The Impact of Operator Education Level on the Safety and Tolerability of Transcranial Magnetic Stimulation

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Abstract

The Food and Drug Administration (FDA) approved the NeuroStar Transcranial Magnetic Stimulation Therapy system for the treatment of major depressive disorder in the fall of 2008. Since that time more than 175 devices have been placed in both public and private practice settings. Transcranial Magnetic Stimulation (TMS) therapy requires psychiatric prescription and supervision, however there are no specific standards articulated by the FDA, the State Boards of Medicine or the State Boards of Nursing regarding TMS Operator qualification. Neuronetics, the manufacturer of the NeuroStar TMS Therapy systems holds that the device is so safe and well tolerated that anyone may be trained to be an effective and safe TMS Operator. Registered Nurse (RN)/Medical Doctor (MD) TMS Operators predominate in hospital, academic and institutional settings, whereas unlicensed allied health workers predominate in private practice settings. Using both quantitative and qualitative research methodologies, this study demonstrated the safety and tolerability of TMS therapy provided by non-RN/MD TMS Operators in our communities. This study suggests a role for a future prospective randomized controlled trial to demonstrate the efficacy of TMS provided by non-RN/MD TMS Operators.

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Chapter 1: Introduction to the Problem

Introduction

Over the last two decades, a number of different neurological stimulators that deliver pulsed magnetic fields have been tested in basic research for a variety of clinical uses by research clinicians licensed at the registered nurse or medical doctor practice level (Demitrack, 2009). The initial application of most of these devices was low repetitive rates of single-pulse diagnostic studies such as in cortical mapping (Janicak, 2010). When repetitive Transcranial Magnetic Stimulation (TMS) emerged as a potential therapeutic application, these stimulators were modified to accommodate higher pulse rates (Gershon et al., 2003). While these devices served to expand research knowledge, they were not designed to create reproducibly safe and efficacious treatment for a given medical indication nor were they intended for routine clinical use (McDonald, 2010).

The NeuroStar TMS Therapy system has been designed expressly for clinical practitioners and major depressive disorder patients and is unlike any other TMS system. Specifically, the NeuroStar TMS Therapy system incorporates a host a key design and technology advances over the types of TMS systems typically used in research settings, including:

- Ferromagnetic Core Coil
- Gantry Floating Balance Arm
- Graphical Touch Screen
- Head Support System
- SenStar Treatment Link
- Practice Data Management System (computerized database/medical records)

- MT Assist (motor threshold identification and calculation algorithm)
- SMT Standard Motor Threshold Unit (Riehl, 2008)
- User Interface tools

These advances allow repetitive TMS therapy sessions to be provided in a highly standardized and precise fashion that is readily reproducible from one machine to another and from one operator to another (Aaronson, 2010). On October 9, 2008 the NeuroStar TMS Therapy system became the first and only TMS therapy device with FDA marketing clearance for the treatment of major depressive disorder (Demitrack, 2008).

With the FDA approval in place, Neuronetics aggressively marketed the NeuroStar TMS Therapy system to psychiatrists in private practice, academic, and institutional settings with placement of more than one hundred and seventy five devices throughout the country within the next eighteen months. Although the FDA requires that the NeuroStar TMS Therapy to be prescribed by a physician (usually a psychiatrist) it does not make any comment on who may administer the treatments under the prescribing physician's supervision.

This stance is typical for the FDA when providing marketing clearance for medical devices. For example, when the FDA approves medical devices for laser hair removal, the approval indicates if the device requires physician prescription and supervision, but does not articulate the qualifications of the staff that the physician may select to be the operator of the device. In some states, the physicians may supervise estheticians, electrologists and medical assistants to operate a device that is restricted to use by the RN, NP and PA professions in other jurisdictions.

Neuronetics, the manufacturer enclosed a statement in the user manual (2008) provided to the FDA prior to approval which reads:

> The system can only be operated by licensed medical professionals who have medical training and who assist as part of the staff and who are operating under the direction of a physician. The user of the NeuroStar TMS System must be trained on its operation, and must have knowledge of the operational environment. NeuroStar operators must complete Neuronetics provided training before using the system. (p.18)

Though this advice appears in the manufacturer's user manual, it carries no legal weight. Experience indicates that the Neuronetics TMS training team will provide free operator training to anyone designated as a future operator by the TMS device purchaser. Currently, there are no guidelines for minimum TMS operator qualifications, education or training articulated by any medical, nursing, or allied health state licensing boards.

Problem Statement

The TMS operators for the original research provided to the FDA were all licensed at the RN or MD level. Following FDA approval of NeuroStar TMS Therapy for the treatment of major depressive disorder in the community, there has been no formal uniform statement with regards to TMS operator licensure or training except by the manufacturer.

A disproportionate number of TMS devices are now located in private practice mental health settings (80.0%) and of the TMS Therapy operators in these settings a very low percentage are licensed at the RN level (Demitrack, 2009). Within the first 18 months following FDA approval, there is the first ever report of a NeuroStar TMS Therapy induced seizure.

Hypothesis

TMS is a technically complex psychiatric procedure performed on the most critically ill and highest risk psychiatric population, as such, to maintain safety and tolerability the procedure must be provided by an RN with psychiatric training and experience, APRN, PA or MD.

Research Questions

The following research questions were addressed in this study:

1. Can NeuroStar TMS Therapy services be safely provided by non-licensed health workers?
2. Do the NeuroStar TMS Therapy services provided by non-licensed health workers demonstrate the same incidence of adverse events as those services provided by RN and MD level TMS operators?

Definition of Terms

Table 1 (Neuronetics, 2008)

Term	Meaning
Alignment Guide	A mechanical system that the clinician uses to register a patient's anatomical landmarks to help identify the coordinates and replicate the motor threshold and treatment positions on the patient's head.
A/P	Anterior/Posterior (used in locating the patient's MT)
Coil	Electromagnet that is connected to the mobile console and gantry and placed against the side of the patient's head for therapy delivery during treatment sessions.
Contact Sensing	Sensor and software used to detect contact between the coil and the patient's head.
HIPAA	Health Insurance Portability and Accountability Act, a Federal law that covers healthcare-related data processing identifiers and transactions, and that mandates security and privacy in data processing and communication.
Interval	The period of time between pulse trains (seconds).
MDD	Major Depressive Disorder
MEP	Motor Evoked Potential
MT	Motor Threshold.
MT Assist	A patented computer program that enables the NeuroStar TMS System user to pinpoint a patient's MT location and MT level.

