Transcranial Magnetic Stimulation for Depression in Emerging Adults

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Psychiatrists experience some version of the “difficult to treat” patient everyday when presented with the need to treat depression. An added layer of complexity arises when working with emerging adults (ages 18 to 29) who present with age- and stage-specific conditions and issues. For example, there is the twenty-four year–old patient who refuses to try SSRI antidepressants after reading the black box warning that tells him the medication may cause him to experience suicidal thoughts. There is the twenty–three year old woman on a staggering list of medications for various medical comorbidities; this makes the provider cringe at all of the possible drug interactions. Still there is the nineteen–year old young woman who wants to know if this antidepressant is going to interfere with her birth control pills, and, if she does conceive, is the antidepressant going to hurt the fetus? And there are those patients for whom treatments have been ineffective, such as the twenty–five year old young man who has “tried everything;” his frustration and agitation is accelerated by ineffective treatments.

Complicated cases of medicating young patients suffering from major depressive disorder require psychiatrists to deviate from standard protocol. This is a particularly frustrating concern when the psychiatrist acknowledges that emerging adults are, for the first time, learning to be responsible for their own mental health care. The impetus to find a curative therapy in the emerging adult patient is magnified by recognition of the amount of life yet to live.

Despite the complexity of these cases and the current lack of a literature guiding their treatment, psychiatrists see opportunity for successful treatment given the exceedingly high neuroplasticity normative to this age period. Brain tissue has an unparalleled opportunity to organize and reorganize its function on the basis of stimuli and functional demands. In no developmental epoch beyond emerging adulthood will the brain be able to change on the basis of its environment.

The burden of depression

Depression is a particularly insidious psychiatric disease given its associated burden. The burden of depression stretches across the life span; the earlier it begins, the more damaging its course. By 2020, the WHO projects depression to reach 2nd place of disability adjusted life years (DALYs), the sum of years of potential life lost due to premature mortality and years of productive life lost due to disability. For male and female emerging adults (ages 15 – 44 years; WHO data), depression is the 2nd most leading cause of DALYs. For the majority of patients treated for depression, remission is possible and even predicted. Findings from the Sequenced Treatment Alternative to Relieve Depression (STAR-D) study, considered the largest and most comprehensive treatment of depression study to date, reveal that 2/3rds of depressed patients will eventually achieve remission from psychotropic medications and/or psychotherapy. Of the 2/3rds who experience effective treatments, 1/3rd of patients achieve remission from the first medication trial, and the other 1/3rd of patients after trying between one and three other medications eventually achieve remission from psychotropic medications and/or cognitive behavioral therapy (CBT) (Rush, 2006).

At greatest risk for depression-related burden are those for whom standard treatments are not effective. Results from the same STAR-D study indicate that nearly 1/3rd of depressed patients with access to care will not achieve remission from their depression even after multiple medication trials and the addition of CBT. The incomplete efficacy of psychotherapeutic and psychopharmacologic approaches to the treatment of depression leaves psychiatrists with a relatively large minority of patients to treat for whom standard treatments do not work—a constituency of patients with treatment–resistant depression (TRD) (Rush, 2006).

In addition to those for whom standard treatments for depression prove ineffective, a second set of emerging adults is at-risk—those patients for whom medication is contraindicated. There are several reasons why this may be the case. Some patients are unable to tolerate the side effects of antidepressant medications. Others have comorbid medical conditions that disallow the use of such medications. One condition that presents a specific challenge is pregnancy given that emerging adulthood is the era of peak fertility and pregnancy. Ongoing concerns about the use of antidepressants during pregnancy and the post-partum period, a time of increased probability of experiencing depression, complicate the decision to use medications to treat depression. With such a large number of patients unable to find relief from the available psychotropic medications, a number of non–medication approaches to the treatment of depression have been researched and found to be effective. These approaches fall under the broad category of neuromodulatory therapies.

