat of the initial incident that occurred to cause the damage. Secondary injury-based hyperalgesia occurs when the pain sensitivity impacts the surrounding undamaged tissues rather than just being isolated to the previously damaged tissues. Secondary injury-based hyperalgesia could be the result of damaged nociceptors or nerves within the peripheral nervous system (Gebhart, 2013).

The second situation which could cause an individual to experience hyperalgesia is from overdosage of opioids. Opioid-induced hyperalgesia is a paradoxical response to an individual receiving opioid analgesics either when unnecessary, such as Sam Quinones discusses in his book *Dreamland: The True Tale of America's Opiate Epidemic* (2012) or when given higher and higher doses after the body begins adjusting to the level of opioids in the bloodstream. Quinones discusses how Purdue Pharma hired the ad firm, William Douglas McAdams. As a company, they would put "sales reps through several weeks of training. One question they address involved the risk of addiction to pain patients when treated with narcotics. The correct answer was 'less than one percent.'" With an increase of individuals battling the opioid epidemic, opioid-induced hyperalgesia is the primary type of chronic pain that this review will focus on. In a later chapter in this review, we will revisit the impact that Purdue Pharma had on managing pain and other reports that have impacted the opioid epidemic.

Allodynia. The second physical pain focused on in this review is allodynia. Allodynia is categorized as pain sensitization, usually following non-painful, sometimes repetitive stimulation (Purves, 2012). The stimuli typically take one of three different forms, mechanical, thermal, and movement. Mechanical allodynia is in response to the touch of any kind on the individual. Thermal allodynia is the body's response to skin temperatures that are generally mild but instead provoke a range of pain sensitivity in the individual. Movement allodynia is in response to normal movement of joints or muscles, but the sensory neurons have misfired and signaled that the stimuli have the potential to be damaging.

Defining Narcotics, Opioids, and Opiates

Now that base knowledge of how the brain interprets pain has been established, let us now look at how analgesics work towards lessening pain and how the three most common names for addictive painkillers compare in the definition. Contrary to what the current media and average household believe, narcotics, opiates, and opioids are not interchangeable. These three terms have three different meanings that mainly boil down to the chemicals and substances used to create them. The term narcotics is a wide-reaching term that covers any drugs that suppress feelings of pain. According to Mosby's Dictionary of Medicine (2012), the term narcotics is now "used to refer to any illicit drug and its use is therefore discouraged in medical settings, opioid is now the preferred term" (p. 1196) for these types of analgesics. The terms opioid and opiate refer to types of narcotics that both interact within the brain to mimic the body's natural chemicals or neurotransmitters. When comparing the differences between opiates and opioids, one should note that opiates are "derives of opium or any of the semisynthetic drugs with opium-like activity" (p.1273). In contrast, opioids derive from "natural and synthetic chemicals that have opium-like effects similar to morphine, though they are not derived from opium" (Mosby's dictionary of medicine, 2012, p.1273). In other words, naturally occurring opium creates opiates, and synthetic chemicals create opioids.

How Pain Killers Work

Opium derived painkillers, and their synthetic counterparts work within the brain to block nociceptors by binding to opiate receptors. Opiates and opioids work by acting like the brain's natural neurotransmitters, which bind to specific receptors within the brain. Opioids work by depressing or decreasing the sensations of pain to the central nervous system and increasing the feelings of relaxation (Hokemeyer, 2014). Since the neurotransmitters created by the analgesics only act like the body's natural neurotransmitters, they fail to allow the nervous system to maintain its standard patterns and instead decrease the ability of the central nervous system to manage the body's reaction time, the individual's speech, and respirations.

The way that these analgesics become addictive is, in part, also how they work within the brain. Due to the ability of the substance to mimic the neurotransmitters that the body naturally produces, the body then believes that it has created too much of the dopamine neurotransmitter. The body then stops producing the neurotransmitter usually, and the individual must rely on the opioid substitute to relieve their pain. This phenomenon helps to explain the paradox behind how opioid-induced hyperalgesia has become the social issue that it is in today's policies behind what medicines doctors can give their patients and whether or not they need to provide them with an explicit warning of the prescription's ability to become addictive.

