Use of Transcranial Magnetic Stimulation for the Treatment of PTSD

11

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E. C. Ritchie (ed.), *Posttraumatic Stress Disorder and Related Diseases in Combat Veterans,* DOI 10.1007/978-3-319-22985-0_11

Posttraumatic stress disorder (PTSD) is a complex illness that rarely occurs in isolation from other psychiatric morbidities, and often fails to remit with standard therapies. Traditionally, PTSD is treated with psychotherapy and/or pharmacotherapy, with treatment choices often based on availability, patient preference, and patient tolerance. One of the more commonly recommended psychotherapy treatment modalities is exposure-based therapy, where a patient recalls traumatic events, usually with some form of relaxation, with the hope of inducing extinction of the anxiety response to the stimulus [1]. In addition to treatment with psychotherapy, pharmacotherapy is also commonly administered, despite potentially adverse side effects and the risk of polypharmacy. Many patients are prescribed psychotropics to ameliorate symptoms, particularly if PTSD exists with other comorbid conditions. While psychotherapy and pharmacology may have utility for many patients, their limited efficacy promotes the need for novel treatment options. One possible alternative treatment option is transcranial magnetic stimulation (TMS), which is a noninvasive brain stimulation technique that has a broad range of therapeutic capabilities.

11.1 Care Presentation/History

A 35-year-old African American male with a history of recurrent depression since age 14 and PTSD symptoms resulting from two deployments to Afghanistan, self-referred for repetitive transcranial magnetic stimulation (rTMS) after hearing about the technology on the radio and investigating its features online. His depressive symptoms were characterized by depressed mood, anhedonia, low energy, fragmented sleep, hyperphagia with unintentional weight gain, guilt, a sense of worthlessness, and recurring thoughts of dying without suicidal ideations or intent. Since age 14, these had been present to varying degrees, without any complete resolution. For the past 9 years, he reported his symptom severity continually met criteria for a depressive episode with no periods of partial resolution.

Approximately 10 years prior to his presentation to the transcranial magnetic stimulation (TMS) clinic, the patient had deployed twice to Afghanistan with direct combat operational duties. Since that time, he admitted to feeling on edge, experiencing ease of startle, daytime intrusive recollections of combat, nightmares associated with the trauma, and efforts to avoid stimuli that reminded him of the trauma. He found relationships difficult due to a sense of disconnectedness and was profoundly socially isolated. There was also a sense of foreshortened future, which propagated a sense of hopelessness that his symptoms would not abate.

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11.1.1 Developmental History

The patient denied any history of physical, emotional, or sexual abuse, with no history of legal troubles. He graduated high school on time and had earned a 4-year college degree. After serving in the military, he obtained work as a Department of Defense government employee. The patient had never been married and had no children. He had been without a sustained romantic relationship since returning from Afghanistan. His predominant recreational activity was weight training several hours each day.

11.1.2 Past Medical History

On presentation, there were no known medical illnesses and no history of seizures. He denied any metallic fragments or implants above the neckline. The patient had not received any surgical procedures to date. He took several supplements, including a daily multivitamin, Omega-3 supplements, probiotics, and amino acids. He did not report any allergies. He admitted to occasional 1–2 cigarette use when he was out with friends. There was no report of illicit drug use, including anabolic steroids.

Alcohol use was a concern. He admitted to daily use of alcohol, up to six drinks each night, over the past 10 years. He had developed a tolerance to alcohol, would have trouble limiting the amount he did drink, struggled to cut back his drinking, and admitted that it worsened his mood over time. Three months prior to presentation, he made a conscious effort to limit his intake on the advice of his therapist, drinking 3–4 drinks once a week, but he continued to struggle with strong alcohol cravings.

11.1.3 Family History

Both of his biological parents suffered from major depression. His sister was diagnosed with bipolar disorder type I and had been psychiatrically hospitalized once. There had been no suicides in the family.

11.1.4 Military History

The patient served a total of 7 years, achieving the rank of staff sergeant before an honorable discharge at the end of his enlistment period. During his deployment, he served with special operations units early in the Afghanistan campaign. He received several commendations for his service and never received any disciplinary actions.

