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Practitioner's Corner

Transcranial Magnetic Stimulation: A Clinical Primer for Nonexperts

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Transcranial magnetic stimulation (TMS) is a safe and effective therapeutic modality for a rapidly expanding range of neuropsychiatric indications. Among psychiatric conditions, it is presently approved by the US Food and Drug Administration for treatment-resistant unipolar major depressive disorder and obsessive-compulsive disorder, 2 highly prevalent conditions with a considerable public health impact. There is also mounting evidence for its clinical utility in numerous other neuropsychiatric conditions. Nonetheless, many mental health providers, as well as primary care and other providers, remain unfamiliar with its clinical use. In this primer, we seek to describe in nontechnical terms how the magnetic field is applied to the brain, the unmet needs that may be remediated with TMS, the present state of evidence for clinical effectiveness, particularly in major depressive disorder, the safety profile of TMS, what patients experience during TMS, and some recent developments that serve to advance the use of this still novel intervention. TMS is poised to assume an important place in the armamentarium of interventions to better serve our patients, especially those with serious, chronic conditions with high rates of resistance to more conventional treatments. Consequently, it is essential that mental health providers gain as adequate a working knowledge of device-based interventions such as TMS as they currently have of psychopharmacological and psychosocial interventions. Among other potential benefits, this information should aid the process of obtaining informed consent from patients who are candidates for these treatments.

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WHAT IS TRANSCRANICAL MAGNETIC STIMULATION (TMS)?

TMS is a relatively new treatment approved for several neuropsychiatric conditions. It uses a pulsed, rapidly changing magnetic field produced by the electrical current running through a coil housed in a metal box. The magnetic field is applied to the head at roughly the same magnetic field strength as used in a magnetic resonance imaging scanner. The magnetic field penetrates the brain and induces very small electric currents in the brain tissue, to safely and effectively modulate the function of brain circuits to remediate clinical symptoms. Unlike in electroconvulsive therapy, no electric current is directly administered to the patient.

FOR WHAT CONDITIONS IS TMS INDICATED?

The first TMS device was approved by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD) in 2008. TMS devices from several manufacturers are currently approved by the US FDA for treatment-resistant major depressive disorder (TRD), and, in 2018, the FDA also approved a single device for the treatment of obsessive-compulsive disorder (OCD). TMS is currently provided or reimbursed by most major

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private (employer-based) health plans, such as preferred provider organizations and health maintenance organizations, as well as by the Veterans Health Administration and Medicare. More recently (as of summer 2020), it has begun to be reimbursed by Medicaid in some states as well.

WHY IS TMS NEEDED?

MDD is very common worldwide. Estimates of the lifetime prevalence of MDD are as high as 20%, with a 1-year prevalence of 5% to 8%.[1] It is estimated that 35% to 40% of patients with MDD experience TRD, usually defined as having had an inadequate clinical response to at least 2 adequate trials of antidepressant medications (at an adequate dose, duration, and adherence) during a current depressive episode.[2] In routine practice, large numbers of patients with MDD do not respond clinically to many more treatments for depression, including 5 to 10 or more antidepressants, psychotherapy, and adjunctive treatments which can be biomedical (eg, lithium, atypical antipsychotics, lightbox therapy) or psychosocial in nature. These patients with TRD experience considerable suffering and functional impairment (eg, inability to maintain a job or social relationships or to live independently), have significantly higher rates of suicide,[3] and involve a considerable cost for health care systems.[4] Before the advent of TMS, the only option available for these patients was electroconvulsive therapy, with its significant adverse effect profile and burden on healthcare resources (requirement for in-hospital outpatient care, anesthesiology).