Psychological Pain

Thus far, the review has discussed physical pain or nerve-based pain and the analgesics that work towards lessening it, however understanding how psychological pain impacts the individual will also help in understanding how alternatives to managing chronic pain could work. First, we must establish the basics of psychological pain. Psychological pain has many different names, including emotional pain, social pain, psychic pain, and mental pain. While this nonphysical pain has many different names, it also does not have a singularly recognized definition in any of the common layman dictionaries. It is instead defined differently depending on the study or review discussing it. Various medical dictionaries use the term psychalgia rather than psychological pain to describe the terms used.

According to Merriam-Webster, psychalgia is defined as mental distress (Psychalgia, n.d), whereas American Heritage defines psychalgia as physical pain that is possible of psychological origin (Psychalgia, 2008). Psychological pain can manifest itself as psychogenic pain or physical pain that has origins within the individual's psychological health rather than the nociceptors system, according to Biology Online dictionary (Psychogenic pain, n.d.). Psychogenic pain works as a link between physical pain and the harder to define psychalgia pain and thus harder to adequately treat than its sibling physical pain.

By understanding psychogenic pain and how it is the physical manifestation of psychological pain, psychogenic pain could be used as the link to explain why using a treatment for depression could potentially work as a treatment for chronic pain. Current advancements and the advancements yet to come in the world of medicine have allowed psychogenic pain to be a topic explored in terms of finding a link between how people's emotions impact the sensations that they feel shows how far modern medicine has come.

CHAPTER TWO

What is the Relationship Between Pain and Depression?

Piggybacking Symptoms

Now that we've established the possibility of psychological or emotional pain, causing the individual to feel physical pain by looking at the dictionary definitions. We need to look at other studies and reports to help build our understanding of the connection between the mechanisms for chronic pain and depression. By looking at how the comorbidity of chronic pain and depression impacts one another, we can also look at how current treatments for depression can influence future treatments for chronic pain. First, we must dive deeper into the connection between depression and chronic pain to see if it is possible to define new management options for chronic pain.

Depression is highly prevalent in individuals living in chronic pain; however, these conditions are also highly derailing by themselves and impact the quality of life in their ways. Many studies have looked at how these two chronic disorders correlate and thus influence one another. Outcalt et al. (2015) for example took the results from the Brief Pain Inventory (BPI), the American Shoulder and Elbow Surgeons standardized assessment form (ASES), the Coping and Strategies Questionnaire (CSQ), and the Patient-Reported Outcomes Measurement Information System (PROMIS) to see how individuals diagnosed with chronic pain and depression compared to individuals diagnosed with PSTD and chronic pain. They examined the comorbidity and individual impacts of depression and PTSD on chronic pain. The findings showed that while PTSD and depression both have similar effects on chronic pain, the common effects of depression were more significant in their impact of the individual than that of the impact of PTSD.

Other studies such as Lerman et al. (2015) looked at how chronic pain and depression impact the individual over time in a longitudinal study with a sample size of over four hundred (n = 428) subjects from two outpatient pain specialty clinics. This study found that symptoms of depression predicted the levels of pain, but neither pain nor pain-related disability predicted levels of depression. One limitation of Lerman et al. (2015) is the fact that the study only had participants from two pain specialty clinics, which limits the ability of the results to be generalized. Future studies should look at individuals who are not just clients at specialty pain clinics but rather individuals diagnosed with chronic pain that only see their primary physician for treatment. This allows greater generalizability in the results, which could lead to a great understanding of how these two chronic conditions impact each other.

In terms of quality of life, chronic pain and pain-related disability impact how involved the individual can be in their community and how they interact with their social group. Li (2015) describes the relationship between the pain and the depression as often coexisting and exasperating or piggybacking off of each other and notes the similar mechanisms that the two conditions work along within the brain. Li (2015) comprised the findings from several different animal studies to create a preclinical look at how specific treatments could potentially impact human clinical studies. The study also looked at the relationship between pain and depression to see if the two conditions exasperate or increase the negative impacts of one another. Chronic pain can impact depression by causing a decrease in social interactions and an increase in withdrawal because chronic pain limits their mobility. The impact of depression on chronic pain is murkier and not as defined in the study done by Li (2015). The study claimed mixed results on whether or not depression impacts chronic pain by moving the pain threshold. In some results, the individual's pain tolerance decreased, which suggests that depression has a negative impact on chronic pain. However, other animal study results showed either no change or a decrease in the pain threshold, which indicates that depression does not negatively impact chronic pain. These mixed results require more animal studies, which could potentially lead to human clinical studies to test the generalizability and reliability of these findings in human subjects.

