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Original Research Article

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.

KEYWORDS: Nursing; Food and Drug Administration; Transcranial Magnetic Stimulation (TMS) therapy.

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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[1]. The initial application of most of these devices was low repetitive rates of single-pulse diagnostic studies such as in cortical mapping[2]. When repetitive Transcranial Magnetic Stimulation (TMS) emerged as a potential therapeutic application, these stimulators were modified to accommodate higher pulse rates[3]. While these devices served to expand research knowledge, they were not designed to create reproducibly safe and efficacious treatment

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for a given medical indication nor were they intended for routine clinical use[4].

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 of key design and technology advances over the types of TMS systems typically used in research settings.

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[5]. 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[6]. 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 aestheticians, 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 their 2008 user manual provided to the FDA prior to approval which reads[7]:

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.

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[1]. Within the first 18 months following FDA approval, there is the first ever report of a NeuroStar TMS Therapy induced seizure, reported to the FDA as a serious adverse event.

MATERIALS AND METHODS

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[8]. 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.

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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, 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 Neuro Star 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 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 OF MATERIALS AND METHODOLOGY

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.

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RESULTS

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.

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 1 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 1. 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

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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.

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.

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.

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 of 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

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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 less 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.

REFERENCES

1.Demitrack, M. (2009, January 28). Discussion of TMS research trials. Philadelphia, PA. Discussion with Paul Boatman. (2010, January 28) (interviewed at Clinical Training & Research Institute). San Francisco, CA.
2.Janicak, P. G. (2010, May 26). Long-term durability of acute response to transcranial magnetic stimulation (TMS) in the treatment of pharmaco-resistant major depression. In New research poster session 7. July 1, 2000 conducted at the APA, APA, San Francisco, CA.
3.Gershon, A. A., Dannon, P. N., &Grunhaus, L. (2003, May 1). Transcranial magnetic stimulation in the treatment of depression [Psychiatry Online]. American Journal of Psychiatry, 160, Reviews and overviews. Retrieved July 19, 2010, from http://ajp.psychiatryonline.org/cgi/content/full/160/5/835.
4.McDonald, W. (2010, May 24). The clinical safety and efficacy of transcranial magnetic stimulation results from recent pivotal clinical trials. In Focal brain stimulation for psychiatric disorder: Clinical update. APA.
5.Aaronson, S. T. (2010, May 25). An open-label study of transcranial magnetic stimulation combined with antidepressant medication of the treatment of MDD. [Poster NR4-76]. In New research poster session 6. TMS Therapy Presentation at APA, APA, San Francisco, CA.
6.Demitrack, M. (2008, October 9). FDA clears NeuroStar TMS Therapy for the treatment of depression. Retrieved July 19, 2010, from Medical News Today: http://www.medicalnewstoday.com/articles/124958.php.
7.Neuronetics. (2008). (Neuroneticsneurostar TMS system user manual). Retrieved July 19, 2010, from FDA: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_15-NeuroStarUserManualRevision.pdf.
8.Hopkins WG. Research designs: choosing and fine-tuning a design for your study. Sportscience. 2008;12:12–21.

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