MTL	Motor Threshold Level. The minimum value of electromagnetic pulse output needed to stimulate a patient's motor strip to cause a thumb twitch.
PDMS	Practice Data Management System, the optional NeuroStar TMS system patient management and reporting software that runs on a separate personal computer and communicates with the NeuroStar TMS System mobile console through a wireless connection.
Pulse Repetition Rate	Measurement that defines the number of magnetic pulses occurring in a second. The unit for this parameter is in Pulses per Second (PPS).
Pulse Test	A preliminary NeuroStar TMS System test in which the system generates pulses of 1.2 and 2.1 SMT units. The system takes a reading for each set. If the system fails to generate these pulses, it displays a failure message and prevents the user from performing treatments or MT.
Pulse Train	The group of NeuroStar TMS System electromagnetic pulses occurring during treatment stimulation time.
SenStar	A single-use disposable integrated flexible circuit that must be attached to the coil prior to treatment to facilitate contact sensing and magnetic field detection and to decrease the magnetic field at the scalp surface to enhance tolerability during treatment.
SMT	Standard Motor Threshold
SMT Unit	The amount of voltage required to stimulate the neurons in a person's brain 2 cm below the scalp. A measurement unit used to specify a stimulator output level.
Stimulation Time ("Stim Time")	The length of a pulse train (seconds).
Treatment Chair	Patient treatment platform in the form of a chair that seats the patient comfortably at electromagnetically adjustable heights and angles (between 45 and 90 degrees) for treatment and includes the head support.
Treatment Coil	The active and fully functioning electromagnetic coil that is connected to the mobile console and placed against patient's scalp for treatment delivery during a TMS session.
TMS	Transcranial magnetic stimulation, a method of using very short pulses of magnetic energy to stimulate nerve cells in the brain. TMS will be used synonymously with Repetitive

	Transcranial magnetic stimulation, which refers to TMS with repetition rated greater than 1pps.
Treatment Record	Electronic record containing the details of the patient's treatment sessions.

Summary

This research project is the first study to formally evaluate the impact of TMS operator education and license on the safety and tolerability of the TMS provided in our communities. This study will compare the incidence of serious adverse events and events impacting tolerability and compliance in the TMS population served by non-licensed TMS operators with the data collected by the manufacturer and presented to the FDA for device approval for use with the general public (10,094 TMS sessions provided by RN and MD level operators).

The outcomes of this study may impact how current and future psychiatrists staff operators for their TMS devices. The study may also provide clinical data that state medical and nursing boards may use with regards to a decision to establish a minimum level of education and licensure for TMS operators.

Chapter 2: Literature Review

Introduction to TMS Therapy for Major Depressive Disorder

The currently available Food and Drug Administration (FDA) approved Transcranial Magnetic Stimulation (TMS) system has been developed by Neuronetics with the goal of specifically addressing many of the unmet needs in psychiatry for more effective treatment of patients who have had an inadequate therapeutic response to initial antidepressant treatment. The Neurostar TMS Therapy system possesses several clinical advantages by design. Advantages highlighted by the manufacturer include:

Patient adherence. Because TMS is administered by the treating clinician, unlike most pharmacotherapeutic approaches, the patient is not directly responsible for delivering the treatment; therefore, non-adherence issues are significantly reduced, although not fully eliminated. For TMS, like psychotherapy the burden remains on the patient to show up for treatment.

Observed treatment. Since TMS treatment is psychiatrist controlled, issues of under-dosing, inadequate duration of treatment and drug interactions are significantly reduced. Under-dosing with TMS may occur when patient discomfort prevents optimum TMS electromagnetic dosing. Under-dosing may also occur when TMS patients interrupt a course of therapy to accommodate activities and events in their personal or professional life.

No systemic side effects. Since TMS therapy does not involve systemic exposure for its therapeutic benefit, and is only actively administered in brief courses of treatment, the incidence of side effects is dramatically lowered. TMS therapy does not create side effects such as interference with sexual functioning, cardiac disturbances, fatigue or

insomnia. These side effects are commonly reported with the use of psychotropic medications.

For all of these reasons, TMS therapy is particularly well positioned as a treatment option for patients who have failed to achieve satisfactory improvement from prior antidepressant treatment.

In the clinical management of Major Depressive Disorder, treatment resistance is the norm, not the exception. Since no antidepressant treatment works for all patients, it is important to match the evidence for efficacy of a psychiatric intervention with the patients most likely to benefit from that treatment. Neurostar, the manufacturer reports that the greatest benefit from TMS therapy was obtained in patients who failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. In the initial research data presented to the FDA for TMS approval, the patients had received a median of 4 antidepressant exposures with only one reaching the minimum effective dose and duration. Based on these findings, TMS therapy addresses a critical need in psychiatry for a more effective, safe, tolerable and non-invasive intervention for major depression.

The Basic Biophysics of TMS

In 1839, the British scientist Michael Faraday discovered that a moving magnetic field can induce an electrical current in conductive material. According to Faraday's Law, only changing, or time-varying, magnetic fields can induce an electrical current. Stationary or static (unchanging) magnets cannot exert any type of therapeutic effect on the body, since they do not induce an electric current.

Since brain tissue and neurons are good electrical conductors, pulsed magnetic fields can induce electrical currents within the cranium. This is the basis of all magnetic resonance imaging (MRI) and transcranial magnetic stimulation (TMS) technologies.

Neuroanatomical Considerations in TMS Therapy

Research has demonstrated considerable inter-subject variation in the strength and balance of electrical activity between the cerebral hemispheres of the prefrontal cortex and that these differences correlate strongly with mood (Davidson, 2004). In general, increased activity in the left prefrontal cortex correlates with expansive personality traits and positive moods.

Conversely, higher activity levels in the right prefrontal cortex relative to the left are correlated with more introspective behaviors and depressed moods. These generalities are corroborated in both animal lesion studies and observations of patients with focal damage to the left prefrontal cortex, who are more likely to be depressed or exhibit depressive symptoms (Sutton & Davidson, 1997). A wealth of neuroimaging data also supports these findings. For instance, a reduction in metabolism in the left prefrontal cortex is one of the most consistent, state related observations in patients with major depression (Drevets, 1998).

In addition to the prefrontal cerebral cortex, various subcortical areas have also been implicated in mood regulation, such as the basal ganglia (putamen and caudate nucleus) and limbic system structures (Drevets, Gaddle, & Krishnan, 1999).

Mayberg (2003) has proposed a useful working model that unifies these findings into a dysfunctional limbic-cortical network. Specifically, the model presumes dorsal neocortical decreased metabolism, along with increases in ventral paralimbic structures, with the rostral anterior cingulated as an important intermediate element in this network.

The left prefrontal cortex is the preferred target for TMS therapy, because it is directly involved in mood regulation and is richly innervated by various subcortical areas that are less directly accessible to the TMS electromagnetic field. TMS stimulation of the neurons in the prefrontal cortex in humans has been shown to produce a number of physiological changes, both locally and in more distant brain structures (Speer, Kimbrell & Wassermann, 2000). Imaging studies that used fMRI interleaved with TMS therapy have shown significant changes in blood flow in both local and remote brain regions (Nahas, Lomarev & Roberts, 2001).

PET scanning has shown that PFC TMS therapy causes dopamine release in the caudate nucleus and has reciprocal activity with the anterior cingulated gyrus (Strafella, Paus, Barrett & Dagher, 2001). Similarly, lateral prefrontal TMS therapy produces immediate blood flow increases in the orbitofrontal cortex, hippocampus, and left prefrontal cortex (Teneback, Nahas, Speer et al., 1999). Such stimulation has also been correlated with increased levels of thyroid stimulating hormone (Szuba, O'Reardon, Rai et al., 1999). More directly, TMS stimulation of the left prefrontal cortex is associated with positive changes in mood and behavior and a lifting of depressive symptoms in patients who respond to this therapy (Martin, Barbanoj, Schlaepfer et al., 2002). The brain imaging studies to date thus far strongly suggest that TMS delivery over the prefrontal cortex has immediate effects in important subcortical limbic regions that are involved in mood and anxiety regulation.