Finding the Connecting Mechanisms

One critical pathway to finding the connecting mechanisms between depression and chronic pain is finding the connection between physical and psychological or social pain. Dewall (et al., 2010) conducted a study finding evidence of acetaminophen reducing social pain. The reason is that social and physical pain share many of the same neurobiological mechanisms. The study explained the evolutionary and developmental aspects of why psychological pain and physical pain might share neurological pathways. Dewall (et al., 2010) used not only behavioral surveys to see how acetaminophen use impacted the subjects but also fMRI to see what areas the brain utilized following the participants' socially painful simulations. The study showed a decrease in activity in the dACC and the anterior insula, which plays an essential role in how the brain interprets pain. While the study provided evidence for the sharing of mechanisms between psychological and physical pain, more studies need to be conducted to verify the results.

One such study, conducted by Fasick (et al. 2015), looked to further the current knowledge about how physical and social pain mechanisms are connected. The study found that while the specific brain pathways themselves are widely unknown, general regions are commonly shared, including the hippocampus, which both processes and modifies pain stimuli. The connection between the hippocampus and depression is well documented in that loss of hippocampus volume correlates with an increase in depression and anxiety. Another well-documented concept is the comorbidity theory of pain and depression. This theory looks not only at the depression symptoms but also at many of the symptoms of chronic pain itself and is better expressed through the use of tricyclic antidepressants. We will cover the topic of tricyclic antidepressants later in this section.

Impacts of This Comorbidity.

Dahlhamer (et al., 2018) used a study that looked at the broad range of chronic pain among US adults. Population-based estimates range from 11% to 40%, so the CDC agreed to fund a study in 2016 to help establish a more reliable and accurate nationwide estimate. The finding from the study was that an estimated 50 million or 20.4% of US adults suffer from chronic pain. If taken from the perspective of chronic pain leading to depression due to a decrease in mobility and an increase in disability, the study means that 50 million individuals already suffering from chronic pain are at risk of developing comorbid depression. However, if you look at this study from the viewpoint of depression manifesting itself as chronic physiological pain, then treating the depression would result in an increase in the individual's pain threshold and a decrease in their physiological symptoms. Due to this unknown paradox of the origin of chronic pain, many doctors have taken to prescribing lose doses of antidepressants to help their patients combat both their depression and their chronic pain symptoms.

Treatments for chronic pain and depression

While using antidepressants to manage chronic pain might sound new, the first use of tricyclic antidepressants as a treatment for chronic neuropathic pain was almost 60 years ago (Leo & Khalid, 2019). Since the first use of antidepressants as a form of chronic pain treatment, there have been numerous other antidepressant classes created, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). These antidepressants have recently become more popular due to the many adverse side effects related to the use of tricyclic antidepressants. However, future studies are needed to show how tricyclic antidepressants, SSRIs, and SNRIs compare to placebos.

One such study comparing amitriptyline, a tricyclic antidepressant, and a placebo conducted by Urquhart (et al. 2018) produced mixed results. The study found that while amitriptyline showed no significant improvements in participants over six months, it did slightly reduce disability after three months of participation. Overall, this study showed that while low doses of amitriptyline are commonly used as pain killers and are viewed more favorably than their opioid counterparts, there is not yet proof of their efficiency. There is a need for more studies that show how varying the dosage might impact the outcome.

The future of treating pain and comorbid depression. Considering that both pain and depression often compound their symptoms and are given similar treatments, this opens the door for a discussion about pain management using the holistic approach.

