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The role of Transcranial Magnetic Stimulation in the treatment of Treatment Resistant Depression

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PERMISSION

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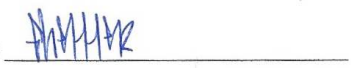
Signature 

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Abstract

C is a 62 year old married Caucasian women who has suffered from debilitating symptoms of depression and anxiety for over 40 years. Her depressive symptoms have been refractory to treatment despite adequate trials of sufficient length, and various pharmacological interventions. Patient has experienced periods of symptom remission from depression with past treatment with electroconvulsive treatment therapy. She is no longer willing to again pursue this treatment modality. Patient has lost hope that medications will effectively treat her current state of distress. Patient is interested in possible alternative treatment options.

Transcranial Magnetic Stimulation for management of treatment resistant depressive disorder (TRD) is supported by review of the literature. Research has concluded treatment efficacy in numerous studies involving treatment resistant depression. The plan of care for this case is supported by clinical evidence. TMS has demonstrated efficacy for symptoms of treatment resistant depression.

Clinical implications for mental health care professions include conduction and utilization of independent research. Clinical knowledge of transcranial magnetic stimulation should be a consideration for cases of treatment resistant depression. Clinicians should consider TMS as a safe and effective treatment intervention for individuals suffering from debilitating TRD.

Background

Major depressive disorder (MDD) is a common disabling and debilitating disorder affecting an estimated 10-15% of the population annually (Al-Haribi, 2012). This disorder is often associated with significant morbidity, disability, and reduction in overall quality of life (Abera, Tesfay, Dejene, Kerie, & Morankar, 2013). The treatment of MDD often classifies the outcomes of interest in regards to: response, remission, recovery, relapse and recurrence. Response is often considered the first goal of therapeutic treatment, and can be subdivided by magnitude and duration of symptom relief (Thase, 2011). Full remission described from the DSM-V includes no significant signs or symptoms of the disturbance present during the past two months (American Psychiatric Association, 2013). The specification of partial remission is described as, the presence of ongoing symptoms without meeting full criteria, or a period lasting less than two months in length without any significant major depressive episode symptomology following the end of an episode. The occurrence of remission is described as a period of two months or greater with either no symptoms or only one to two symptoms to no more than a mild degree (American Psychiatric Association, 2013). Depression has been recognized as a significant public health concern and one of the leading causes of disease burden worldwide. Remission has been adopted as the optimal treatment outcome of an episode of MDD.

An estimated 60-70% of these individuals diagnosed with MDD exhibit a positive treatment response to antidepressant medications. Clinically, 10-30% of depressed individuals endorse treatment resistant symptoms of depression as evidence by lack of remission after multiple medication trials (Al-Harbi, 2012). TRD defined as an episode of depression that has not responded to an adequate therapeutic medication trial including adequate dose, duration and treatment (Thase, 2011). Incomplete remission contributes to the increased risk of relapse,

increase in chronic depressive symptoms with reduction of time between episodes, impairment in vocational and social functioning and the increased risk of suicide (Thase, 2011).

The accuracy of diagnosis is imperative. Differential diagnosis and untreated medical conditions can appear similar to MDD. Subsequently, untreated medical conditions will not appropriately respond to treatment with pharmacology treatment modalities targeted for MDD.

Repetitive transcranial magnetic stimulation works by use of powerful, magnetic pulses inducing electrical currents in target regions within the brain. The pulses are delivered through an induction coil placed against the scalp over the pre-determined target area. Action potentials in the target region can be produced by a single rTMS pulse. The mechanism of neuroplasticity, the formation of new neural connections; is responsible for the changes in synaptic connections resulting from repeated trains of pulses. High frequency stimulation (5-20 Hz) is considered excitatory and (1-5 Hz) characterizing low frequency as inhibitory. Multiple sessions of repetitive transcranial magnetic stimulation over the course of several days, can result in lasting increases or decreases in the activity of the targeted brain regions. Consequently, repetitive transcranial magnetic stimulation can normalize the activity of brain regions that are either hyper or hypoactive occurring in major depressive disorder (Downar, Blumberger, & Daskalakis, 2016). The purpose of the report is to determine if current literature supports the clinical efficacy of transcranial magnetic stimulation for treatment and care of treatment resistant depression.