A relatively new TMS device was recently approved by the FDA for treatment-resistant OCD. OCD is also highly prevalent, and along with MDD, is among the highest impact conditions in medicine (in terms of disability), according to global health surveys.[5,6] Both treatment approaches and rates of treatment resistance for OCD are very similar to those for MDD (which is commonly comorbid with OCD).[7] In general, awareness and detection of OCD lag behind MDD, both in primary care and mental health settings, and awareness of the efficacy of TMS, as well as pathways for TMS referral, are currently less well established for OCD. In addition, only a single TMS device has so far been approved by the FDA for OCD. Nonetheless, TMS represents an emerging treatment modality with considerable potential for treatment-resistant OCD.[8]

There is also a substantial unmet need, together with preliminary evidence for the efficacy of TMS, in many other high-impact psychiatric conditions, including schizophrenia, anxiety disorders, and drug craving.[9–12] At this time, these conditions are primarily treated with TMS in academic centers under investigative protocols and rarely as off-label conditions. Nevertheless, in the foreseeable future, one can reasonably expect an expanding range of FDA-approved (and reimbursed) indications for TMS.[13]

TMS also shows efficacy for a range of neurological conditions, such as pain syndromes (including migraine), poststroke rehabilitation, movement disorders (such as Parkinson disease), tinnitus, and other conditions.[14] At present, TMS is approved by the FDA for migraine and presurgical motor and language mapping. These various conditions are generally beyond the scope of expertise or practice for providers in mental health, although they are often comorbid with classic psychiatric syndromes.

DOES TMS WORK FOR PATIENTS WITH TRD?

It does for many patients who are candidates for TMS treatment. Considerable and consistent evidence from well-designed clinical trials supports the clinical efficacy and effectiveness of TMS in patients with TRD.[15–17] Furthermore, anecdotal evidence (from large clinical TMS programs both in academia and in the community) suggests that TMS is effective for patients with MDD whether they have experienced a clinical lack of response to a few, many, or no previous antidepressant trials; whether they are in concurrent treatment with medications, psychotherapy, or neither; at ages ranging from adolescence to old age; and whether or not they have co-occurring medical or psychiatric problems (excepting a few conditions such as severe substance use disorders, late-stage dementia). Most studies indicate that ~50% to 60% of patients with TRD undergoing a standard 6- to 7-week course of treatment with TMS will have a significant clinical response, with cumulative effects (for both individuals and groups) over the course of treatment.[18,19] Approximately half of this 50% to 60% of patients will achieve clinical remission (with very low or absent symptom severity) and the other half will be

identified as "responders" by showing symptom reduction of at least 50% but not remission (using standardized symptom scales). It remains unclear how to preidentify those patients with the greatest likelihood to benefit from TMS. These benefits are durable, as most of those who have a significant response will continue to be well at least 1 year later.[20] For those who experience a significant recurrence of symptoms, they typically will achieve a significant benefit upon returning to TMS treatment.[21] Some of these patients can benefit from maintenance TMS treatment, which is typically initiated ad hoc with less frequent treatment sessions over a longer period of time. Maintenance TMS remains an issue warranting further study to support its utility and optimization.

WHAT IS THE PROCESS FOR A PATIENT TO ENTER TMS TREATMENT AND WHAT IS REQUIRED OF THE PATIENT?

Patients are most often referred for a mental health condition by a provider such as a psychiatrist, other mental health provider, and less often, a primary care provider or neurologist. Often, referring providers are relatively unfamiliar with TMS treatment, which presents an opportunity for informal education of peers. Occasionally, patients self-refer after exposure to social acquaintances or direct marketing. In any event, patients must undergo a routine clinical evaluation to ascertain their eligibility and appropriateness for TMS, including their likely risk to benefit ratio, to support informed consent. This includes taking a conventional clinical history, a mental status examination, and obtaining collateral history from the referring provider, including the history of previous treatment trials (though none is strictly necessary to potentially derive clinical benefit), all to ascertain the appropriate diagnosis, evaluate potential contraindications (eg, seizure disorder, severe substance use disorder, previous lack of response to a course of TMS, intracranial ferromagnetic objects), and consider the burden on the patient (in terms of issues such as cost and transportation). TMS is somewhat unusual among biomedical treatments for mental health conditions in the intensity of visits, in that patients must come to the clinic 5 days each week, continuously for at least 6 to 7 weeks, to maximize their likelihood of benefit. Anecdotal experience suggests that reduced treatment adherence is associated with less benefit. During the course of treatment, the TMS clinical provider usually maintains a consultative role, in close coordination with the referring provider, who remains the primary responsible provider for the patient. However, in some TMS programs, the TMS provider may offer other mental health interventions (most often pharmacotherapy), and can assume primary responsibility, especially in the absence of other outside providers.