This discussion takes us back to the early nineteen sixties. In 1960, John Bonica founded the University of Washington's School of Medicine Department of Analgesia and then opened the United States multidisciplinary pain center (Quinones, 2015). Bonica believed that pain could only be solved when many disciplines worked together. At this clinic, patients would see as many as 14 pain specialists who worked together to curate an individualized treatment. Bonica's successors, Fordyce and Mosher, expanded the clinic and hired on occupational and physical therapists, psychologists, and social workers. They spent three weeks working individual patients before sending them out into their communities to continue their treatment at home (Quinones, 2015). This biopsychosocial approach to pain management was often effective in helping chronic pain sufferers control their pain. While the multidisciplinary approach was effective, the push from pharmaceutical companies to sell medicine ultimately caused the clinic, and many like to downside and then close altogether due to lack of funding.

Since the holistic approach has lost its economic value among most insurance companies, looking at ways to reconnect the holistic approach to pain is the first step. This step includes shinning a light on the comorbidity between chronic pain and depression. Assess where the next step for treatment of pain and comorbid depression needs to lead, we must first look at what studies are currently saying. In the following sections, we will explore landmark studies and how their impacts have changed the landscape for treating chronic pain without the potentially addictive factors of current painkillers. While future studies are needed to produce quality in line with the growing changes in technology, looking at the results of prior studies shows a viable alternative to the use of narcotics and other potentially addictive painkillers.

CHAPTER THREE

What is Transcranial Magnetic Stimulation?

Transcranial Magnetic Stimulation

Before we can dive into the how's and why's of this procedure potentially being used to manage chronic pain, we need to understand what Transcranial Magnetic Stimulation (TMS) is. What better way to explain what TMS is than to explain what happens during the TMS procedure itself? The following section in this chapter will focus on the procedure and the issues brought up in attempting to create blind studies. Next, we will cover the timeline of TMS, starting with the search for a seizure-inducing medicine and ending with the creation and current advancements of TMS. The final sections in the chapter will focus on the ongoing changes and improvements of TMS.

The procedure According to the National Institute of Mental Health (NIMH), a trained laboratory technician places an electromagnetic coil above the target region of the brain. In most cases, the target region involves the areas that control mood regulation (2016, para. 24). The electromagnetic coil produces changing magnetic fields, which causes an electrical current in the targeted region of the brain. The magnetic fields generated during a TMS session match the magnetic fields produced during a Magnetic Resonance Imaging (MRI) scan. Since the procedure creates a magnetic field similar to an MRI, it is less harmful than other non-invasive brain stimulation types that use direct or alternating electrical currents such as electroconvulsive therapy. One drawback of the procedure is the loud clicking that the machine makes during the administration of the magnetic impulse, which, if the patient is not wearing proper protective gear, may lead to acute or chronic hearing loss (George Post, 2011).

Issues regarding the procedure. One of the main problems the FDA had before they approved of TMS for the medication-resistant major depressive disorder was creating a sham procedure that mimicked the sound and feel of real TMS. Some of the common immediate side effects include head discomfort from the magnet placement and facial muscle ache from slight contractions that occurred during the actual TMS procedure, which the sham procedure cannot mimic. Since the two studies that he FDA approved the use of TMS were double-blind, randomized controlled studies, it meant that the sham procedures had to imitate more than just the loud clicking that TMS produces. According to George & Post (2011), one side effect found in similar frequencies among both the sham and real TMS procedures was headaches.

The FDA's approval. A literature review by George & Post (2011) examines the studies leading to and following the FDA's approval of TMS for depression. One case highlighted in the article describes how repetitive Transcranial Magnetic Stimulation (rTMS) allowed one woman to achieve three years of remission with medications that had previously not worked for her depression. So far, the FDA has only approved TMS for the treatment of medication-resistant depression. However, more studies have looked towards using TMS in helping alleviate some types of chronic pain. One issue is that I found in my research is that since the FDA approved TMS for treatment of medication-resistant depression, is that studies are not looking at the impact TMS could have on other regions of the brain.