Table 11.1 Drug, dose, and result of medication trials in which the patient participated

Trial date	Treatment (dose)	Result
2006	Lamictal starter pack	Rash
2006	Depakote (250 mg qday)	Tinnitus, sedation, dysarthria
2006–2008	Trazodone (100 mg qday)	Sedated during the day
2006–2009	Wellbutrin XL (300 mg qday)	Insomnia
2007–2013	Xanax (0.5 mg prn for anxiety)[a]	
2010–2013	Prozac (40 mg qday)	Weight gain and insomnia
2010–2013	Hydroxyzine (50 mg tid)	Ineffective

[a] Used several times a week for anxiety

11.1.5 Past Psychiatric History

No prior psychiatric hospitalizations were reported, and he had never attempted suicide. His psychiatric care was fragmented over the past 10 years. An attempt at exposure-based therapy several years prior was not tolerated. He was currently engaged in weekly cognitive behavioral therapy over the past 10 months. The patient had previously participated in several medication trials (Table 11.1).

11.2 Diagnosis/Assessment

Psychiatric review of systems was otherwise unremarkable for symptoms of obsessive-compulsive disorder, generalized anxiety, panic disorder, simple phobia, mania, psychosis, eating disorder, or other psychiatric conditions not already mentioned.

11.2.1 Mental Status Examination

The patient arrived wearing a suit and tie, having come straight from his workplace. He was an articulate male, obviously muscular, and remained well composed and professional during the interview. His speech was slightly decreased in volume, but was of normal rate. His motor activity was normal. The patient described his mood as depressed, and while his affect was congruent, he did display brief periods of levity before drifting back to an apathetic baseline. Thought content was without suicidal or homicidal ideation. He denied delusions but did admit to recurrent thoughts of his own mortality. The patient's thought process was goal directed, logical, and linear, with good insight, and intact judgment and impulse control. Cognition was intact as evidenced by a normal Montreal Cognitive Assessment (MoCA), ease of recall of his historical narrative, and varied vocabulary with appropriate low-frequency word use. The patient scored a 22 on the Patient Health Questionaire-9 (PHQ-9), which is indicative of severe depression. On the PTSD Checklist-Military version (PCL-M), the patient scored a 60, which is indicative of PTSD.

The patient's blood was analyzed as follows: Complete blood count (CBC), comprehensive metabolic panel, B12, folate, lyme, thyroid stimulating hormone, rapid plasma reagin, HIV, total and free testosterone, which were all normal or negative. Total cholesterol was 230 mg/dl (125–200). Triglycerides were 194 mg/dl (<150), high-density lipoprotein (HDL) was 38 mg/dl (> or =40), and low-density lipoprotein (LDL) was 153 mg/dl (<130).

Genetic analysis by commercial genetic assay (Genecept™ Assay) showed no clinically significant variations of Ankyrin G (ANK3), Methylenetetrahydrofolate reductase (MTHFR), Cytochrome P450 2D6 (CYP2D6), and Cytochrome P450 3A4 and 3A5 (CYP3A4/5). SLC6A4 was L(G)/L(G) variant suggesting the likelihood of poor or slow response and greater side effects with Selective serotonin reuptake inhibitors (SSRIs) [2]. Catechol methyl transferase (COMT) was Val/Val variant suggesting a reduction in frontal lobe dopamine [3] Serotonin 5HT2C receptor (5HT2C) was C/C variant which may be associated with an increased incidence of weight gain with atypical antipsychotics [4]. Dopamine receptor D2 (DRD2) was INS/DEL, which is associated with reduced efficacy and increased incidence of side effects with antipsychotics [5, 6]. calcium channel, voltage-dependent, L-type, alpha 1C subunit (CACNA1C) was A/A variant, which is a common variation associated with altered function of brain calcium channels [7], altered neuronal excitability, and possible mood instability. Cytochrome P450 2C19 (CYP2C19) was the Ultrarapid Metabolizer variant [8].

11.2.2 Assessment

This 35-year-old male has a genetic predisposition for mood disorders, likely accounting for much of his early age of onset and persistent symptoms despite the absence of a childhood trauma or maladaptive personality function. His genetic profile showing a variant of the serotonin transporter gene Solute carrier family 6 (neurotransmitter transporter), member 4 (*SLC6A4*) suggests suboptimal response to SSRI's. COMT Val/Val variant resulting in decreased frontal lobe dopamine may have contributed to his depressive symptomatology. His historically heavy use of alcohol likely hindered his recovery, and he remained at risk of full relapse if this was not addressed adequately. The patient's admission of weight gain and hyperphagia associated with his depression were reflected with his hyperlipidemia, which also adds a risk of cardiovascular morbidity if not addressed.

