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A Review of the Use of Transcranial Magnetic Stimulation in Psychiatric Disorders

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Abstract

Transcranial Magnetic Stimulation (TMS) is a minimally invasive brain stimulation technique that has been approved by the US Food and Drug Administration (FDA) in 2008 for treatment resistant depression and in 2018 for treating obsessive compulsive disorder. Over the past three decades, clinicians are beginning to use it for treatment of several psychiatric conditions, with ongoing evolving research for its potential diagnostic and therapeutic indications in a wider spectrum of medical and neuropsychiatric disorders. This review will summarize some of the potential utility of TMS as a diagnostic tool and its use in non - FDA approved indication for the treatment of depression during pregnancy, depression in the geriatric population, Schizophrenia, Bipolar disorder,Anxiety disorders, Posttraumatic stress disorder, Eating disorders, Tourette's syndrome,Attention deficit disorder, Conversion disorder, Autism spectrum disorder, Substance use and Addictive disorders,Borderline personality disorder and Mild cognitive impairment

Keywords: *Transcranial magnetic stimulation, repetitive transcranial magnetic stimulation, psychiatric disorders, review, diagnosis, treatment*

Prelude

Transcranial magnetic stimulation (TMS), or repetitive transcranial magnetic stimulation (rTMS), is a minimally invasive technique of brain stimulation where a changing magnetic field is used to induce an electric current at specified brain regions through electromagnetic currents. Depending on the equipment used an electric pulse generator, or a stimulator, is connected to a magnetic coil, which in turn is connected to the scalp. A changing electric current within the coil induces a magnetic field which then causes a second inductance of inverted electric charge within the brain itself [1]. In contrast to the direct application of electrical current, as in electroconvulsive therapy (ECT),the magnetic fields can easily cross the skull and penetrate the brain, then converting into electrical current that can interfere with and modulate cortical excitability, through mechanisms of long-term potentiation and long-term depression. These changes occur when TMS is delivered in the form of repeated sequences of stimuli or rTMS [2]. TMS has shown preliminary diagnostic and therapeutic potential in the treatment of several psychiatric disorders, with ongoing evolving research on exploring its utility as an alternative diagnostic and therapeutic intervention in a wide spectrum of psychiatric conditions.

Introduction

The basic concept of TMS involves the extracranial application of time-varying magnetic field generator, or "coil", which penetrates the skull in a painless manner and results in trans-synaptic excitation and inhibition of the principal output of the cortex pyramidal neurons. During the TMS procedure, the coil produces small electric currents in the region of the brain just under the coil via electromagnetic induction. A pulse generator, or stimulator, is connected to the coil and delivers the needed electric current [2]. Since

its FDA approval in 2008, for treatment resistant depression; the scientific and medical community had the opportunity to evaluate TMS and rTMS and found both methods to be relatively safe with minimal adverse effects [3]. The reported adverse effects of TMS include discomfort of scalp muscles, contraction or tingling of the jaw or the face during the procedure. Mild headaches or brief lightheadedness may result. Rare occurrence of syncope and even less commonly seizures [4]. Other adverse effects of TMS include transient induction of hypomania, transient cognitive changes, transient hearing loss, and transient impairment of working memory [3]. Certain populations, including adolescents, pregnant women, older adults and those with metal or electronic implants, require special consideration when implementing treatment protocols and courses. With adequate assessment and monitoring processes, TMS can be administered safely to most patients [4].

Diagnostic Potential of TMS

Due to TMS minimally invasive method of brain stimulation it has been used as a diagnostic tool for certain conditions. The TMS-induced motor evoked potential can be recorded using electromyography (EMG) from the contralateral muscle group corresponding to the region of primary motor cortex that is being stimulated. The physiological effect of TMS to other cortical regions can also be evaluated by combining TMS and electroencephalography (EEG) in measuring evoked potentials and other EEG-related indices of cortical activation [5]. These TMS properties have been used as an adjunctive tool in diagnosing strokes, multiple sclerosis, amyotrophic lateral sclerosis, movement disorders, motor neuron disease, other disorders affecting the facial and other cranial nerves and the spinal cord, mild traumatic brain injury and in detecting certain areas of the frontal cortex that are activated by visual imagery and information processing in Autism Spectrum Disorder and in differentiating Alzheimer's disease from mild cognitive impairment and in identifying certain brain regions that predispose the development of addiction and related disorders [5,6].