Debates-over-magnet-placement. So far, the FDA has only approved of TMS as a treatment for depression, but recently, more studies have looked at using TMS on other regions of the brain. Without the FDA's approval, TMS coil placement over the motor cortex is not as regulated or fixed as coil placements used for treating depression. This lack of regulation over the motor cortex has lead to several researchers placing coils over its different regions and a debate over which coil placement is better for maximum stimulation of the motor cortex. One study conducted by Ahdab, Ayache, Brugieres & Lefaucheur compared the 'standard' or blind method of targeting regions of the brain with the 'navigated' or guided method, using functional magnetic resonance imaging (fMRI) to see how the placements compared (2010). The goal of the study was to compare the primary motor cortex (M1), dorsolateral premotor cortex (dlPMC), and dorsolateral prefrontal cortex (dlPFC) regarding the standard or assumed location of these regions and then compare them with locations guided by fMRI. The study found that standard measurements for the placement of the electromagnetic TMS coil in 36% of participants were inaccurate in locating the dlPMC and was instead positioned over the M1 and dlPMC border. When comparing the location of the dlPFC, the inaccuracy rate was 64% and instead positioned of the coils was over the dlPFC and dlPMC border.

Timeline for Non-Invasive Brain Stimulation

Metrazol. The timeline for the creation of TMS starts with the search for effective therapy to treat treatment-resistant depression. Early asylum keepers noticed that psychiatric patients who had a comorbid diagnosis of epilepsy showed improvement in their psychiatric symptoms following a seizure (Ruffalo, 2018). This observation led to the search for seizure-inducing procedures and medications; one medication was

Metrazol discovered by a Portuguese psychiatrist Ladislas Meduna in the early 1930s. This medication produced seizures but also resulted in an extensive list of deadly side effects, including damage to the individual's vertebrates from the seizures. Because of the severity of the side effects, psychiatrists began looking for alternative means of producing seizures in their patients.

Electroconvulsive therapy. The subsequent development on the timeline leading to the creation of TMS is electroconvulsive therapy. According to psychiatric legend, in 1937, Italian neurologist Ugo Cerletti walked past a butcher shop and watched the butcher administer an electrical shock to pigs before killing them (Ruffalo, 2018). According to Ruffalo, Cerletti wondered if the same anesthetic properties that occurred in the pig's brains during the shock might also apply to humans if given a similar shock (2018). By 1938, Cerletti, in collaboration with his colleague, psychiatrist Lucio Bini developed the first ECT device. Soon after they developed the first device, they treated their first patient with successful results.

Transcranial electrical stimulation. While electroconvulsive therapy (ECT) was effective, it had many drawbacks, including memory loss and stigma from the public due to it being an inhumane procedure in the early stages of its use. Many looked towards more humane treatments for mental disorders. Thus, transcranial electric stimulation was born. Transcranial electronic stimulation (tES) like ECT uses an electrical current to stimulate, however, "the current delivered in tES techniques is not powerful enough to elicit an action potential" (Reed & Kadosh, 2018). Meaning the electrical currents are given at lower levels to cause cortical stimulation but not to induce seizures, as was the primary goal of ECT.

Transcranial magnetic stimulation. Breaking off from a similar vein as tES but following Michael Faraday's law establishing that "a time-varying current creates a magnetic field which in turn can induce an electric field and hence a secondary current within a nearby conducting medium" (Lefaucheur et al., 2014). In 1985, A. T. Barker, R. Jalinous, and I. L. Freeston published a proposal for "the first magnetic stimulator designed to stimulate the human brain transcranially" (Lefaucheur et al., 2014). With that first stimulator, they created transcranial magnetic stimulation (TMS). However, the Food and Drug Administration (FDA) would not approve of TMS as a therapy for depression for another twenty-three years. When the FDA finally approved TMS in 2008.

Advances in Transcranial Magnetic Stimulation Technology

Following approval by the FDA for TMS as medication-resistant depression treatment in 2008, many advancements in coil size and thus area of the brain stimulated began. One study from 2010 (Ahdab et al., 2010), looked at standard vs. navigated positioning source. The study showed that while there is a general layout of the location of specific regions of the brain, there are slight variations between individuals due to shrinkage or enlargement of areas. These variations in individuals have caused a rife in the community of doctors trained in administering this procedure.