Case Report

C is a 62 year old Caucasian married women referred by her outpatient psychiatric provider for symptoms of depression and anxiety. She has been on a medical leave of absence following a panic attack that happened at work. Panic attack was triggered by her inability to

find a folder of documents needed for an upcoming meeting. She has a long history of depression and anxiety. She had been working with outpatient psychiatry for medication management, undergoing medication changes but continuing to decline with worsening symptoms. She had intermittently worked with an individual therapist to address symptoms of depression and anxiety. She continued to experience ongoing difficulty with focus and concentration despite prescribed stimulant medications. Problems with concentration are likely a result of her symptoms of depression and anxiety. She denied any current or past suicidal ideation or thoughts of other self- injurious behaviors. She has had one prior inpatient psychiatric hospitalization. ECT treatment in 1995 and 2011 were beneficial. She was hospitalized at Abbott Northwestern Hospital and underwent 8 rounds of bilateral electroconvulsive therapy (ECT) treatments in 2011. She reported numerous previous failed medication trials prior to ECT. Medications that were trialed included antidepressants, mood stabilizers and antipsychotic medications. She admits the ECT was helpful for symptom reduction. However, she is not interested in further ECT treatment stating “it was an inhumane experience”. She carries a diagnosis of Major Depressive Disorder recurrent severe with mixed features and Generalized Anxiety Disorder with panic attacks. She has been prescribed medications for ADHD inattentive type diagnosed by her outpatient Psychiatric provider with no formal testing conducted.

Anxiety manifested as crying, describes “black thinking,” feeling shaky, and feels she is shaking to the point of physical exhaustion. She admits to circular thinking and ruminative thoughts specifically about her medications. She becomes fixated on potential side effects of medications. She denied obsessive or compulsive behaviors. Denied history of trauma, physical, emotional, or sexual abuse or any specific symptoms of post traumatic stress disorder. Denied social or specific phobia.

She describes a long history of both depression and anxiety dating back to her freshman year of college. Prior episodes of severe depression have resulted in the need for ECT due to symptoms of treatment resistance. Depressive symptoms identified included tearfulness, overwhelming feelings of guilt, impaired focus and concentration, disrupted sleep, low mood, lack of motivation, low energy, chronic feelings of low self -worth and feelings of hopelessness. She denied any suicidal ideation or thoughts of self-harm. Denied any history of violent, aggressive behaviors, and denied homicidal ideation. Denied episodes of impulsivity, risk taking behaviors, elevated mood, decreased need for sleep, or increase in goal directed activities that support a history of hypomania or mania.

Previous attempts at psychiatric treatment include: inpatient hospitalization, electroconvulsive therapy, individual psychotherapy, and psychiatric medications. Past medication trials include selective serotonin reuptake inhibitors sertraline, paroxetine, fluoxetine, citalopram and escitalopram were ineffective. Serotonin norepinephrine reuptake inhibitors duloxetine and venlafaxine were ineffective. Norepinephrine dopamine reuptake inhibitors bupropion was ineffective. Alpha 2 agonists mirtazapine was ineffective. Tricyclic antidepressants including amitriptyline and nortriptyline resulted in ineffectiveness and intolerable side effects. Benzodiazepines lorazepam and clonazepam were ineffective. Antipsychotic medication trials of lurasidone and quetiapine were ineffective. Unsuccessful trials of anticonvulsant/mood stabilizing agents including lamotrigine and oxcarbazepine were ineffective in the management of symptoms of TRD.