TMS Mechanism of Action

The TMS system approved by the FDA for use in the states generates a powerful magnetic field pulse with the strength at the surface of the coil of about 1.5 Tesla. By comparison, the magnetic fields used in magnetic resonance imaging are known to typically range from 1.5 to 3 Tesla.

During treatment, the TMS magnet is positioned on the head over the region of the left prefrontal cortex. The rapidly changing magnetic field generated by the device passes through the scalp and skull and induces an electrical current within the local region of the cortex under the device.

It is generally assumed that TMS therapy produces its behavioral effects through the production of electrical current directly in the cortex of the bran and indirectly by subsequent stimulation of the subcortical (limbic) structures and circuits that are themselves functionally connected to the superficial cortical regions. The magnetic field induced by the TMS device declines rapidly with distance away from the coil. Deeper brain structures can be influenced by TMS therapy because of the cortex's massive interconnections and redundant cortical-subcortical loops.

Since the biological origins of depression remain unclear, it is not yet possible to pinpoint which of the various physiological effects of TMS therapy on brain neurobiology contributes most significantly to it antidepressant effects. Yet, a wide range of human and animal studies have shown that TMS has effects similar to those of other known antidepressants (Lisanby & Belmaker, 2000). A recent review by Lisanby and Belmaker (2000) of the state of knowledge regarding the mechanisms of action of TMS concluded that TMS shares many of the behavioral and biochemical actions of other established antidepressant treatments.

Overview of TMS Development

As early as 1902, patents were issued for devices that claimed therapeutic effects for stimulation of the brain with electrical and electromagnetic fields (Walsh & Pascual-Leone, 2003). These devices were extremely crude and did not, in fact, have any clinical value beyond placebo effect.

It was not until the early 1980s, with the work of Antony Barker and his colleagues at the University of Sheffield, England, that evidence for the reliable physiological consequences of pulsed magnetic fields was published in the scientific literature (Barker, Jalinous, & Freeston, 1985). These early devices were used to create maps of the motor cortex and other functional areas of the brain.

Early TMS devices used magnetic coils of a shape and construction that differs significantly from the coil used in the NeuroStar TMS therapy system approved by the FDA for use in clinical practice. Early coils were often shaped in figure eight or circular patterns and had hollow, non-ferromagnetic cores. Such coils are less effective at translating electrical current into a magnetic field, dissipating a large portion of the magnetic energy as heat, and are thus prone to over-heating. The coil shapes also did not allow precise spatial focusing of the magnetic energy, such that the actual volume of brain tissue stimulated was less predictable. The NeuroStar TMS system design innovations overcome these early limitations.

The idea of using TMS for the treatment of depression arose from observations that patients receiving TMS for brain mapping and other neurological studies sometimes experienced mood changes (O'Reardon, Peshek, Romero, & Christancho, 2006). The non-invasive nature of TMS, the relative lack of side effects compared to other treatment modalities, and the non-response of many patients to current treatment options also played a role in stimulating interest in using TMS to treat depression. When TMS was approved by the FDA, the choices for management of depression for patients that had failed multiple medication trials was limited to 1) more medication trials, 2) VNS (vagus nerve stimulation) which required a surgery to implant a permanent pacemaker and a delay in efficacy of up to 18 months, and 3) Electroconvulsive

Therapy with repetitive anesthesia risks and a small but real risk of short and long term memory losses.

Modern TMS Research

Recent research has demonstrated statistically and clinically significant antidepressant effects of TMS in carefully designed, controlled, single-center clinical trials (Fitzgerals et al., 2006). Cumulatively, these analyses have shown that TMS exerts clinically meaningful antidepressant effects with an overall effect size that is comparable to effect sizes found in clinical studies of antidepressant medications (Khan, Warner, & Brown, 2000).

In 2006 a study by Avery and colleagues reported that patients with medication resistant depression were randomly assigned to receive 15 sessions of active or sham TMS delivered to the left dorsalateral prefrontal cortex. The primary end-point was treatment response, defined as a decrease of 50.0% or more in the HAMD17 score at both 1 and 2 weeks following the final TMS treatment. Remission was defined as a HAMD17 score <8. The response rate for the TMS group was 30.6% (11 of 35), which was significantly (P=0.008) greater than the 6.1% (2 of 33) rate in the sham group. The remission rate for the TMS group was 20.0% (7 of 35), significantly (P=0.033) greater than the 3.0% (1 in 33) rate in the sham group. The report concluded that TMS can produce statistically and clinically significant antidepressant effects in patients with medication resistant major depressive disorder. These and other non-clinical studies of TMS provide compelling evidence for the efficacy of TMS as a treatment for major depressive disorder.

Overview of the TMS Process

Orientation to the major elements of the overall process of assessment and planning for a TMS treatment course is necessary to assess the education level required of TMS operators who administer the therapy under medical supervision.

Screening

All patient undergoing treatment with TMS should be thoroughly evaluated with a comprehensive physical exam and thorough medical and psychiatric history according to the manufacturer. Specific attention is paid to an assessment of potential medical risk factors for the use of TMS therapy, including but not limited to:

Implanted Electronic Devices and/or Conductive Objects

The TMS therapy system treatment coil produces strong pulsed magnetic fields that can affect certain implanted devices and objects. It is contraindicated for use in patients for who such ferromagnetic devices cannot be removed or are too close (approximately 12 inches) to the treatment coil. Although the prescribing psychiatrist will provide an initial screening for non-removable ferromagnetic implants or devices within the treatment field of the magnet, the operator must be able to effectively screen for removable ferromagnetic items on each subsequent treatment.

Risk of Ineffective Therapy

Ineffective therapy carries the risk of worsening depression, including the possibility of suicide. The TMS operator must possess the skills necessary to intervene effectively when the depressed patient's mood, thoughts, behavior and impulse control deteriorate in the setting of ongoing TMS therapy. Access to ongoing psychiatric care is required during the provision of TMS therapy.

Risk of Seizure

No seizures were reported in the initial 10,000 TMS treatments presented by NeuroStar to the FDA for approval. In the 18 months (20,000 additional TMS treatments) following the FDA approval of TMS for use outside the research setting, one episode of seizure has been reported

during TMS treatment. Investigation reveals that the patient that experienced a seizure during TMS had undergone medication dose adjustments with psychoactive substances that impact seizure threshold prior to the treatment. The calibration of the motor threshold done prior to the initial TMS treatment should be repeated following any change in psychoactive medications that may impact the seizure threshold.

Concomitant Use of Antidepressant Medications

NeuroStar TMS therapy was evaluated as a monotherapy in the controlled clinical trial presented to the FDA. TMS has not been systematically evaluated for safety and efficacy in a controlled trial during concomitant antidepressant use. Many TMS studies have safely delivered TMS in the presence of concomitant antidepressant medications (Burt, Lisanby, & Sacheim, 2002).