WHAT DOES THE PATIENT EXPERIENCE IN TMS?

In a TMS treatment session, the patient typically sits comfortably in their own clothes in a large reclining chair (somewhat like a dentist's chair), in a quiet and private room, and the coil (in its housing) is placed in contact with the patient's scalp at the predetermined treatment target site. The patient puts earplugs in place to attenuate the clicking sound of the coil, which occurs as it switches on and off. Then, with a signal from the provider or the device itself, the device initiates a series (a "train") of pulses. These pulses can be at a relatively high frequency (eg, 10 times/s, or 10 Hz), low frequency (eg, 1 Hz), or a more complex "patterned" type of stimulation (each of these stimulation protocols has roughly comparable efficacy for TRD). The treatment sessions typically last 40 to 60 minutes, although there are newer, effective stimulation protocols with durations as brief as 3 to 4 minutes (see the discussion below on "What are the recent developments in TMS?"). The patient hears a clicking sound (or a buzzing for the "patterned" stimulation) and feels a tapping sensation at the point of contact, which is typically cyclic and repetitive in nature (see discussion below on "What are the adverse effects of TMS?"). Patients can rest, engage in conversation with companions in the room, view a television or other screen during the treatment session, or other activities that are not excessively activating and do not require head movement. Some patients may even fall asleep, due to the monotony of the experience, although there is some informal concern that administration of TMS treatment during sleep may mitigate clinical efficacy, due to state-related variation in TMS effects. This possibility remains uncertain and is an

important topic for empirical research. Patients are instructed to adopt a comfortable position but not to move their heads, as head movement will change the point of contact with the coil, moving it off-target. On occasion, patients will have > 1 treatment site on the head, and these treatments are given sequentially, with the next treatment administered immediately after the coil is moved to the next target. Patients are typically continuously monitored by clinical staff, and they can be sent home immediately after the completion of the treatment session. Over time, sessions tend to be similar, although routine adjustments may be made, especially related to stimulation parameters (eg, intensity, number of pulses, target). Patients generally do not experience benefits in the first week, and the time of onset of efficacy is highly variable; however, the longer treatment continues, the more likely that patients will experience benefit. Dropout rates are quite low, well under 10% in most practices. In routine practice, if patients do not exhibit signs of clinical improvement after 2 to 3 weeks, significant adjustments (eg, to the target or in the stimulation pattern) are typically made. It remains unclear if mid-course treatment adjustments are advantageous, or if these patients merely require relatively more sessions to achieve clinical response. Patients usually maintain all other concurrent treatment regimens (medications, psychotherapy) as a conservative measure; however, it also remains unclear whether, how, and which concurrent psychotropic medications or psychotherapies might modify the clinical effects of TMS, which could potentially be in either a positive or negative direction.

WHAT ARE THE ADVERSE EFFECTS OF TMS?

The adverse effect profile of TMS overlaps slightly with that of psychotropic medications, but in general, it differs substantially.[22,23]

Common side effects experienced during treatment sessions include modest discomfort (or mild-moderate pain) in the head, most commonly at the point of contact with the coil; sensations elsewhere in the head and/or face or twitching of facial muscles (both related to either conduction through the skull or the unintended stimulation of peripheral nerves in the head); and tears from the eyes. Patients may also experience movement in their extremities, which is probably related to either suboptimal placement on the head (ie, placement too close to motor cortical areas), or possibly intracortical transmission from the intended target to motor cortical areas. This movement usually necessitates adjustment of the placement of the coil and/or a decrease in stimulation intensity.