Other advancements outside of coil placement include new coil types, including the H-coil and figure-8 coil, the primary goal of their configuration was to reach deeper regions of the brain. A study by Roth et al. compared the differences between the H-coil and the figure-8 coil in more depth (2014). The results of the study show that while the newer H-coil is effective, more adjustments are needed to make them as effective as the figure-8 coil. The creation and review of the H-coils are relatively new; the first studies began in 2002. Since 2002 there has been an increase in studying these deeper reaching coils due to their ability to stimulate regions that had previously required an implant in the individual's skull. Since TMS is a non-invasive type of brain stimulation, being able to reach these deeper regions without needing to alter an individual's brain surgically is a huge step in reducing the stigma surrounding brain stimulation and its previously inhumane nature. The following sections will look at the impact that newer and deeper reaching coils have had on branches of medicine outside of mental health.

CHAPTER FOUR

Using Transcranial Magnetic Stimulation to Target Pain

Bringing It All Together

Thus far, in this review, we have discussed the relationship between pain and depression, investigated the procedure of transcranial magnetic stimulation (TMS), and touched on the impact the holistic approach has on pain management. This section will focus on incorporating all of the previous concepts and look at using TMS for pain management since we have already established the connection between depression and chronic pain based on their shared regions of processing within the brain. The following sections will look at advancements in coil designs, which has led to the creation of deep transcranial magnetic stimulation (dTMS). dTMS has expanded the number of clinical trials, and the adoption of dTMS as a treatment for depression. Since dTMS is still reasonably new, there are still many studies being conducted to see how it differs from repetitive or single-impulse TMS and thus what it can treat.

rTMS and Pain

This section will look at TMS studies and reviews before the adaptation of dTMS coils and see how TMS worked on regions of the brain to manage types of chronic pain. In a systematic review by Babiloni, Guay, Nixdorf, Beaumont, and Lavigne (2018), multiple studies were analyzed from five different scholarly search engines and held against rigid criteria for inclusion. Babiloni et al. divided the criteria for inclusion into four parts; population, intervention, comparison, and outcome of the study. The result of their research found that using TMS and transcranial direct-current stimulation (tDCS) provided significant relief for orofacial pain. However, they also reported a high rate of bias and poor study quality overall among the studies they found that fit their criteria. In response, they called for more studies and analytical reviews to see how TMS impacts pain.

An analytical review by Nizard, Lefaucheur, Helbert, de Chauvigny, and Nguyen (2012) looked at the use of repetitive transcranial magnetic stimulation (rTMS) to treat pain that was not managed by typical analgesics or painkillers. They rationed the analgesic effect of rTMS, when applied to the motor cortex, was nearly equal to procedures that involve surgically implanting a stimulation device into the motor cortex. In their review of a multitude of studies, they discuss the different types of pain that rTMS has proven to alleviate as well as new developments with rTMS in treating other chronic illnesses outside of pain and depression. In the conclusion of their review, they recommended that rTMS be used to treat neuropathic and non-neuropathic pain symptoms. They gave this recommendation due to the safety and low cost in comparison to implantation procedures and the overall cost of chronic pain.

One study conducted by Kisler et al. (2018)**,** looked at the role that the primary motor cortex in processing and expressing neuropathic pain. To do so, they created virtual lesions, or reversible brain damage, using single-pulse TMS rather than rTMS. While they found no that there was no significant impact on the participant’s level of pain, they attributed this to the fact that the primary motor cortex is not the central pain region within the brain. They suggested further studies looking at more intense interventions for the primary motor cortex. Using single-pulse TMS rather than rTMS might explain the differences in the results between these two studies. However, research by Kisler et al. impacted the development of new coil types that reach deeper into the brain, leading to the creation of dTMS.

Coil Modification

The landmark study by Zangen, Roth, Voller, and Hallet (2005) introduced the Hesed coil (H-coil) and was the first to use the H-coil on human subjects. Extensive calculations before the use of human participants showed that the H-coil could use a fifth of the power required by the double cone coil to send 50 volts per meter (V/m) to a depth of 5cm. From these calculations, Zangen et al. predicted that the "excitation threshold could be reached at 4-6cm using the H-coil without inducing pain and other side-effects" (p 778, 2005). The results of their study showed that the H-coil was able to impact deeper areas, including the cerebellum and deep motor cortex. Regarding the side effects of the 6 participants, one participant reported a significant hearing loss due to their hearing protection falling out during the study.

