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REVIEW

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Transcranial Magnetic Stimulation Treatment for Smoking Cessation: An Introduction for Primary Care Clinicians

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ABSTRACT

Tobacco use remains the number one preventable cause of death in the United States, resulting in significant public health and economic costs. Despite progress in reducing tobacco use through pharmacotherapy and psychotherapy smoking cessation interventions, additional treatment options are still needed to improve treatment effectiveness. As an adjunctive treatment, the US Food and Drug Administration recently cleared transcranial magnetic stimulation (TMS), a noninvasive brain stimulation technique, as an aid for smoking cessation in adults. Given that most smoking cessation interventions occur in the primary care setting, this article aims to introduce TMS, to provide an overview of the evidence of TMS for smoking cessation, and to outline the procedures for implementing TMS in the primary care setting when referral to an interventional psychiatrist is not possible. With growing scientific evidence and increasing regulatory approval of TMS for smoking cessation, this novel treatment option is now available for patients who want to quit smoking but have been unsuccessful with pharmacologic approaches.

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KEYWORDS: Addiction; Smoking cessation; TMS; Tobacco; Transcranial magnetic stimulation

BACKGROUND ON TOBACCO USE DISORDER

Smoking contributes to 480,000 deaths per year in the United States and 7 million worldwide, making it the leading preventable cause of death and disease in the world.[1] In addition to negative public health consequences, tobacco smoking results in a substantial economic burden. In the United States alone, $170 billion is spent on direct medical care related to smoking and $160 billion is lost in productivity each year.[2]

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) recognizes smoking addiction as tobacco use disorder and characterizes it as "a problematic pattern of tobacco use leading to clinically significant impairment or distress" over a 12-month period.[3] Nicotine is the psychoactive ingredient in tobacco that binds to the alpha-4-beta-2 nicotinic cholinergic receptor, resulting in the release of dopamine and other neurotransmitters underlying reward processing in the brain. Neuroadaptation

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occurs with repeated nicotine exposure, resulting in tolerance and a withdrawal syndrome when a smoker tries to quit, which may include irritability, cravings, nausea, and dizziness, among other symptoms.[4]

Due to the presence of nicotine in tobacco products, individuals who smoke find it challenging to quit. In 2015, 68.0% of adult smokers in the United States reported a desire to quit smoking, and yet, only 7.5% were successful in this endeavor.[5] The rate of quitting remains low despite US Food and Drug Administration (FDA) clearance of several methods for aiding in smoking cessation. For example, current pharmacologic treatment options, including nicotine replacement therapy and varenicline (a partial agonist at the nicotinic acetylcholine receptor), result in 6-month abstinence rates of 19% and 33.2%, respectively.[6] Given the health burden of tobacco use and low success rates of approved treatments, there is a critical need to develop more effective treatment.

CLINICAL SIGNIFICANCE

- Tobacco smoking continues to be the top preventable cause of death.
- Smoking cessation interventions include pharmacotherapy, psychotherapy, and most recently, neuromodulation.
- Transcranial magnetic stimulation (TMS) uses powerful electromagnetics to non-invasively activate the brain and modulate neural circuitry.
- Evidence supporting TMS for smoking cessation includes a multi-center, industry-sponsored, randomized clinical trial comparing active vs sham high-frequency TMS over the lateral prefrontal cortex and insula bilaterally.
- Integrating TMS for smoking cessation into primary care practices has the potential to positively impact health outcomes.

WHAT IS TRANSCRANIAL MAGNETIC STIMULATION (TMS)?

One method that has emerged as a promising treatment for tobacco use disorder is transcranial magnetic stimulation (TMS). As a non-invasive brain stimulation modality, TMS allows for modulation of underlying neural activity through the application of time-varying electromagnetic fields. A TMS coil is placed against an individual's head (see Figure, A) and brief electromagnetic pulses (~4 ms) within the coil create small electric currents in the brain via electromagnetic induction, decreasing cortical excitability at lower stimulation frequencies (<1 Hz) and increased excitability at higher frequencies (>5 Hz).[7]

A typical TMS intervention begins with calibration of the TMS stimulation intensity by determining the resting motor threshold (rMT) for the individual. rMT is assessed by stimulating the motor cortex, which causes a contraction of the contralateral hand muscles that can be visually observed or measured using electromyography (Figure, B). The minimal machine output that results in either a visually observed muscle twitch or measured electromyographic response (>50 μV peak-to-peak) on half of the pulses is defined as the rMT. Subsequent treatment is then calibrated based on this intensity, allowing for individualization of TMS dose based on cortical excitability.