Safety and Tolerability

The design innovations incorporated into the NeuroStar TMS therapy system make it an effective, tolerable, and safe treatment option for patients with major depressive disorder. The key safety issues related to TMS are (1) the potential for seizure induction and (2) the risk of ineffective therapy in the depressed population, which could lead to worsening depression, including suicide and death. It was important to the FDA that in NeuroStar clinical studies submit for review there were no reports of seizure in over 10,000 treatments and no reports of suicide or death.

Seizure

Unlike electroconvulsive therapy, in which the goal is to induce seizures by using relatively strong and direct electrical stimulation, the goal in TMS is to stimulate brain circuitry

indirectly with magnetic pulses and via associated induced electrical currents without intentionally creating a seizure.

However, the inadvertent induction of a seizure remains the most significant medical risk associated with the use of TMS in the community. The risk of this event was identified early in the research literature on TMS. Even before the introduction of more specific parameter guidelines for the use of TMS, however the reported incidence is low. In 1998, when the NINDS consensus safety guidelines were published, only 7 instances had been recorded in the world experience with TMS. Currently, it is presumed that the most critical parameters that may contribute to an increased seizure risk are: 1) the duration of the TMS pulse train at a given frequency and magnetic field intensity (Wassermann, 1998), and 2) the duration of the off-time between trains (Chen et al., 1997). With the publication of recommended safety limits for the use of TMS, the reported incidence of seizures appears to have been reduced in studies adherent to these parameters.

In the previously mentioned case of a seizure occurring once in the 20,000 post-marketing TMS treatments provided since FDA approval, though the TMS machine settings for that individual case was within established safety parameters, the provider and/or operator failed to re-establish the motor-threshold following dosage adjustments of a psychoactive pharmaceutical known to impact seizure threshold. There has also been a report that the operator may have placed the magnet in a site other than over the dorsal lateral prefrontal cortex, the established target area for TMS for which the machine's safety parameters are established (Boatman, 2010).

Risk of Ineffective Therapy/Worsening Depression

The risk of worsening depression is an important issue due to the fact that major depression can be a lethal disease. NeuroStar TMS Therapy is established as safe and effective in the treatment of major depressive disorder in patients who failed to achieve satisfactory improvement with one prior antidepressant medication at minimal effective dose and duration in the current episode. Efficacy was not established in patients who failed to benefit from 2 or more antidepressants. NeuroStar's TMS Therapy system was not studied in patients with no prior antidepressant treatment.

Tolerability and Adverse Events

Data from the clinical trials performed as part of the Neuronetics Clinical Development Program strongly support the safety and tolerability of the NeuroStar TMS Therapy system. As presented to the FDA, TMS was well tolerated, with few device-related adverse events. This safety profile included extended acute exposure (e. g., up to 12 weeks of TMS plus three weeks of TMS taper) in some patients and reintroduction of NeuroStar TMS Therapy as an adjunct to antidepressant medication during the 24-week open-label maintenance of effect study. These data are consistent with the excellent safety profile of TMS as reported in the prior literature, which also supports the view that TMS monotherapy and TMS administered concurrently with antidepressant pharmacotherapy show similar safety profiles with no evidence of unexpected effects under these conditions of use (P. Boatman, personal communication, 2010).

Adverse events associated with acute, extended, or repeated course of TMS were generally mild to moderate in severity. Headache and treatment stimulation site discomfort during TMS session itself were the most common events. The occurrence of these adverse

events was predictable over repeated courses of treatment, and there was clear evidence of adaptation to these events in most patients (Janicak, O'Reardon, Sampson et al., 2008).

Many of the adverse events experienced by patient taking antidepressants (weight gain, sexual dysfunction, nausea, dry mouth, or sedation) are absent with TMS therapy. Discontinuation due to treatment intolerances was sizable in the STAR*D trial, reaching as much as 42.0 % in level 4. By comparison, discontinuation due to adverse events for TMS treated patients in Study 101 of the Clinical Development Program presented to the FDA was 4.5% through the primary efficacy time point.

Electroconvulsive therapy (ECT) as an antidepressant treatment option involves even greater issues of tolerability. Unlike ECT, TMS does not involve general anesthesia during the procedure. Also unlike ECT, there is no evidence of impact on short-term or long-term memories or cognitive changes with TMS.

Summary of Overall Safety

The three NeuroStar clinical studies presented to the FDA provide the largest, most comprehensive safety dataset reported to date for the use of TMS in adults with major depressive disorder (Janicak, O'Reardon, Sampson et al., 2008).

Across all three studies, a total of 10,094 TMS treatment sessions occurred. A total of 268 patients received at least one session in one or more of these three studies. Twenty-three serious adverse events were reported in the randomized controlled Study 101. Of these, 11 (47.8%) occurred in patients in the indicated population, consistent with this population representing 54.5% of the full study population. No seizures or deaths were reported.

In Study 102, the type and incidence of serious adverse events were consistent with those reported in Study 101, with the expectation of a single serious adverse event of facial numbness

that occurred during the open-label TMS treatment and fully resolved following discontinuation of treatment.

Serious adverse events in Study 103 were also consistent with the two prior studies. It is notable that serious adverse events in Study 103 also reflect the concurrent exposure of all patients in the study to antidepressant pharmacologic monotherapy.

Device Malfunctions

A mild first-degree burn to the scalp located under the treatment coil was reported in two patients in Study 101 and were found to de due to overheating of the first-generation disposable component of the NeuroStar TMS Therapy system. The disposable component used in the clinical trial was a prototype version of the current SenStar Treatment Link and was used to reduce the magnetic field at the patient's scalp to aid in the patient comfort during treatments. The overheating was due to a manufacturing defect that was addressed in the clinical study, and no further events were reported after this point in the clinical trial (Janicak, O'Reardon, Sampson et al., 2008).

Adverse Events

The most commonly reported adverse event was headache. However, this event was reported at a similar incidence in both sham and active treatment groups. Among those adverse events that occurred with an excess incidence in the active TMS treatment condition (i. e., more than 5.0 % and twice the incidence in the sham TMS group), the most commonly reported was application site pain. This was reported by 35.8% in the active TMS group compared with 3.8% in the sham TMS group. The investigator characterized the pain as "severe" in 6.1 % of patient in the active TMS group and in no patients in the sham TMS group. The other reports of application site pain were characterized as mild or moderate. Study investigators classified all

instances of application site pain as “probably or definitely” related to the study device in both groups. A decline over time in reports of headaches and application site pain in some patients was noted, suggesting there can be at least some degree of accommodation to these events (Janicak, O'Reardon, Sampson et al., 2008).

Adverse events were similar in study 102 and during reintroduction to TMS treatment in Study 103. During the taper phase of Studies 101 and 102, antidepressant medications were added to the TMS therapy, and no additional adverse events related to the device occurred in this period.