As the H-coil build a reputation for itself as a safe option for reaching deeper regions of the brain, others looked to see if they could recreate this reputation. Thus, began the modifying of coils to reach depths of 5cm without causing significant side effects. One study conducted by Deng, Lisbany, and Peterchev (2014) explored the different characteristics and tradeoffs in coil design for dTMS. For this study, they compared a crown coil and a C-core coil to five commercial coils, including the H-coil, the double cone, and figure 8. The findings of this study were that of the double cone coils were the most effective in delivering the electromagnetic impulses at the depth required for dTMS while at the same time ensuring safety for the participants. The FDA approved two of the commercial coils, the H-coil, and the ferromagnetic core figure-8 coil, for the treatment of depression.

dTMS and Pain

A few years before Kisler's study using single-pulse TMS, Roth, et al. (2014) were studying a different type of TMS. They studied the impact the H-coil, and the figure-8 coil had at various depths have on the motor cortex. Different depths within the motor cortex correlate with varying limbs. For this study, the resting and active motor thresholds of the participant's right leg and right arm were measured to keep the study simple rather than measuring both arms and legs. The results of the study showed that the H-coil had significantly lower resting and active thresholds than the figure-8 coil. The results from this study held the results from Zangen et al. (2005) study showing the H-coil as more compatible for reaching deeper regions of the brain.

In 2017, Shimizu et al. produced the results of their efficacy study of deep rTMS for the use of neuropathic pain. They found that the H-coil could stimulate the motor cortex even from a distance of 5.5 cm from the scalp while the figure-8 coil could only stimulation within a range of 2cm. Their study consisted of three types of TMS, dTMS with the H-coil, rTMS with the figure-8 coil, and a sham procedure. Patients were assigned at random to one of six different randomized, double-blind groups. The study was considered double-blind because neither the participant or administrator knew which procedure was used. Shimizu et al. ensured that the study would be blind by placing the sham coil in the same helmet as the active H-coil. The study also explained how the sham procedure worked. Many previous studies reviewed did not explain how the sham procedure worked. The sham procedure works by delivering the electrical current in opposite directions. This cancels the electromagnetic field while at the same time creating the same sounds and energy waves as real TMS. They found that deep rTMS using the H-coil provided short-term relief from neuropathic pain.

Drawbacks of Using TMS

While it may seem like deep rTMS works to alleviate pain and should be used more with patients seeking help in managing their chronic pain, there are several drawbacks to using TMS. In many of the studies and reviews, they discuss how rTMS is safe and effective at providing short-term pain relief to those suffering from chronic pain. Which then leads to the question of why is TMS not seen as a useful long-term tool? One part of why rTMS is not viable as a long-term tool lies in the length of time during which relief is felt. For example, in the study by Shimizu et al., “significant pain relief was no longer observed by 17 days after the end of 10 daily sessions of rTMS” (p 1178, 2017). Other drawbacks to using TMS include the cost, which can range from $400 to $500 per session and is not covered by most insurance companies. Then you also have the health aspects, as with any stimulation that impacts the brain directly, there is a chance of inducing seizures. In a letter to the editor, Tendler, Roth, and Zengen (2018) discussed the rate of seizures induced from reckless mistakes over eight years. They reported, “thirty-one seizures and two pseudo-seizures” having been reported to the manufacturer and in various published literature. This brought the rate to 0.087% overall, which is consistent but slightly lower than the 1% reported by one coil manufacturer. Nineteen seizures were related to the motor threshold being impacted by the participants’ alcohol intake and withdrawal, changes in medications, poor sleep the night before the procedure, and excessive caffeine intake. Tendler-et-al gave several suggestions for lowering the rate of deep rTMS induced seizures. The two most beneficial for this review are 1) checking the intensity of the individual's motor threshold prior to every treatment, or session if the patient has a change in medication; 2) ensuring that all TMS centers have a plan in place in case of seizures.

CHAPTER FIVE

Impacts of Targeting Pain with Transcranial Magnetic Stimulation

Why Does This Matter?