While the first clinical use of TMS was as a diagnostic measure for neuromotor disorders, the technique has since gained approval for several psychiatric and neurological conditions. Following successful findings in multicenter, randomized controlled trials in the early 2000s, repetitive TMS was approved by the FDA as a treatment modality for major depressive disorder in 2008. Under this indication, TMS is approved for "treatment-resistant" patients who have failed to respond to at least one antidepressant medication. Subsequently, TMS was approved for the treatment of other brain-based disorders, including migraine headaches in 2013 and obsessive-compulsive disorder in 2018. Because TMS can modulate circuit-level function in the superficial cortex (within about 3 cm of the scalp) and connectivity with deeper limbic areas, this approach has potential for continued development across a range of neuropsychiatric indications, including Parkinson Disease,[8] epilepsy,[9] posttraumatic stress disorder,[10] and Alzheimer disease.[11]

EVIDENCE OF TMS FOR SMOKING CESSATION

Prior to the pivotal, industry-sponsored trial that resulted in FDA approval of TMS for smoking cessation in 2020, there were numerous early studies of therapeutic TMS to improve smoking cessation outcomes. These studies largely focused on modulating activity of brain regions associated with the pathophysiology of smoking addiction, such as the dorsolateral prefrontal cortex and insular cortex. Using primarily 10-Hz protocols,[12-16] but also 1-Hz,[17] 20-Hz,[18,19] intermittent theta-burst,[20] or multifrequency[21] protocols, these studies reported largely positive impacts on cravings, tobacco use, and smoking abstinence rates (reviewed in Hauer et al).[22] Stimulation of these cortical targets is thought to modulate mesolimbic and mesostriatal dopaminergic structures implicated in tobacco use disorder, a mechanism that also has implications for treatment in a wide range of addiction disorders (see Hanlon et al[23] for review of TMS for addiction treatment).

The promising results of these prior studies led to a pivotal, multicenter, industry-sponsored trial evaluating the BrainsWay H4 TMS system for smoking cessation (see Figure, C). This prospective, double-blind, randomized sham-controlled trial (ClinicalTrials.gov #NCT02126124) recruited at 12 sites in the United States and 2 sites in Israel from 2014 to 2019. Enrolled subjects (n = 262) were randomized 1:1 into active or sham groups. Inclusion criteria included ages 22 to 70 years old, chronic and heavy smokers (>10 cigarettes/day for >1 year) meeting DSM-5

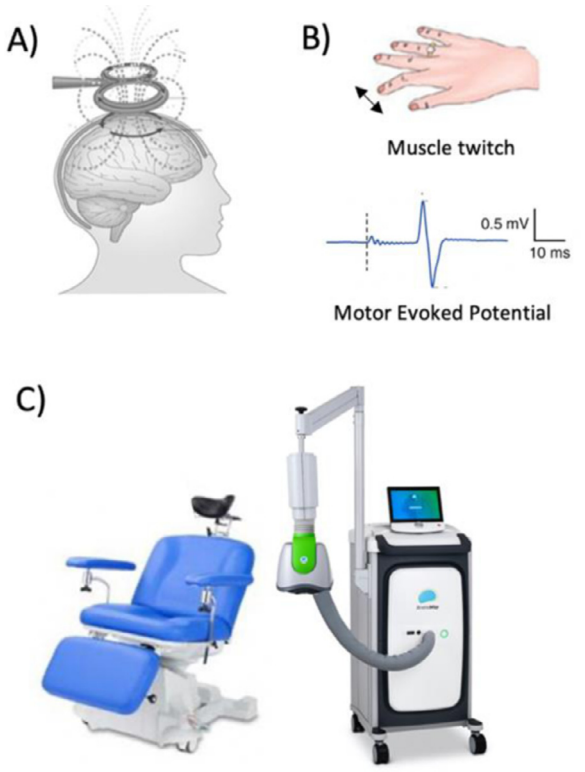

Figure **(A)** Illustration of transcranial magnetic stimulation (TMS) magnetic field in the head. **(B)** Visual detection of muscle twitch and motor-evoked potential used for establishing resting motor threshold. **(C)** BrainsWay TMS System including H4-coil, Magstim TMS stimulator, and treatment chair.

criteria for tobacco use disorder without a period of abstinence >3 months in the past year, "very likely" or "somewhat likely" motivated to quit, and without concerns on the TMS safety screening. Exclusion criteria included current smoking cessation treatment, active current psychiatric/neurological diagnosis, or substance use disorder diagnosis other than tobacco in the past 12 months, taking psychotropic medications, and safety concerns including seizure risk or metal in the head.

This pivotal trial utilized a Magstim (Plymouth, MN) TMS stimulator equipped with a BrainsWay H4-coil (Burlington, MA). The treatment dose was calibrated according to rMT of the right abductor pollicis brevis muscle, with treatment delivered 6 cm anterior to the rMT hotspot. Stimulation parameters were 120% rMT, 60 repetitive TMS trains of 30 pulses each (1800 pulses total), applied at 10 Hz in 3-second trains with 15-second inter-train intervals. Importantly, each TMS session was preceded by a 5-minute provocation procedure that induced cravings for nicotine; subjects were asked to recall their largest trigger for smoking, listen to an audio recording about handling a cigarette and a lighter, and view images of smoking. Each session included 18 minutes of repetitive TMS (rTMS), provided 5 days per week for 3 weeks and then once weekly for 3 weeks. Every TMS treatment was followed by 2 minutes of motivational dialogue to encourage smoking cessation. Participants randomized to the blinded control condition received sham TMS through a separate coil built into the helmet, which produced similar acoustic and scalp sensations but without stimulation strong enough to activate neural tissue. Clinical outcomes included acute 4-week continuous quit rates (CQR), prolonged abstinence rates at short- and long-term (4 month) follow-ups, and changes in cigarette consumption and cravings. Weekly abstinence was self-reported and biochemically verified using urine cotinine levels (<200 ng/mL).