Study participation adherence is commonly used as a marker for tolerability of a treatment. During Study 101, the adherence rate to the study protocol through the primary efficacy time point was high. Through Week 4, the all-cause discontinuation rate was similar in the active (7.7%) and sham (8.2%) TMS groups. Discontinuation due to adverse events was also similar across treatment conditions (i.e., 4.5% in active TMS vs. 3.4% in sham TMS patients). In a recent large-scale meta-analysis of randomized controlled trials of standard antidepressants, the all-cause discontinuation rate was 37.0 % (Khan, Warner, & Brown, 2000).

Table 2: Summary of Serious Safety Events

Related or probably related to the TMS device or TMS Operator (Studies 101,102,103)

2	Device malfunction / first degree scalp burns
1	Severe pain at treatment site
1	Left-sided facial numbness

Table 3: Summary of Adverse Events in Randomized Controlled Trial at a Rate of ≥ 5% and at Least Twice that of Sham TMS (Study 101)

Body System Adverse Event	Sham TMS (N=158) N (%)	Active TMS (N=165) N (%)
Eye Pain	3(1.9)	10(6.1)
Toothache	1(0.6)	12(7.3)
Application Site Discomfort	2(1.3)	18(10.9)
Application Site Pain	6(3.8)	59(35.8)
Facial Pain	5(3.2)	11(6.7)
Muscle Twitching	5(3.2)	34(20.6)
Pain of Skin	1(0.6)	14(8.5)

Summary

All of the 10,094 TMS treatments reported to the FDA by Neuronetics as part of its application for approval of the NeuroStar TMS Therapy system were performed by research clinicians at the RN or MD license level. Conversations with the original principle investigators for the Studies 101, 102 and 103, estimate that the physician researchers performed most of the motor threshold determinations (+/- 500 sessions) and the remaining approximately +/-9500 TMS treatment sessions were performed by RN research clinicians.

When the FDA approved NeuroStar TMS Therapy for the treatment of major depression in the community, it made no statement regarding the licensure or training level of the TMS operators. An informal survey of physicians at two separate Neuronetics sponsored TMS

conferences in 2009 revealed that the vast majority of the TMS machines located in private practice are owned by private practice physicians who use non-licensed nursing or administrative staff as TMS operators, whereas those TMS machines located in private hospitals and on university campuses are more likely to be staffed by RN level operators. The NeuroStar sales team representative in northern California, on informal discussion, estimates that for every TMS machine sold to a hospital or university setting another five are being sold directly into the private practice setting, these estimates are supported by the company's website that lists all TMS locations in the country.

None of the research reviewed on TMS from 1998 to 2010 comments on operator licensure or training level, however it is notable that since the FDA approval for use TMS with the general public, there has been a dramatic and steady drift away from the RN operators that provided the vast majority of research TMS to non-licensed healthcare staff.

The manufacturer holds that the device is so safe, that the private physician may train anyone on his or her staff to provide the service. This research project compared the safety and tolerability of TMS provided by non-licensed operators in private practice with the data reported to the FDA by Neuronetics for the initial 10,094 sessions provided by RN and MD research clinicians to determine the extent to which professional health education and licensure impacts safety and tolerability of the TMS provided in our communities.

Chapter 3: Methodology

Introduction

This chapter discusses the research methodology used in this study. The discussion is divided into six sections: 1) research design, 2) research setting, 3) population and sample, 4) data collection procedures, 5) data analysis methods, and 6) protection of human subjects. The protocol for this study was approved by the Institutional Review Board of the Western Governor's University prior to initiation of the study.

Research Design

This study has both a quantitative and qualitative research design. A retrospective, descriptive quantitative assessment of an established medical archive of TMS interventions provided by a group of non-licensed workers was undertaken. This initial design was chosen to examine the relationship between variables that are not manipulated in this study (Hopkins, 2008). The findings from this retrospective analysis is then compared to the findings reported by Neuronetics to the FDA based on their clinical archive of TMS interventions provided by operators with either the RN or MD license. The qualitative data generated from a root-cause analysis of untoward events is used to assess the relationship between identified adverse events and the TMS operator.

Setting

This study was set in a multi-site TMS practice that used only non-licensed health workers in the role TMS operator. The data was collected from three clinical sites, two urban and one suburban.

Participants

The data for this study was collected from the population of TMS Therapy recipients at the San Francisco TMS Centers and the Peninsula TMS Center for the period April 1, 2009 to August 15, 2010. Forty-seven TMS recipients received a total of eight hundred and twenty-three sessions during this study period. The study population's ages range from 18.3 to 72.4 years with a mean of 42.2 years. The study population was 52.3 % male and 47.7 % percent female with one male identified FTM transgender patient. The total number of TMS treatments per patient ranged from 1 to 114 with a mean number of TMS treatments per patient of 20.1 sessions.

Description of Research Tools

All of the patients received transcranial magnetic stimulation provided by the NeuroStar TMS Therapy system using the disposable SenStar Treatment Link designed specifically for use with the NeuroStar TMS Therapy system. Clinical data were collected from the PDMS (patient data management system) clinical data archives associated with each NeuroStar TMS Therapy device as well as the individual medical records kept by the prescribing TMS psychiatrist.

Data Collection and Procedures

After receiving permission from the owner of the TMS clinical records and following approval from the Institutional Review Board of Western Governors University, the researcher arranged with the TMS clinics' administrative staff to access the redacted copies of TMS related clinical data.

The clinical progress notes and data were collected from the NeuroStar TMS machine that is stored in the PDMS system for each TMS session performed during the study period with the three NeuroStar TMS devices under study. The clinical data were reviewed manually by the researcher to identify safety issues and adverse events with a specific eye toward identification of

those untoward events recognized as potentially related to the TMS therapy in the original research presented to the FDA by the NeuroStar TMS system manufacturer.

Following the collection and analysis of the quantitative data, every safety or adverse and untoward incident identified then triggered a root-cause analysis of the event. The semi-structured root-cause analysis using established tools from the National Center for Patient Safety included detailed interviews with the associated supervising psychiatrists as well as the non-licensed TMS operators involved in the events under investigation.

Data Analysis

A quantitative research method was used to establish the risk of safety and tolerability events expressed in this study population provided TMS therapy by non-licensed health workers. This risk is expressed as an incidence rate or percentage both in this current research and in the research submitted to the FDA by the device manufacturer, NeuroStar. Qualitative research methods were used to analyze each actual safety or tolerability associated adverse event in terms of its causal relationship to the TMS operator. Lastly, the incidence rates for TMS related untoward events (adverse, tolerability and safety) reported in the initial Neuronetic study with RN and MD operators presented to the FDA was compared with those identified in this study of TMS therapy provided by non-licensed operators to identify any statistically significant trends.

Human Subjects Protection

This retrospective descriptive quantitative and qualitative study does not expose any patient to any new clinical interventions. This study relied on a retrospective analysis of archived data. Institutional review board approval from Western Governors University was secured prior to initiation of the study data collection and review process. Patient privacy was preserved through the use of redacted computerized clinical records and redacted copies of

archived medical records that fully removed identifying patient information prior to release to the researcher.

Summary

The quantitative data for analysis in this study were collected through a review of existing records. The qualitative data for analysis in this study were generated through a root-cause analysis that used standardized tools from National Patient Safety Center of the Veteran's Administration to guide individualized interviews with clinicians associated with the events under investigation. Secondary quantitative analysis relied on data previously collected and presented in the public domain by the device manufacture. Data collection and analysis were deferred until after IRB approval.