Patients with preexisting psychiatric conditions remain at risk of development of PTSD, and many service members with direct combat exposure will endorse some degree of PTSD symptomatology [9]. The presence of PTSD raises the risk of comorbid depression and certainly will hinder recovery from the depressive episode.

The constellation of alcohol dependence, major depressive disorder, and PTSD form a self-perpetuating cycle, where each condition reinforces the others. Therefore, a treatment plan was developed to account for all three of these conditions to maximize the chance of full psychiatric recovery.

11.3 Treatment/Management

Patient preference should figure into any treatment plan, and for this case, the patient had indicated a wish to receive non-pharmacologic treatment for his psychiatric symptoms. The patient was also not interested in receiving electroconvulsive therapy due to stigma and fears of cognitive impairment.

The decision was made to pursue TMS with an off-label pulse sequence to attempt amelioration of both depressive and PTSD symptoms. The decision to use TMS and the pulse sequence selected was based on existing literature and theoretic constructs for the neurophysiologic consequences of both depression and PTSD.

TMS uses a pulsed magnetic field to create neuronal action potentials within areas of the cerebral cortex [10]. Delivery of TMS incorporates several variables including the type of coil utilized, frequency of stimulus delivery, duration of pulse sequence, interstimulation rest periods, strength of the magnetic field delivery, total number of pulses delivered, and regularity of scheduled treatment delivery during the week [11].

11.3.1 Physics of Biological-Modulation

TMS device discharges a strong current through a coil, which produces a rapidly changing magnetic field, with lines of flux perpendicular to the coil's ion flow [12]. As this magnetic field changes with respect to the current in the coil, an electric field is induced that is proportional to the time rate of change of the magnetic field; yet, opposite in direction from the original current in the coil [12, 13]. Since the coil is adjacent to the scalp, and the neuronal tissue of the brain is electrically conductive, the electric field will stimulate a change in the flow of the ionic current [13]. This leads to modulation of the release of neurotransmitters of neurons affected by the induced field. This effect on those proximal neurons creates effects on the downstream neural networks [14]. The overall affect can have broad effects on neural function resulting from focal stimulation.

Both the target area and the power level of the induced-electric field are dependent on the shape of the coil. This allows variation in the field depth and spatial resolution [10]. There are numerous coil designs with corresponding variations of magnetic field production affecting area of spread and depth of penetration of the field.

Frequency of pulse delivery refers to the number of pulses delivered over time. While debate remains over the precise effects of different frequencies, the literature often denotes pulses delivered at less than 1 Hz as promoting long-term inhibition and pulses delivered at greater than 5 Hz as having long-term potentiating effects [11].

When magnetic pulses are delivered, they are typically delivered in trains. For example, a 10 Hz-frequency would be administered over 4 s, for a total of 40 pulses in that train. A rest interval occurs between trains to allow for restoration of the resting state. Higher-frequency stimulation, longer-train sequences, or shorter-recovery interval increases the risk of secondary generalization of the stimulation and subse-

quent induction of seizure activity. International guidelines exist for these parameters to ensure safe delivery of TMS [15].

The strength of the magnetic field affects the propensity to depolarize cortical neurons. Motor threshold is the amount of the magnetic field needed to depolarize cortical neurons in the primary motor cortex with subsequent contralateral muscle contraction. This level varies by individual and is affected by medications and substances that impact neuronal excitability. Treatments are often referred to as a percentage of this motor threshold. Sub- and supra-threshold stimulations may contribute to long-term inhibition or potentiation, though the impact when coupled with frequency remains ill defined.

The optimal number of pulses per session remains uncertain and likely varies depending on the intended treatment effect. The frequency of delivery also likely impacts the total number of pulses needed to start the cascade of events needed for long-term network changes. Up to 18,000 pulses per day have been administered, sixfold greater than the Food and Drug Administration (FDA) clearance for the figure-8 coil device, and yet was found to be safe and well tolerated [16]. Any treatment sequence also needs to consider the labor intensity to the patient and to the clinic providing care, and sequences that require hours per day are likely to be met with noncompliance and clinical impracticality. While depression is typically treated five times a week for 4–6 weeks, it is unclear if that intensity is needed for other conditions such as PTSD.