Therapeutic Potential of TMS

The FDA in 2008 approved TMS for treatment resistant depression, then in 2013 for treating pain associated with certain migraine headaches, and in 2018 for treating obsessive compulsive disorder. Over the past three decades,TMS has been used by some practicing psychiatrists and other mental health professionals as an adjunctive therapeutic intervention for, depression during pregnancy and depression in the geriatric population, Schizophrenia, Bipolar disorder, Anxiety disorders, Posttraumatic stress disorder, Eating disorders, Tourette's syndrome, Attention deficit disorder, Conversion disorder, Autism spectrum disorder, Substance use and Addictive disorders, Borderline personality disorder and Mild cognitive disorder.

The Use of TMS in Depression

Treatment Resistant Depression

Treatment resistant depression (TRD) is defined as the lack of response to two antidepressant trials, given in succession, at adequate doses and for an adequate time frame, in patients who have been adhering with the recommended treatment [7]. Major Depressive Disorder (MDD) is considered a severe and disabling condition with increased association with co-occurring medical and psychiatric disorders and increased mortality. In 2018, 17.7 million adults in the United States had at least one MDD episode, which represent 7.2% of the population [8]. The core symptom of MDS is low, or depressed mood, and or anhedonia, it is always accompanied by other symptoms such as irritability, disturbances in sleep, appetite, energy and cognitive functions. Approximately 50% of patients with MDD may not respond to psychotherapy and initial antidepressants treatment. Strategies for achieving remission in non-responders may include switching among various antidepressants, combination or augmentative therapies with different class of antidepressants, mood stabilizers, atypical antipsychotics and other agents. Many patients withdraw from these augmenting pharmacological interventions due to the potential occurrence of side effects, such as weight gain and sexual dysfunctions, which are also known to develop with long-term pharmacological treatment. It is also estimated that approximately 2% to 15% of all patients with MDD are refractory to pharmacological treatment [9]. For patients with TRD and for those who are refractory to psychopharmacological treatment, different treatment strategies include electroconvulsive therapy (ECT), TMS, deep brain stimulation (DBS), transcranial direct current stimulation (tDCS) and vagus nerve stimulation (VNS) could be implemented [10]. Among

these treatment modalities, prefrontal rTMS therapy repeated daily over 4-6 weeks (20-30 sessions) has been approved by the FDA in 2008 for treating TRD in adults. Most patients with TRD who initially responded to rTMS in the acute setting maintained a sustained response for a period of 1 year.

Depression during Pregnancy

Although certain antidepressants and ECT are the recommended treatments for pregnant women who develop moderate to severe depression. The relative safety and effectiveness of TMS could offer an alternative option for women who choose not to take antidepressants or to undergo ECT during their pregnancy [11]. It is not yet known if TMS is as effective as antidepressants or ECT in preventing the recurrence of depression during pregnancy and on whether it is effective in treating pregnant women with severe depression [6].

Depression in the Geriatric Population

Vascular depression (VD) is considered a subtype of late-life depression characterized by a distinct clinical presentation and an association with cerebrovascular disease. Although the term is commonly used in research settings [12], it has not been widely accepted and its distinct diagnostic criteria are still lacking. The recent 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) does not include VD among its diagnostic categories [13], which could limit the use of VD in clinical settings. Elderly patients with VD who developed poststroke depression and who were not appropriate candidates for either antidepressants or ECT treatment,showed a robust clinically significant effects to rTMS over sham[14]. However more studies are still needed before adopting TMS as an evidence based treatment for geriatric patients who develop VD.