Chapter 4: Findings

Introduction

A detailed review of the redacted electronic medical records found in the patient data management system (PDMS) attached to each transcranial magnetic stimulation therapy device was undertaken at the three designated clinical sites. This review of electronic records was followed by a detailed review of the redacted paper-based medical records including entries extending three months past the last Transcranial Magnetic Stimulation (TMS) treatment event.

Findings

In the review of the clinical data from the 47 patients treated with TMS for a total of 823 TMS doses there were no episodes of emergent suicidality, suicide attempts, worsening depression or seizures which are the serious safety events that TMS patients are considered to be at highest risk for by both the manufacturer and the FDA. One patient did proceed to voluntary outpatient electro-convulsive therapy (ECT) following completion of his course of TMS, however it is notable that his depression was not described as worse, just not substantially improved by the TMS course (an issue of efficacy, not safety).

It is notable that the 165 patients treated in the initial research study presented to the Food and Drug Administration (FDA) with registered nurses and psychiatrists in the role of TMS operator there was one episode of worsening of depression and three episodes of suicide ideation. Other serious adverse events reported by the initial research group staffed with RN and MD level TMS Operators included two device related first degree burns, one episode of left-sided facial numbness and one episode of device malfunction with severe pain at the treatment site. The device related malfunctions were addressed by the manufacturer prior to release of the TMS system for use in the community by non-licensed operators. There were no

episodes of severe pain, burns or facial numbness identified in the study group of non-RN/MD TMS Operators.

Table 4 presents the tolerability data expressed as adverse events by body system for this study group with non-RN/MD Operators with the data collected by the manufacturer with RN/MD Operators. For the purposes of submission to the FDA, the manufacture considers an adverse event significant when it occurs in more than 5.0% of the active TMS population and with twice the incidence seen in the sham (placebo) group. The data for this study did not identify any new adverse events that met the manufacturer or the FDA's criteria for clinical significance.

Table 4: Tolerability Data

Body System -Adverse Event	Sham (placebo) TMS (N=158) N (%) Manufacturer Data RN/MD Operators	Active TMS (N=165) N (%) Manufacturer Data RN/MD Operators	Study TMS (N=47) N(%) Study Data Non-RN/MD Operators
Eye Pain	3(1.9)	10(6.1)	2(4.3)
Toothache	1(0.6)	12(7.3)	3(6.4)
Application Site Discomfort	2(1.3)	18(10.9)	6(12.8)
Application Site Pain	6(3.8)	59(35.8)	17(36.2)
Facial Pain	5(3.2)	11(6.7)	4(8.5)
Muscle Twitching	5(3.2)	34(20.6)	9(19.5)
Pain of Skin	1(0.6)	14(8.5)	5(10.6)

The manufacturer reports a high tolerability for active TMS provided by RN/MD Operators with a discontinuation rate of less than 10.0% through the first four weeks of treatment (20 doses). The data from the study group of non-RN/MD Operators demonstrated a similar experience with a discontinuation rate of 4.2%.

A root-cause analysis of the two discontinuation events in the study group revealed that one patient interrupted her course of TMS treatment when the non-RN/MD level TMS Operator failed to acknowledge the patient's complaint of pain and her belief that the TMS magnet had been placed in a location different than on previous treatments. Interview with the supervising physician during the root-cause analysis revealed that it was the psychiatrist's belief that the patient discontinued a potentially useful TMS treatment course because of lack of appropriate response by the non-RN/MD TMS operator to the patient's assertion that the coil placement was off and that as a result the patient was experiencing more pain. Financial reasons unrelated to the TMS Operator were identified as the root-cause for the second discontinuation of TMS.

Results and Interpretation

TMS operators in this study included the following type of health providers: one licensed vocational nurse (LVN), four certified medical assistants, a certified nursing assistant, a certified massage therapist, a certified reflexologist and a psychotherapy intern. Though this diverse group of allied health providers all share a widely divergent theoretical and clinical education foundation, all of the operators did complete the TMS Operator training program provided by the manufacturer and were clinically supervised by board certified psychiatrists. This training experience includes both theoretical and clinical components that allow the participant to work individually with both the TMS trainer from the manufacturer as well as the supervising (prescribing) psychiatrists prior to being assigned clinical responsibility for TMS patients.

The quantitative data on safety and tolerability appear to be quite comparable between the RN/MD level TMS operator group described by the manufacturer and the non-RN/MD level TMS Operator study group. The qualitative root-cause analysis of the TMS discontinuation data in the non-RN/MD level Operator study group identified a clinical interaction between a patient and a TMS Operator that was sub-optimal and that in the opinion of the prescribing TMS psychiatrist likely impacted tolerability as evidenced by discontinuation, but not safety.

Summary

These findings confirm safety and tolerability and are supported by the discontinuation data. The qualitative data suggests clinician experience with difficult personalities seen in the severely mentally ill may impact tolerability and the subsequent discontinuation pattern. However, the quantitative statistics do not differentiate tolerability outcomes for the non-RN/MD TMS Operators in the community from the RN/MD TMS Operators of the original clinical research settings.

Chapter 5: Discussion and Conclusions

Overview

What is the relevance of this study? This last chapter explores the research findings; their limitation and implications; draws conclusions and make recommendations for future study.

Discussion

The absence of serious adverse events in this study population suggests that Transcranial Magnetic Stimulation (TMS) can be safely administered by non-RN/MD health providers. The device related safety issues reported by the manufacturer to the Food and Drug Administration (FDA) included first degree burns and severe pain at the treatment site seemed to have been resolved prior to release of the device for use in the community and these events were not deemed to be operator related. Episodes of suicidality and worsening depression are theoretical safety issues that did not arise in this study cohort.

The tolerability data expressed as risk for serious adverse events is comparable between the RN/MD Operator group and non-RN/MD Operator group suggesting that tolerability for this type of treatment intervention is largely independent of the TMS Operator's education level. This study cohort confirmed the experiences of the manufacturer that patients typically adapt to treatment discomfort and pain as they progress through the treatment course and rarely do they require adjunctive pain management or comfort measures to continue in with the treatment course as originally prescribed.

The fact that the discontinuation data in this study cohort was < 5.0% whereas the discontinuation data in the original manufacturer's studies were reported as < 10.0% confirms that the treatments provided by non-RN/MD Operators are well tolerated. The lower

discontinuation rate in the community may reflect a level flexibility and accommodation of patients in the community that did not exist in the research settings.

The root-cause analysis of the one TMS discontinuation event in this study cohort that was TMS Operator related identified a clinical misadventure that might well have been avoided with a different patient-operator dyad. Clinical experience reveals that despite the best intentions, not every patient-clinician match is necessarily therapeutic. Neither the TMS Operator's education level nor clinical skills were identified in the root cause analysis as contributing factors to the discontinuation event. It was the conclusion of the root-cause analysis that substantial clinical experience working with the seriously mentally ill population on the part of the TMS Operator would reduce the incidence of such events.