Treatment goals included stabilization of psychiatric symptoms with potential pharmacological interventions coupled with intensive outpatient group and individual therapy.

Treatment strategies such as TMS will be considered to obtain symptom remission. Suicide risk assessments will be conducted to ensure patient safety.

Literature Review

A meta-analysis of randomized controlled trials over 2 decades conducted by Sehatzadeh et al. (2019), revealed approximately 35% of those with depression do not respond to 2 courses of adequate dose trials of antidepressant medications. TRD remains a significant clinical concern due to the chronic nature of the disease. MDD presents a substantial burden for patients, family members, society and the health care system (Sehatzadeh et al., 2019). Twenty-three studies met the inclusion criteria evaluating the efficacy of unilateral and bilateral repetitive transcranial magnetic stimulation (rTMS) in patients with unipolar TRD. Pooled remission and response rates for unilateral rTMS versus sham treatment were 16.0% and 25.1% for rTMS and 5.7% and 11.0% for sham treatment. The pooled remission and response rates for bilateral rTMS versus sham treatment were 16.6% and 25.4% for rTMS, and pooled remission and response rates for sham treatment were 2.0% and 6.8% respectively (Sehatzadeh et al., 2019). The Hamilton Rating Scale for Depression was utilized and the primary outcome was improvement in depression scores. Two independent review authors screened the studies and extracted the data. The study suggests that rTMS has moderate antidepressant effects with promising short term treatment of patients with unipolar TRD (Sehatzadeh et al., 2019).

A double-blind placebo-controlled trial by Fitzgerald, Brown, Marston et al. (2003) revealed treatment efficacy with both high-frequency left-sided repetitive transcranial magnetic stimulation (HFL-TMS) and Low-frequency stimulation to the right prefrontal cortex (LFR-TMS) in patients with treatment resistant MDD. Patients were diagnosed by the treating psychiatrist using DSM-IV criteria with either MDD or Bipolar disorder. The Montgomery-

Asberg Depression Rating Scale was the primary outcome measurement tool for the study. All study participants scored greater than 20 on the Montgomery-Asberg Depression Rating Scale (MADRS). Participants had also failed a minimum of two antidepressant trials of a minimum of six weeks in duration. There did not appear to be significant difference in efficacy between the two active TMS treatments. Repetitive TMS was noted to be generally well tolerated without associated major adverse events. The study conclusion noted reduction in mean MADRS scores within the two active treatment groups. The sham group showed minimal change on MADRS scores. In addition, there was a notable increase in the Global Assessment of Functioning scale scores between the two active groups, with no observed change in the sham group (Fitzgerald et al., 2003).

A controlled study by Avery et al. (2006) support the conclusions made by Fitzgerald, Brown, Marston et al., further indicating transcranial magnetic stimulation can produce clinically and statistically significant antidepressant effects in individuals suffering from TRD. Study participants with medication resistant depression were randomized to receive 15 treatments of repetitive active or sham TMS. Treatments were administered to the left dorsolateral prefrontal cortex. Treatment response was defined as a decrease in the Hamilton Depression Rating Scale of equal to or greater than 50% weeks one and two following the final TMS treatment. Remission was defined as a Hamilton Depression Rating Scale score of less than eight. The results of this study concluded a response rate from the TMS group to be 30.6% significantly greater than the 6.1% response rate of the sham group. TMS remission rate was 20% which was significantly greater than the sham group remission rate of 3%. The Hamilton Depression Rating Scale scores of the TMS group also showed a significantly greater decrease over time when compared with the sham group (Avery et al., 2006).