The results of this trial demonstrated a significantly higher CQR of 28% in the active TMS treatment group vs 11.7% in the sham treatment group for subjects who completed 4 weeks of treatment (P = .0063). Intent-to-treat analysis (including subjects who dropped out of the study) found a CQR of 17.1% in the active group and 7.9% in controls. Using diary records, the study found that participants who received active TMS smoked significantly fewer cigarettes per day compared with sham (P = .0311). Safety outcomes were consistent with prior TMS smoking cessation trials, with no reported seizures, and headache as the most common adverse event, although this did not differ significantly between groups.

As the first large multicenter randomized controlled trial on TMS for a substance use disorder, this trial demonstrated safety and efficacy of daily high-frequency rTMS over the lateral prefrontal cortex and insula during the induction of nicotine craving. Based on these data, the FDA granted 510 (k) clearance in August 2020 for the BrainsWay H4 TMS coil as an aid in short-term smoking cessation in adults.[24]

HOW CAN PRIMARY CARE BENEFIT FROM RECOMMENDING PATIENTS FOR TMS?

Comprehensive primary care includes preventative interventions that aim to reduce the risk of poor health outcomes. Given the clear cardiovascular, pulmonary, and cancer-related health outcomes associated with smoking, reducing smoking is of paramount importance. Patients who smoke should be offered all available smoking cessation interventions. While the US Preventative Services Task Force has already recommended the use of behavioral interventions and pharmacotherapy for smoking cessation, the recent FDA clearance of TMS now provides primary care physicians another treatment approach to offer patients. Given the limited efficacy of pharmacotherapy and psychotherapy, the addition of TMS could make a substantial impact on patient health.

INTEGRATING TMS INTO CLINICAL PRACTICE

The evaluation of patient appropriateness and clinical administration of TMS requires an understanding of risks, benefits, and alternatives. Adequate evaluation includes an assessment for contraindications for TMS, including history of epilepsy or seizures and metallic foreign objects in the

Table Procedures for Providing TMS for Smoking Cessation

1. Safety clearance and monitoring (e.g., TMS Adult Safety Screen)
2. Resting motor threshold determination at the optimal position ("hot spot") to activate the right abductor pollicis brevis muscle
3. Treatment
   - BrainsWay TMS coil aligned symmetrically and moved 6 cm anteriorly
   - Cravings provocation with smoking cues for 5 minutes prior to TMS
   - Parameters: stimulator output 120% rMT; 60 trains of 30 pulses at 10 Hz
   - Motivational language provided for 2 minutes following TMS
   - Daily treatment, 5 days a week, for 3 weeks, followed by one weekly treatment for 3 weeks

rMT = resting motor threshold; TMS = transcranial magnetic stimulation.

head (see[25] for safety guidelines). Patient preference should also be considered, as some patients may prefer a procedural intervention as opposed to medication or counseling. While FDA clearance of rTMS for smoking cessation is based on a schedule occurring 5 days per week, for at least 3 weeks (see the **Table** for TMS procedures), treatment is provided on an outpatient basis, without anesthesia, so patients can drive to and from appointments, making it a relatively accessible option for many.

Practice management costs must also be considered. To integrate TMS into a clinical practice, clinicians should expect to incur startup costs, which include the cost to purchase or rent a TMS device, additional equipment (eg, treatment chair), and salaries for staff providing treatment. Physicians must also be adequately trained and credentialed to administer TMS, including calibration steps to properly dose treatments, as well as how to respond to emergencies (e.g., seizure management). Alternatively, primary care physicians may collaborate with and refer patients to interventional psychiatrists who offer TMS therapy for psychiatric indications.

CONCLUSIONS

Despite public health and policy advances, FDA-cleared medications, and psychotherapy options, many Americans continue to smoke and struggle with quitting. With the recent clearance of TMS for the treatment of tobacco use disorder, clinicians now have the option to utilize noninvasive brain stimulation to directly modulate the neural circuits that contribute to this disorder. Primary care doctors seeking to expand clinical procedures may now offer TMS in their outpatient offices or refer patients to interventional psychiatrists who already provide TMS for other indications. Clinically integrating TMS in the primary care setting will enhance patients' ability to quit smoking and ultimately improve the health care outcomes.

RECOMMENDED RESOURCES

Resources for additional training on TMS include consensus safety guidelines (e.g., Rossi et al.[25]), medical associations such as the Clinical TMS Society, and academic institutions that provide hands-on training, such as the Duke Fellowship on TMS. In addition, the websites of the following organizations provide useful information: US FDA, BrainsWay (the manufacturer of the first TMS device cleared for smoking cessation),and Neuromodec (a free listing on neuromodulation events, jobs, news, and service providers).

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