Implications

Analysis of the results supports the manufacturer's position that TMS is both a safe and well tolerated procedure that can be administered by non-RN/MD Operators. The study does not address the issue of efficacy. It could be that although the TMS provided by non-RN/MD operators is both safe and well tolerated it might show to be less effective than those treatments provided by RN/MD Operators. An example of such a scenario might arise when the non-RN/MD TMS Operator responds to patient complaints of discomfort by moving the TMS coil away from the therapeutic treatment area identified by the psychiatrist during the initial motor-threshold assessment session. In such a scenario the TMS Operator has worked to create a more tolerable treatment only to sacrifice efficacy.

Limitations

The number of patients in this study cohort (47) and the volume of treatments provided in this study (823) is roughly is roughly one third of the size of the active TMS treatments in initial

safety and efficacy study presented by the manufacturer to the FDA. Review of the FDA discussions with the manufacturer during the initial research indicates that efficacy was more difficult to demonstrate than safety. It seems likely that the size (number of subjects) recruited for the original research reflects the sample size necessary to distinguish efficacy in the active TMS group from the sham (placebo) TMS group.

This study cohort followed the same treatment recommendations as the manufacturer's research with the recommendation for five treatments per week for four weeks followed by three weeks of tapering. Though there was some inherent variability to the treatment schedules, it is notable that most clinical research with psychiatric medications will typically collect the efficacy, safety and tolerability data over a similar treatment time frame. Though this study cohort failed to identify any serious safety events (suicide, worsening depression, burns, severe pain) this does not appear to be a function of sample size, as other serious adverse events were successfully identified and found to be consistent with the original research findings of the manufacturer.

Recommendations

Whereas most nurses are well trained to give "the dose" as prescribed unless it is unsafe, many other allied health professionals do not share this same clinical orientation. The impact on non-RN/MD TMS Operators on TMS treatment efficacy has yet to be demonstrated and is a worthy topic for further research.

Conclusions

While this study clearly demonstrates that non-RN/MD TMS Operators can safely provide well tolerated TMS therapy the question of efficacy remains. While the use of non-RN/MD TMS Operators may lower the overhead associated with TMS therapy and may also facilitate expansion of TMS centers away from institutional medical centers into suburban and

rural communities the impact on treatment efficacy remains unclear. Though TMS is less expensive than ECT or a prolonged partial-hospital stay, it is not inexpensive for patients and insurers. Resistance to coverage of TMS by payers has been focused on the question of clinical efficacy. An increase in the use of non-RN/MD TMS Operators though safe may not be cost effective if treatment efficacy is at risk.

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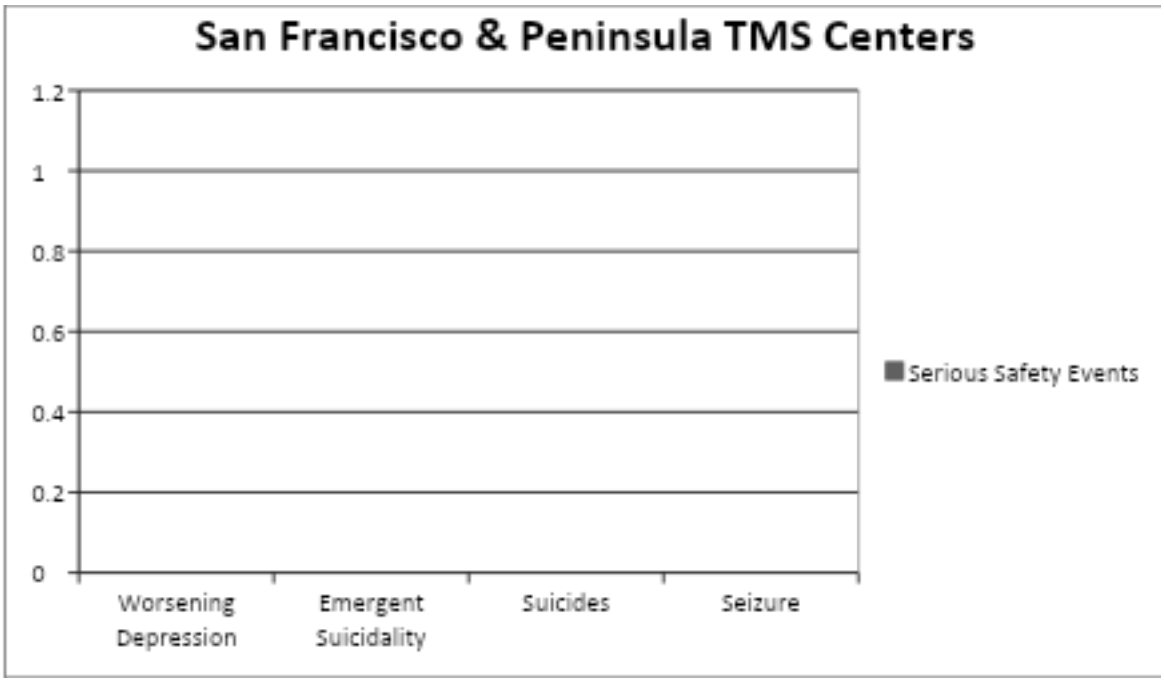
Appendix A