In the previous section, the results from several studies stated that the use of transcranial magnetic stimulation (TMS) was not compatible with the long-term management of chronic pain. So that begs the question of why should TMS be seen as an alternative for pain management? Maintenance of pain relief using TMS requires ten daily sessions every two weeks, which interferes with daily activities such as working or providing family care. Not to mention the cost of rTMS treatment, the average cost of a 10-day session costs roughly $5,000, and insurance companies do not cover rTMS as a pain treatment. Couple this with the financial burdens already associated with chronic pain and that makes using TMS to aid the chronic pain sufferer seem impossible. This leads to the question of how can the average chronic pain sufferer finds any relief outside of taking a prescription? The answer to this question lies in the use of a holistic approach to chronic pain management.

What is a holistic approach? Having mentioned the holistic or multidisciplinary approach through the work of John Bonica, let's dive deeper into understanding how a holistic approach can have a positive impact on patients' pain levels. If we were to apply the holistic approach found within Bonica's pain clinic, we would see social workers and psychiatrists working with medical professionals (Quinones, 2015). One of the most important roles that a social worker has is to advocate on behalf of their clients, which leads into two of the core values of social work; understanding the importance of human relationships and seeing the dignity and worth of the individual. At Bonica's clinic, social workers would have advocated for their clients by ensuring that they were given all the required resources to be successful before they returned to their communities. Psychiatrists would ensure work towards getting the client mentally prepared to reenter the community and help the client work through any obstacles that are preventing them from reaching their potential.

Relating TMS to the holistic approach. The next question that might arise is how does TMS relate to the holistic approach when TMS is a non-invasive brain stimulation procedure, not any type of psychoanalytic therapy? In short, TMS relates to the holistic approach by playing a pivotal role in linking the emotional and physical aspects of pain. TMS targets the shared regions of the brain that express and interpret pain. This treatment shows researchers and medical providers that there is a definite link between the physical and emotional aspects of pain. While the holistic approach looks at the cultural, emotional, and financial components that make up chronic pain, if these two separate components are inspected together, researchers could use TMS as a stepping stone towards the rebirth of the holistic approach as a mainstream pain management practice.

How Should the Future of Pain Management Look?

The future of pain management should return to the ideology that John Bonica used when he founded his first pain clinic. However, many insurance companies do not see a holistic approach to pain management as profitable. Currently, some pain specialists are looking to bring the holistic approach back to the forefront of pain management.

Kress et al. (2015) reviewed literature from the different stakeholder groups involved in pain management. They identified many various stakeholders, including physicians, nurses, pharmacists, psychologists, payers, and the patients themselves. After discussing the different stakeholders, they dug into addressing the issues they identified within the world of pain management. They identified education and training among pain specialists, diagnosis of chronic pain and the treatment planning, and long-term management of chronic pain as the key issues.

Outside of the United States, Finestone, Jurrlink, Power, Gomes, and Pimlott (2016) analyzed the guidelines set in Canada for prescribing opioid medications. They concluded that the lack of external resources through the use of social workers and therapists lead to more internal and external pressure on medical professionals to prescribe more painkillers. While Quinones (2015) was writing from the perspective of the United States, the demands in Canada might also include the push for medical providers to give their pain patients a quick solution that physicians in the United States were also experiencing.

While some pain specialists see the holistic approach as the answer for long term chronic pain management, others are coming to terms with the need to bridge the gap between alleviating chronic pain and reducing the impact of the opioid epidemic. A literature review by Murray, Stone, Pearson, and Treisman (2018) falls into the latter category; they analyzed different clinical solutions for chronic pain. In the conclusion of their analysis, they found that a systematic change is needed to address both the opioid epidemic while providing needed pain relief. They called for better evaluations and treatment options for patients and seemed to be angling towards a holistic approach type of systematic change. As more medical providers and researchers begin to feel as though the current way in which we treat chronic pain needs a reboot, more individuals will see the need to bring the holistic approach back to the forefront of the chronic pain treatment.

Looking to the future, trained professionals seeing one individual from so many different angles, creates a plethora of options for referrals. Professionals working out in the communities can network with professionals working within pain clinics and be equipped with pamphlets and questionnaires. The questionnaires can range in topics from levels of pain to be placed at counseling offices to the more widespread use of PHQ-9 Depression scale at medical clinics rather than just giving the questionnaire to individuals complaining of anxiety.

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