Considerations of clinical delivery factored into the pulse sequence that would be used for this patient. Without definitive guidance on a treatment paradigm, understanding the pathophysiology would help guide a TMS treatment program.

11.3.2 Pathophysiology of PTSD

TMS had been used as a diagnostic technique to measure brain GABAergic and glutamatergic tone using paired pulses, whereby a conditioning pulse is followed rapidly by a stimulating pulse. The interval between the two pulses will result in a motor threshold stimulation that is dependent on a gamma-aminobutyric acid (GABA) and glutamate tone reflected in short-latency intracortical inhibition and long-latency intracortical inhibition, respectively. Using these techniques, Rossi et al. (2009) reported that 20 drug-naïve patients with PTSD had reduced GABAergic tone in bilateral hemispheres and increased glutamatergic tone in the right hemisphere [17]. Kim et al. (2014) demonstrated reduced GABA levels in chronic unpredictable mild stress rat model brain extracts, and that TMS reversed these neurochemical changes. These findings suggest a possible pulse sequence model with stimulation of the left dorsolateral prefrontal cortex (DLPFC) and inhibition of the right DLPFC [18]. An excellent review by Karsen et al. (2014) identified the right DLPFC as a potential target for treatment with TMS, but there is a lack of consensus in the literature to clarify which frequencies and motor threshold intensities are optimal [19].

Given all of the factors cited above, the patient was offered treatment with TMS using a figure-8 iron core coil. Each session would involve first treating the left

DLPFC at 10 Hz and 120 % MT for 3500 pulses, in 4 s trains and 20 s intervals. This was followed immediately by right DLPFC stimulation at 1 Hz, 120 % MT, in 26 s trains, 4 s rest intervals, for 1500 pulses. The total treatment time was slightly more than an hour, offered five times a week for 6 weeks, followed by a tapering phase of three times a week in week 7, twice a week in week 8, and once in week 9. The goal was to increase activity of the left DLPFC, capitalizing on known antidepressant properties of this treatment location. The following inhibitory sequence at 1 Hz over the right DLPFC was prompted by data suggesting increase in glutamatergic tone in this area as well as some literature supporting this target as discussed previously.

The TMS pulse sequence described above was designed to address the patient's depressive and PTSD symptoms. However, without addressing his alcohol dependence, complete recovery was less certain. The patient's admission of ongoing alcohol cravings was addressed with a trial of naltrexone (25 mg each day for a week, followed by 50 mg each day). Baseline and follow-up liver function tests were ordered. The patient was instructed to obtain and wear a medical alert bracelet and carry a medical alert card in his wallet to identify his use of naltrexone for consideration in cases of emergency medical care and a requirement for opioid administration.

Additional treatments included encouragement to remain in therapy, utilizing a cognitive behavioral therapy technique. Often patients with chronic psychiatric symptoms experience new challenges when faced with recovery. The therapeutic benefit of psychotherapy, when combined with biologic interventions, can assist with acceptance of recovery and the impact this has on the patient's dynamic relationships and interface with life circumstances.

The patient was adamant about avoiding psychotropics for depression, so no further biologic treatment was recommended outside of his TMS pulse sequence. He was encouraged to make lifestyle changes, including total abstinence from alcohol, efforts to engage in social contact, increase cardiovascular activity to compliment his heavy weight training, and to balance work and leisure activities.

Risks and benefits of his treatment plan were reviewed and informed consent was obtained. The off-label nature of his TMS sequence was specifically discussed, including a lack of FDA clearance for PTSD and relatively unknown risks inherent with this specific sequence.

11.4 Discussion

11.4.1 Limitations of Current Therapies

Psychotherapy is a commonly recommended treatment; however, this modality requires skilled therapists who have specific training, which is often the limiting step in availability to patients [1] This patient had attempted exposure-based therapy, but like many he was unable to tolerate the escalation in anxiety that can occur during sessions.