Meta-analyses have concluded the antidepressant properties of high-frequency repetitive transcranial magnetic stimulation when compared to sham rTMS. However the overall response and remission rates in Major Depression remain unclear. Berlim, Van Den Eynde, Tovar-Perdomo and Daskalakis further systematically and quantitatively assessed the efficacy of high frequency repetitive transcranial magnetic stimulation for the treatment of Major Depression based upon randomized, double-blind and sham-controlled trials. Data from twenty nine RCT's were included, totaling 1371 subjects all of which diagnosed with Major Depression. At the commencement of thirteen sessions of high-frequency repetitive transcranial magnetic stimulation 29.3% and 18.6% of subjects were classified as responders and remitters; compared with 10.4% and 5% of those receiving sham rTMS. Additionally, high frequency repetitive transcranial magnetic stimulation was found to be equally effective when utilized as an augmentation strategy or as monotherapy for Major Depression (Berlim, Van Den Eynde, Tovar-Perdomo, & Daskalakis, 2014).

A randomized controlled study conducted by Blomberg et al. (2016) further explored utilization of unilateral rTMS versus bilateral rTMS with remission rate as the primary outcome of interest. A total of 121 study participants were included within the study. The remission rate was significantly higher in the bilateral treatment group when compared to the sham group. Interestingly, the remission rate in the unilateral high-frequency left r TMS group was identified as intermediate and did not differ significantly from remission rating of the sequential bilateral rTMS or sham group (Blomberg et al., 2016).

A study of the long term efficacy of repetitive transcranial magnetic stimulation on depressive symptoms in individuals with drug-resistant major depressive disorder was conducted by Concerto et al. (2015). Study participants were required to be 40-65 years of age, drug

resistant MDD that had not responded to three different antidepressants from at least two different drug classes during the current episode. Additionally, a score greater than or equal to 20 points on the 21 item Hamilton Rating Scale for Depression, or a score of equal to or greater than 25 on the Montgomery-Asberg Depression Rating Scale. The study participants were divided into a test group and a sham group. Test participants received TMS performed five days per week for four consecutive weeks, occurring at the same time of day, conducted by the same operators and experimental conditions. The main finding of this randomized controlled perspective study concluded the effectiveness of repetitive TMS as an adjunct treatment with long lasting antidepressant properties for individuals presenting with drug resistant MDD (Concerto et al., 2015).

Further studies have been conducted to determine utilization of TMS maintenance as an effective alternative to electroconvulsive therapy maintenance treatment. TMS has been determined to be an efficacious and well-tolerated non-invasive treatment modality for MDD. Study participants were transitioned to treatment with transcranial magnetic stimulation due to either patient preference or noted adverse effects from electroconvulsive therapy. At time of transition all participants were either in full remission or had noted clinical response to electroconvulsive treatment for treatment of MDD. With a minimal mean frequency of one TMS treatment session every 3.5 weeks, all patients maintained or improved their clinical status as evidence by improvement in the Beck Depression Inventory score at both three and six months following TMS treatment. Final observation completed 7-23 months following completion of TMS, resulted in a further decrease of Beck Depression Inventory scores of 1-8 points supporting clinical stability. This case study concluded TMS to be an effective and well tolerated

substitution strategy for ECT maintenance (Cristancho, Helmer, Connolly, Cristancho, & O'Reardon, 2013).

Implications

Accurate diagnosis and identification of both major depressive disorder and treatment resistant depression is imperative to providing appropriate treatment referrals, education, and treatment modalities. The psychiatric nurse practitioner must remain knowledgeable and up to date on current research and novel treatment modalities for management of TRD. Patients should be given the opportunity to explore and discuss treatment opportunities beyond psychopharmacological options for acceptable care and treatment of symptoms.

The prevalence and significance of TRD remains an area of clinical concern. Morbidity and chronicity of TRD places a significant burden on patient's, their families and the health care system as a whole. Appropriate psychiatric diagnosis, with implementation of evidence based treatment modalities in response to accurate psychiatric diagnosis are important for improving the health and wellness outcomes of patients. A partnership between clinician and patient using a holistic clinical decision making approach to address individual clinical needs could help patients achieve comprehensive health and wellness outcomes.

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