Obsessive Compulsive Disorder

Obsessive compulsive disorder (OCD), is considered the fourth most common psychiatric illness in the US, affecting 2.2 million adults, or 1.0% of the U.S. population with an average onset age of 19, with 25% of cases occurring by age 14 and with one-third of affected adults first experiencing their symptoms in childhood [15].It is characterized by unreasonable thoughts and unwarranted obsessions, to perform repetitive behaviors, or compulsions[13]. Although most patients suffering from OCD understand that their obsessions and compulsions are unreasonable, they are unable to stop their behaviors without treatment. The recommended treatment of OCD includes psychopharmacological intervention with the serotonin-reuptake inhibitors (SSRIs) or cognitive behavior psychotherapy or both [16]. It has been estimated that 40% of patients do not respond to either treatment, thus requiring the development of alternative treatment strategies [16]. In 2018 the FDA approved the use of TMS as a new treatment option for OCD. The approval was based on data from a multicenter that randomized patients to the TMS or a sham device. Study patients who were receiving pharmacological therapy for OCD were maintained at their existing doses throughout the study. Researchers examined the reduction in patients' Yale-Brown Obsessive-Compulsive Scale (YBOCS) score which is a common measure of OCD severity. Results showed that 38% of patients responded to TMS versus 11% of patients who responded to the sham device; response was defined as >30% reduction in the YBOCS score [17]. In addition to TMS and rTMS, different brain stimulation techniques such as deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS) are promising alternative treatments of refractory OCD that could possibly lead to sustained remission of this severe disabling disorder, their standard methodology still needs to be established[17].

Schizophrenia

Schizophrenia is a serious and chronic psychiatric disorder which affects around 0.3–0.7% of the world population, or approximately 21 million people worldwide [18,19].Since the introduction of chlorpromazine in 1952, antipsychotic medications have been the mainstay of treatment for patients with schizophrenia. Many patients either do not respond to antipsychotic medications, or develop cumbersome adverse effects such as movement disorders, weight gain or metabolic syndrome, which could increase the risk of heart disease, strokes and type 2 diabetes [20]. Furthermore, approximately 30% of patients with schizophrenia are classified as having treatment-resistant schizophrenia (TRS), which is defined as a lack of clinical response to at least two trials of antipsychotic medication of adequate dose and duration [21]. Patients with TRS are usually treated with clozapine, which is subject to strict monitoring requirements because its association with serious side effects, such as neutropenia, agranulocytosis,

seizures, myocarditis and cardiomyopathy. Despite clozapine effectiveness in treating TRS and for reducing the risk of recurrent suicidal behavior in patients with schizophrenia, it may be contraindicated in certain patients with a previous hypersensitivity to its use, and for its potential interactions with so many other medications [22]. As a result, several non-pharmacological options including TMS have been used for the treatment of patients with schizophrenia who do not respond to antipsychotic medications. Many studies have reported beneficial effects of TMS and rTMS in reducing auditory hallucinations in patients with schizophrenia, though some of their effects may be short-lived, their mild side effect profile make them attractive options to treat schizophrenia and, more specifically in TRS [23-25].Due to the scarcity of large clinical trials, more research is needed to delineate TMS and rTMS effectiveness as sole or adjunct treatment agents for schizophrenia and especially TRS.

Bipolar Disorder

According to The World Health Organization, bipolar disorder is one of the top three causes of hospitalization in people aged 15-44 and, it is estimated that 5% of the world's population is affected by this type of mood disorder [26]. Many patients with bipolar disorder may not benefit from various pharmacological interventions, necessitating alternative treatment options that will enable mood stabilization and symptoms remission. Clinical trials of TMS suggest the potential of rTMS in reducing the depressive symptoms of bipolar disorder but have yielded more mixed findings for the treatment of mania and other phases of the bipolar illness with most of the current studies showing lack of benefit over sham [27]. The use of TMS in bipolar disorder have raised clinical concerns about the possibility that it could induce treatment-emergent mania/hypomania (TEM). Although rTMS treatment carries a slight risk of TEM, it is not statistically higher than that associated with sham treatment [28].

Anxiety Disorders

Anxiety disorders rank among the most frequent psychiatric disorders and although there are many psychotherapeutic and psychopharmacological interventions that are effective in treating the many types of anxiety disorders, a considerable number of patients do not respond to these interventions. Currently there is inconclusive evidence to suggest the efficacy of TMS for the treatment of anxiety disorders [27]. While many experts speculate that various TMS parameters could benefit individuals with anxiety, these parameters have not been fully investigated. In addition, some studies have suggested that the therapeutic anxiolytic effects derived from TMS are likely to be transient. While anecdotal reports and open studies have documented the role of rTMS in treating generalized anxiety disorder, social anxiety disorder and panic disorder, they have varied greatly in terms of rTMS administration, have not shown to be superior to placebo. Therefore, to date, there is no convincing evidence for the clinical role of rTMS in anxiety disorders. Further research is needed, drawing on advances in understanding the pathological neurocircuitry in anxiety disorders and the mechanisms of action by which rTMS may alter that neurocircuitry [29].