Serious Safety Events at the San Francisco & Peninsula TMS Centers

Table 5

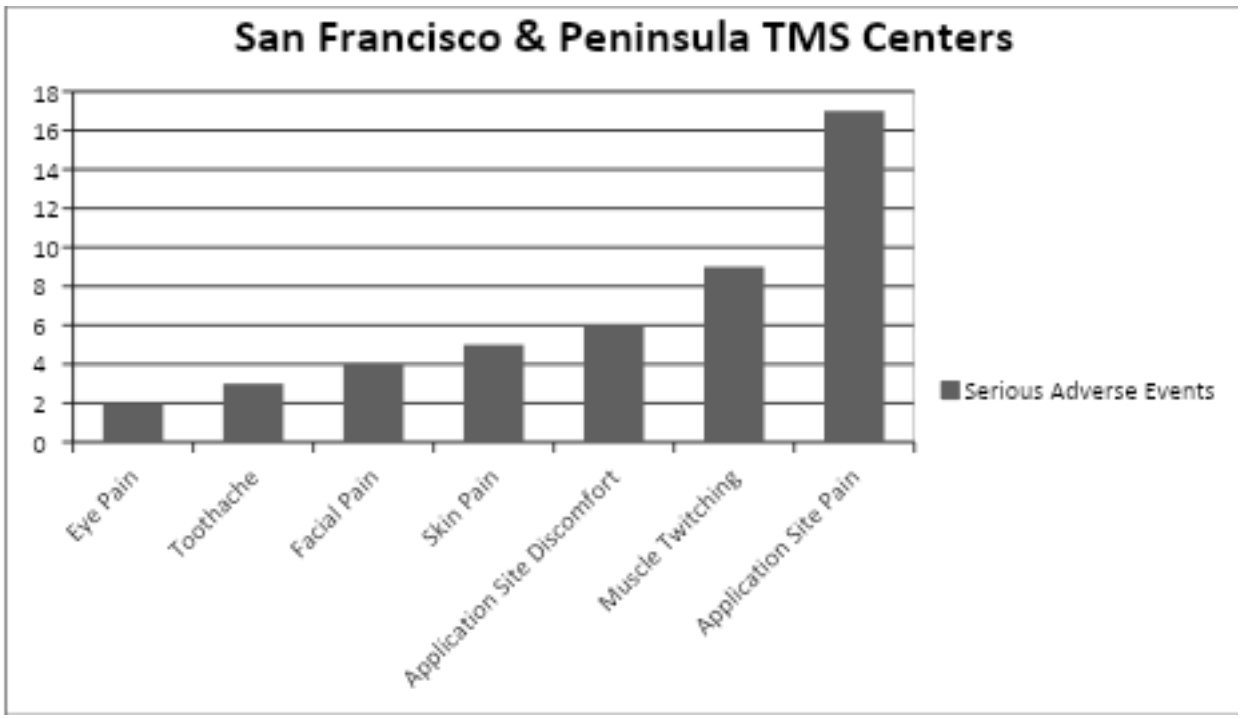


None of the 47 patient charts found any incidence of worsening depression, emergent suicidality, suicides, or seizures.

Appendix B

Serious Adverse Events at the San Francisco and Peninsula TMS Centers

Table 6



Appendix: C

Root Cause Analysis as Qualitative Research

The goal of a Root Cause Analysis is to find out:

- *What happened*
- *Why did it happen*
- *What to do to prevent it from happening again.*

Root Cause Analysis is a *tool* for identifying prevention strategies. It is a process that is part of the effort to build a *culture of safety* and move beyond the culture of blame.

In Root Cause Analysis, basic and contributing causes are discovered in a process similar to diagnosis of disease - with the goal always in mind of preventing recurrence.

Root Cause Analysis is:

1. Inter-disciplinary, involving experts from the frontline services
2. Involving of those who are the most familiar with the situation
3. Continually digging deeper by asking why, why, why at each level of cause and effect.
4. A process that identifies changes that need to be made to systems
5. A process that is as impartial as possible

To be thorough, a Root Cause Analysis must include:

1. Determination of human & other factors
2. Determination of related processes and systems
3. Analysis of underlying cause and effect systems through a series of *why* questions
4. Identification of risks & their potential contributions
5. Determination of potential improvement in processes or systems

To be credible, a Root Cause Analysis must:

1. Include participation by the leadership of the organization & those most closely involved in the processes & systems
2. Be internally consistent
3. Include consideration of relevant literature

Appendix D

Root Cause Analysis - Steps

First:

Was this event thought to be the result of: a criminal act; a purposefully unsafe act related to alcohol or substance abuse (impaired provider/staff), or events involving alleged or suspected patient abuse of any kind (i.e., those situations which are outside the scope of the patient safety program)?

No.

Second:

1. Were issues related to patient assessment a factor in this situation?

   Yes, patient stated that "the coil is not positioned correctly" and "this treatment is more painful today than yesterday." Operator responded the "the computer shows there is good scalp contact, it says it is in the correct position." Patient reports that the operator did not re-check the stored settings for coil positioning. The operator reports that the computer showed good scalp contact, and therefore no need to change the position.

2. Were issues related to staff training or staff competency a factor in this event?

   Yes, the operator should have taken seriously the patient's assertion that the coil was incorrectly positioned and taken seriously the report of worse pain. Both of these statements from the patient should have triggered the operator to re-check the coil position and chair position prior to continuing the treatment.

3. Was equipment involved in this event in any way?

   Yes, the patient was using the NeuroStar TMS system.

4. Was the work environment a factor in this event?

   No.

5. Was the lack of information (or misinterpretation of information) a factor in this event?

Yes, the patient was unable to communicate her concerns regarding coil placement and pain successfully to the operator. The operator states he assumed the patient was commenting on scalp contact (proximity to scalp), not coil placement as in correct treatment location of coil on the head.

6. Was communication a factor in this event?

   Yes, there was one miscommunication between the patient and the operator (coil proximity to scalp vs. coil placement on head) and one failure to act on information communicated (“I have more pain this time”).

7. Were appropriate rules/policies/procedures -- or the lack thereof -- a factor in this event?

   No.

8. Was the failure of a barrier -- designed to protect the patient, staff, equipment or environment -- a factor in this event?

   No.

9. Were personnel or personal issues a factor in this event?

   Yes, operator and patient both admit that there had been a history of discord and ill feelings related to previous interactions that had not been adequately resolved prior to this event.

Appendix E

Root Cause Analysis – Human Factors: Communication

1. Was the patient correctly identified? YES

2. Was information from various patient assessments shared and used by members of the treatment team on a timely basis? YES

3. Did existing documentation provide a clear picture of the work-up, the treatment plan and the patient's response to treatment?
   Including:
   - assessments
   - consultations
   - orders
   - treatment team notes
   - progress notes
   - medication administration record
   - x-ray
   - lab reports
   - -- etc. --

   YES

4. Was communication between management/supervisors and front line staff adequate?
   Was it:
   - accurate
   - complete
   - using standard vocabulary and no jargon
   - unambiguous

   YES

5. Was communication between front line team members adequate?

   YES

6. Were policies and procedures communicated adequately?

   YES

7. Was the correct technical information adequately communicated 24 hours a day to the people who needed it?

   YES

8. Were there methods for monitoring adequacy of staff communication? Were there methods for:
   - "read back"
   - confirmation messages
   - debriefs
   - --etc.--

   YES

9. Was the communication of potential risk factors free from obstacles?
   YES

10. Was there manufacturer's recall/alert/bulletin on file for equipment, medication, or transfusion related elements at the time of the event or close call? Were relevant staff members aware of the recall/alert/bulletin?

    YES

11. If relevant, were the patient and their family/significant others actively included in the assessment and treatment planning?

    Not relevant

12. Did management establish adequate methods to provide information to employees who needed it in a manner that was easy to access/use, and timely?

    YES

13. Did the overall culture of the facility encourage or welcome observations, suggestions, or "early warnings" from staff about risky situations and risk reduction?

    YES

    (Also, has this happened before and was anything done to prevent it from happening again?)

    NO

14. Did adequate communication across organizational boundaries occur?

    Yes

Appendix: F

Root Cause Analysis – Human Factors: Training

1. Was there a program to identify what is actually needed for training of staff? YES
2. Was training provided prior to the start of the work process? YES
3. Were the results of training monitored over time? YES
4. Was the training adequate? YES. If not, consider the following factors:
    - supervisory responsibility
    - procedure omission
    - flawed training
    - flawed rules, policy, or procedure
5. Were training programs for staff designed up-front with the intent of helping staff perform their tasks without errors? YES
   If "No" -- This could be a Root Cause/Contributing Factor.
6. Had procedures and equipment been reviewed to ensure that there was a good match between people and the tasks they did; or people and the equipment they used (i.e., human factors engineering)? YES
   If procedures were not followed as intended, see the Rules/Policy/Procedure questions.
7. Were all staff trained in the use of relevant barriers and controls? YES
8. If equipment was involved, did it work smoothly in the context of:
    - staff needs and experience
    - existing procedures, requirements, and workload
    - physical space and location

   YES