Side effects that are commonly experienced during the treatment course but outside of treatment sessions include headache (usually relieved with over-the-counter, non-narcotic pain relievers); fatigue; mild sleep disruption; physical tension; and slowing of cognition (akin to that with sleep deprivation, rather than frank impairment of memory or attention).[23] It is exceedingly rare, for instance, that a patient is incapable of driving home after a treatment session for any reason if they are otherwise capable. Indeed, there is some evidence that over time, therapeutic TMS may actually improve the mild cognitive deficits that are observed in many neuropsychiatric disorders.[24] TMS can of course cause mood changes (a key feature of clinical efficacy), and this can rarely include the induction of hypomania/mania.[25] Rates of induction of hypomania/mania appear to be low, certainly no higher than for antidepressant medications, and this is usually identified early, probably owing to the frequent contact that providers have with patients during treatment, so that rapid modification of treatment is usually successful in resolving the hypomania.

None of these side effects (both during and outside of treatment) is dangerous, and they typically either resolve spontaneously over time, or can be alleviated with minor adjustments to the stimulation characteristics (eg, adjustments to the precise site, angle, or intensity of stimulation).

The most serious potential adverse effect of TMS is a seizure. A few dozen cases of witnessed seizures during TMS treatment have been reported in the clinical literature.[23] These seizures can be varied in nature, including a generalized, tonic-clonic (grand mal) seizure. None of the reported cases has led to serious sequelae (eg, death), and all seizure types have become much rarer since the widespread adoption of safety guidelines,[23] coupled with greater knowledge of how to balance risk with efficacy. Most clinical practices (both in the community and in academic centers) have never observed a case of seizure, preseizure activity is rare, and even in patients with epilepsy, seizure induction with TMS is rare.[26]

ARE THERE NEW DEVELOPMENTS IN TMS TREATMENT?

Considerable development and advances in the use of TMS in the clinic and the laboratory have occurred since the first FDA approval in 2008. Some of the goals of this work have been to refine and diversify the stimulation protocols and targets to optimize treatment outcome, both in the current depressive episode and for greater durability (ie, resistance to relapse); to accelerate the benefits of TMS, as one way to improve the efficiency of TMS[27]; to further specify symptom profiles that are responsive to TMS (eg, suicide risk[28,29]); and to advance treatment protocols that may more directly relate to the underlying pathophysiology of the illness. Notable among the newer protocols is the so-called "theta-burst stimulation," which may remediate underlying problems with adaptive (plastic) changes in brain structure and function, which appear to be related to both depression and its more conventional treatments (such as antidepressant medications).[30] Theta-burst stimulation protocols are also highly efficient, with clinical effectiveness comparable to the more conventional protocols with as little as 3 to 4 minutes of stimulation per session,[31] although the total number of sessions required may be the same as for conventional protocols. Another technical innovation that aims to optimize clinical efficacy (which is earlier in development) is the synchronization of TMS with the patient's intrinsic brain oscillatory rhythms, which can be measured noninvasively online during TMS with electroencephalography. A wider range of clinical indications is being sought for TMS (note the recent FDA approval for the treatment of OCD), and this can be expected to gain momentum over time. Some of the more nascent work that holds promise includes the use of biological (especially neuroimaging) biomarkers to identify candidates likely to respond to treatment, monitor treatment effects, and elucidate the neurobiology of treatment effects[32,33]; to further characterize the neurophysiological effects of TMS, especially in animal models[34]; and to understand how TMS may relate to (and interact with) other treatment modalities for MDD and other disorders,[35,36] both to optimize the inevitable multimodal treatment of these conditions but also to further elucidate the mechanism(s) of action of TMS, all in the service of providing better care for our patients.

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