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a significant public health problem with a reported lifetime prevalence rate of 6.4% to 7.8% [30]. Clinical guidelines support evidence-based psychotherapies such as prolonged exposure and cognitive processing therapy as first-line treatments for PTSD [31]. However, reviews of randomized clinical trials for military-related PTSD demonstrated that although these therapies do result in meaningful improvement in patients with PTSD, approximately two-thirds of patients do not experience remission of symptoms and enduring ongoing suffering and disability [32]. Thus, new treatment approaches are critically needed to improve treatment outcomes. Case series, open trials, and randomized controlled studies have demonstrated preliminary support for treating PTSD with rTMS alone or combined with psychotherapy [27]. However, the level of evidence is not enough to currently recommend rTMS specifically for PTSD. Future work involving randomized controlled trials of rTMS for PTSD with adequate sample sizes will be required to demonstrate its effectiveness. Understanding the mechanism of action of rTMS for PTSD would dramatically help clinicians in recommending this treatment intervention for those patients who continue to suffer despite adequate psychotherapeutic and pharmacological interventions.

Eating Disorders

Eating disorders (EDs) are serious psychiatric disorders and include Anorexia nervosa (AN), bulimia nervosa (BN) and Binge eating disorder (BED).These disorders are characterized by abnormal eating or weight-control behaviors that are most often, chronic and relapsing, with a deteriorating impact on patients' physical, mental health and life expectancy [33]. Patients with AN have a significantly low body weight for height, age, and developmental stage, associated with unjustified and intense fear of gaining weight despite obvious thinness, and extreme behaviors designed to lose weight, such as food restriction with or without induced vomiting, or use of laxatives. In AN there is an observable extreme and marked weight loss and pathological thinness. In BN and BED there are recurrent episodes of binge eating and loss of personal control over binging. Individuals with BN counteract binge eating with compensatory behaviors such as, induced vomiting, or use of laxatives to prevent weight gain, whereas individuals with BED do not display or indulge in recurrent compensatory behaviors. Quality of life of patients and their families are impaired and adversely affected by EDs and the disorders are associated with increased and mortality and morbidity healthcare costs [34]. The treatment of EDs remain and a difficult clinical issue and few psychotherapeutic and pharmacological treatments have shown to be effective and long lasting and thus the development of alternative therapeutic strategies is of paramount clinical importance [35]. Studies have shown that reduction of craving and consumption in individuals with excessive eating behaviors could be achieved with rTMS [36], and the application of rTMS can reliably reduce food cravings in single and multi-sessions format, particularly in relation to BN, and BED but it is less clear for AN [37]. Despite these few studies, many more randomized controlled trials are still needed to confirm the use of TMS as a standard and safe treatment of EDs which will usher a major source of hope for the crucial development of alternative interventions for these challenging psychiatric disorders.

Tourette's Syndrome

Tourette's syndrome disorder (TS) also referred to as Tourette's disorder, is a developmental neuropsychiatric disorder characterized by a childhood onset, with male predominance, which often persists into the adolescent and adult years and is clinically defined by the presence of impairing motor tics, and at least one vocal tic occurring for over 12 months [13]. It frequently co-occurs with attention deficit hyperactivity disorder, OCD, autism spectrum disorder traits, learning difficulties, and sensory integration disorders [37]. The clinical management of TS usually focus on treating the co-occurring medical and psychiatric conditions to decrease the daily challenges and difficulties of this disorder. Standard pharmacotherapy and psychotherapy treatments have continued to be limited in providing a long-lasting relief of the devasting emotional and social effects of TS [37]. Several studies have documented that the application of rTMS to the supplementary motor area (SMA) have yielded promising therapeutic effects in TS [37,38]. The use of low-frequency rTMS was also found to improve tics and OCD symptoms in patients with severe TS-OCD which was substantially maintained over a period of 3 months follow-up [39].The safety of deep rTMS for TS has also been established in other studies which highlight the importance of treating TS separately when it occurs with OCD [40]. However, a randomized double-blind sham-controlled trial did not demonstrate efficacy of SMA-targeted low frequency rTMS in the treatment of severe adult TS, thus warranting further studies using longer or alternative stimulation protocols [41].