Pharmacotherapy is often another option for treating depression, despite the risk of polypharmacy and potentially adverse side effects. The SSRIs sertraline and paroxetine have FDA approval for the treatment of adults with PTSD. This patient's genetic profile would suggest a propensity for greater adverse effects from this class of medications and less likelihood of achieving a timely and adequate response. Prazosin is another medication that is often used for the treatment of PTSD, particularly to target nightmares. Though it lacks FDA approval, there is mounting evidence for efficacy of not only sleep disturbance symptoms, but also daytime symptoms of PTSD. Effective doses require careful titration and patient compliance, and can be limited by orthostasis, syncope, somnolence, and sexual dysfunction. This patient's past experiences with medication negatively influenced his enthusiasm for further pharmacologic trials, though one could make a valid argument for a trial of prazosin.

Due to issues of limited efficacy of traditional therapies, other off-label strategies are often attempted, including mood stabilizers, benzodiazepines, antihistamines, and antipsychotics. These agents can have significant toxicity and data on effectiveness for core PTSD symptoms are underwhelming [20]. This patient's experience with off-label therapies mirrors the concerns for poor tolerability and lack of effectiveness.

Continued insistence on previously failed modalities is likely to be met with patient resentment, noncompliance, and ultimately disengagement from care. This may prompt the need for novel treatment options. Caution should be exercised; however, since desperation for symptom relief may influence patient consent for ineffective, expensive, and potentially dangerous unproven therapies. Preliminary research and modalities steeped in valid scientific framework should influence provider recommendations for patients who had not experienced adequate relief with traditional therapies. TMS is one therapy with a sound scientific basis, proven safety, and sufficient preliminary data to suggest efficacy for PTSD, as well as FDA clearance for the treatment of depression.

11.5 Outcomes/Resolution

Baseline scores on PCL-M and PHQ-9 were obtained on the day of his first treatment and were 60 and 24 respectively, suggesting severe symptom severity. At the TMS center, great effort is expended to create a pleasant treatment atmosphere. The architectural design was specifically created for an aesthetically pleasing tone. Staff members were hired with priorities given to technical mastery of the TMS device and interpersonal sophistication. From the start of treatment and throughout his course, the patient had great satisfaction with the experience, the impact of which should not be discounted.

The patient tolerated the TMS procedure well and was compliant with all appointments. He filled his prescription for naltrexone and abstained from alcohol use except for 1 day during the July 4th weekend. He attended all therapy appointments.

Over the course of treatment, the patient had a very steady decline in both his PCL-M and PHQ-9.At the conclusion of the tapering phase, his PCL-M had de-

creased to 31, which suggested that he no longer met criteria for PTSD. His PHQ-9 decreased to 9, which ranks in the mild severity range for depression.

The patient's subjective reports mirrored his objective rating scales. His PTSD symptoms had resolved and he was able to engage in crowds, interact in social situations, and had a sense of hopefulness for the future. He was able to abstain from drinking alcohol and wanted to continue the naltrexone to maximize his chances of remaining abstinent. Though there were some residual symptoms of depression, the patient was quite satisfied with his recovery and attributed much of his remaining depression to a grief reaction for the loss of a decade of his life to PTSD. He agreed to meet with a psychiatrist to fill his naltrexone, and was open to the idea of single psychopharmacologic maintenance therapy with considerations taken for his genetic profile report. He also agreed to continue seeing his therapist weekly.

11.6 Clinical Pearl

While TMS is undergoing preliminary clinical trials for PTSD, it should be included in the therapeutic armamentarium.

11.7 Conclusion

PTSD is a complex illness, often does not occur in isolation from other psychiatric morbidity, and often fails to remit with standard therapies. Brain stimulation with TMS offers a novel mechanism for the treatment of this condition with theoretical scientific underpinnings coupled with preliminary clinical trials, and may offer an alternative to methodologies that promote polypharmacy and systemic side effects. Any TMS treatment plan should be part of a comprehensive clinical program tailored to maximize recovery and is best implemented by providers familiar with the bevy of modalities available to assist patient recovery. Further study is needed to clarify how best to utilize TMS for conditions such as PTSD, but preliminary work is quite promising. Most importantly, for some patients this modality may pave the road to recovery and should be considered as a potential option when clinical conditions are appropriate.

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