Attention Deficit Hyperactivity Disorder

According to DSM-5, Attention deficit hyperactivity disorder (ADHD) is classified as a lifelong disorder with the condition of onset before the 12th year of life [13]. In addition, heredity is as high as 75% for ADHD symptoms [42]. Like many neuropsychiatric disorders, ADHD could result from the complex interplay of genetic and environmental factors and thus, preferably described, as a neurodevelopmental disorder [43]. Although the typical symptoms of childhood ADHD of inattention, hyperactivity, and impulsivity, are usually partially modified during the lifespan. In adulthood, the feelings of internal restlessness, disorganization, lack of restrain, behavioral difficulties and impaired executive functions, seem to persist and prevail, and adversely impacting daily functioning, productivity, educational and vocational achievements [44]. Studies suggest that rTMS is a well-tolerated treatment in patients with ADHD and can be a potentially useful therapeutic intervention for reducing ADHD symptoms

including impulsivity, motor hyperactivity, and reduced attention. Available studies differ substantially in both rTMS cortical targets and stimulation protocols. Most studies suggest right brain stimulation with high frequency rTMS; while other protocols suggest low frequency rTMS over the SMA. At this time double-blind randomized controlled studies with enough sample sizes to confirm the evidence base for rTMS treatment in ADHD patients are crucially needed.

Conversion Disorder

The psychological mechanism for conversion disorder is assumed to be subconscious and thus differentiating it from consciously generated ('feigned' or 'malingered') symptoms, although the demonstration of this difference is often practically difficult in average clinical settings [45]. Neuroimaging and neurophysiological studies largely support this differentiation and could provide some insights into the possible etiological mechanisms of this disorder[46]. There is a conspicuous paucity of evidence-based treatments for conversion disorder and most clinicians initiate treatments which combine cognitive behavioral therapy, social support and medications for co-occurring medical and or psychiatric conditions [47]. Preliminary studies suggest that rTMS may be useful for treating weakness or movement disorder related to a conversion disorder [48]. Some patients with 3 years duration of a conversion disorder,who received rTMS, did experience remission of their conversion disorder symptoms [49].Despite this reported promising result, more research is indicated to confirm whether rTMS is a useful adjunct to other treatments in conversion disorder and whether its benefit is due to changing illness beliefs in the patient, rather than being a result of its therapeutic effects [48].

Autism Spectrum Disorders

The Centers for Disease Control and Prevention currently estimate the prevalence of Autism Spectrum Disorder (ASD) in the United States at 1 in 88 children which would translate to 1 in 54 boys and 1 in 252 girls [50]. These alarming data suggest that there are more children that are affected by ASD than those affected by diabetes, AIDS, cancer, cerebral palsy, cystic fibrosis, muscular dystrophy and Down syndrome combined! Most empirically supported treatments for the core symptoms of ASD focus on early intensive behavioral interventions [51]. The pharmacological treatment can be effective in the treatment of ASD secondary features and co-occurring disorders, such as aggression, ADHD, or seizures [52]. There is currently no effective FDA approved medications to treat the core symptoms of ASD of social communication impairments and restricted patterns of behavior [53], except for the atypical second generation antipsychotic medications,aripiprazole and risperidone which are for the treatment of irritability in youth with ASD.The tremendous clinical, social and financial burdens of ASD are in dire need for valid and reliable diagnostic tools and effective treatments that target the debilitating symptoms of this condition. Many researchers and clinicians have used TMS for both its diagnostic and therapeutic potential in ASD [5,6]. Though preliminary data suggest potential benefits of using TMS in ASD, its evidence base is still lacking and does not yet conclusively support a clinical widespread use of TMS in the diagnosis or the treatment of ASD [54].

Substance Use and Addictive Disorders

Addiction and related disorders are devastating with their tremendous social, psychological, and physical consequences. These disorders are considered chronic and relapsing illness with significant economical and medical burden on society and are also characterized by the limited effectiveness of currently available treatment options [55]. A comprehensive understanding of the effects of addiction on altering the brain's chemical, neuronal, and regional networks could lead to the implementation of tailored and individualized more effective treatment interventions. The minimally invasive nature of TMS makes it an appropriate procedure in the field of addiction by providing new insights into neurochemical and neural circuit changes that occur as a result of illicit substance use and it could facilitate the understanding of the role that various brain regions play in modulating cognitive functions, such as drug craving, risky decision making, inhibitory control and executive functions to obtain specific treatment outcomes[5,6,56]. There are reports suggesting that TMS may have a role in the treatment of alcohol use disorder [57], tobacco use disorder [58], and in reducing cigarette consumption in patients with schizophrenia[59].Patients with opioids use disorders could also benefit from rTMS [60].Gambling disorder (GD) which shares pathophysiological and clinical features with substance use disorders, also continues to lack effective therapeutic interventions.

In that context the minimally invasive nature of TMS, could represent a promising treatment option for GD [61]. In spite of TMS emerging therapeutic option for addiction and related disorders, the major important methodological limitations and dearth of knowledge about its precise mechanism of action in these multifactorial disorders, need to be addressed in more randomized trials studies before its wide utilization in regularly diagnosing and treating these disorders.

Borderline Personality Disorder

According to DSM-5, Borderline Personality Disorder (BPD) is characterized by a pervasive pattern of instability in affect regulation and interpersonal relationships, self-image, and marked impulsivity that begins by early adulthood and is present in a variety of contexts [13]. Patients with BPD also have a high mortality risk due to suicidal behaviors with 10% completing suicide which, is almost 50 times higher than the general population [62]. The severity of BPD symptoms reduces patients' quality of life and impair their psychosocial, educational and vocational functioning [63]. One of the core elements in patients with BDP is impaired emotional vulnerability, processing and impulsivity which are often characterized by marked sensitivity to emotional stimuli and is expressed in dangerous and self- destructive behaviors. These core elements of BPD are difficult to treat and are usually resistant to psychotherapeutic and pharmacological interventions [64]. Some studies suggest that rTMS could potentially be highly effective in reducing symptoms of impulsivity and emotion regulation in patients with BPD [65]. Despite these reported encouraging outcomes, there is still a lack of double-blind randomized controlled studies with enough sample sizes that directly compare different stimulation protocols, and the duration of TMS therapeutic effects in treating patients with BPD.

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is usually described in the literature as an intermediary status between normal aging and early manifestation of dementia. Individuals with MCI often report subjective cognitive deficits with clinical findings confirming objective memory impairment, without a marked effect on daily activities [66]. Considering the increasing evidence that disease-modifying treatments for Alzheimer's disease (AD) must be administered early in the course of the disease, the development of diagnostic tools capable of accurately identifying AD at its early disease stages has become a crucial target, and in that context,TMS could be used as an effective tool to discriminate between different forms of neurodegenerative dementia and in the early identification of MCI [67]. Additionally, some preliminary findings have suggested that rTMS can enhance performances on several cognitive functions impaired in AD and MCI [68]. However, further well-controlled studies with appropriate methodology in larger patient cohorts are needed to replicate and extend the initial findings.

Summary and Conclusion

The potential role of TMS in treating various psychiatric disorders has been expanding, especially in the past three decades. Currently TMS is only FDA approved for treatment resistant depression and OCD. The use of TMS as an alternative minimally invasive therapy for most psychiatric disorders is still controversial and not widely accepted in psychiatric practice, due to the lack of adequate randomized placebo controlled studies with appropriate methodology in larger patients population to replicate and extend preliminary and anecdotal case findings. The purpose of this review was to provide a summary of the preliminary findings in the context of using TMS for the treatment of, depression during pregnancy and in the geriatric population, OCD, Schizophrenia, Bipolar disorder, Anxiety disorders, PTSD, EDs, TS,ADHD, Conversion disorder, ASD, Substance use and Addictive disorders, BPD and MCI. It is hoped that this review, would provide practicing clinicians with sufficient findings to trigger their interest in exploring the utility of TMS in managing patients who continue to experience disabling psychiatric symptoms and who have not responded to adequate and comprehensive trials of standard approved and evidence based psychotherapeutic and pharmacological treatment interventions. The use of TMS for non-FDA approved indications should not be routinely introduced as a first line treatment. Informed consent with detailed clarification of potential benefits, risks and costs are also necessary quality assurance measures that should be implemented in the clinical settings whenever and wherever this intervention in administered.

Disclaimer

The Views described in this manuscript are those of the author and do not reflect the official policy of the Sacramento VA Medical Center, or The Department of Veterans Affairs, or UC Davis Health.

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