Neuromodulatory therapies for depression

The use of neuromodulatory therapies is by no means novel. The oldest of these approaches, electroconvulsive therapy (ECT) was first used in 1938 by Cerletti and Bini, two Italian psychiatrists. Introduction of ECT as a treatment for depression predated the advent of the first antidepressant medication, imipramine, by over 15 years. Although other neuromodulatory therapies are FDA approved for the treatment of depression, (e.g., deep brain stimulation, vagal nerve stimulation), ECT stands alone as most effective.

Despite the fact that ECT is the most effective treatment in the psychiatric armamentarium for the treatment of severe depression, the method suffers a poor-fitting reputation. Shocking portrayals of this treatment method—the most famous one the depiction of its use in One Flew over the Cuckoo’s nest—continue to contribute to its underutilization. Graphic depictions of ECT intended to shock audiences do not reflect today’s patients’ experiences. The use of anesthesia during the procedure, changes in the amount and method of delivery of electrical impulses, and alternative lead placements have made ECT far safer and more humane than the procedure portrayed in such films.

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Despite the effectiveness and improvements in ECT, several problems remain often making this therapy an option of last resort. For instance, the use of anesthesia requires either an inpatient stay at the hospital during the treatments, or someone willing to drive the patient to and from the ECT sessions, which typically occur every other day for a period of some weeks. The lingering effects of anesthesia make working during the ECT sessions difficult, if not impossible. And, although the effect on working memory is typically transient at low energies, this can further complicate ordinary function during the treatment period. A small but disconcerting cohort of patients report subtle but persistent cognitive impairment.

**Transcranial Magnetic Stimulation (TMS)**

Responding to the need for a noninvasive, non-convulsive, non-medication theory, Transcranial Magnetic Stimulation (TMS) has been advanced as a promising new approach for use with difficult to treat patients. The use of TMS for the treatment of depression represents a long sought after paradigm shift in psychiatry. TMS is the first noninvasive and nonconvulsive procedure that relies on the stimulation of neurophysiological circuits known to be necessary in maintaining mood. It is FDA-approved for the treatment of patients who have not responded to at least one trial of medications, and might cautiously be considered as a front line therapy in those patients who are unable to tolerate a full trial of an antidepressant medication. TMS is particularly promising for work with emerging adults. It is a 37-minute outpatient procedure requiring no anesthesia or sedation, therefore allowing patients to attend to tasks of daily living with relatively little interruption. In the case of emerging adults, learning tasks of daily living, going to school, planning careers, and establishing intimate relationships all benefit from maintaining focus. Second, the treatment is time-limited, lasting 4 to 6 weeks, which means that this treatment can be delivered during non-pregnancy periods.

**The history of TMS**

TMS was first developed in 1985 as a non-invasive method of mapping the brain, in particular the motor cortex (Barker, 1985). Barker et al employed a principle first understood in the 19th century: transcranial magnetic induction. First discovered by Michael Faraday in 1831, electromagnetic induction describes the production of voltage – or the flow of electron current – caused by a change in a magnetic field. Rapidly alternating the flow of electrical current within a coil of wire produces a magnetic field, which in turn allows for the production of precise electric current within large neurons perpendicular to the coil. By inducing an electric current in a particular part of the brain through the use of TMS, the function of that part of the brain is revealed without damaging the brain tissue. The result was a simulated map of neurons, called a neural network, that synthetically modeled specific brain functions.

Several researchers employing TMS as a tool for brain mapping noted incidentally that some of their research subjects reported improvement in mood after undergoing TMS (Bickford, 1987). As brain-mapping research progressed, prefrontal depolarization of large neurons in the left prefrontal cortex was found to reliably produce improvement in mood. Daily left prefrontal TMS over several weeks was first proposed as a treatment for major depressive disorder in 1993. Since the early 1990s, TMS has been extensively studied for the treatment of major depressive disorder, typically using a left prefrontal cortex placement. Of the studies that have been published, several concomitant meta-analyses of them have concluded that left prefrontal TMS provided statistical superiority over sham treatment for patients with major depressive disorder (George, 2010). A number of clinical features have been demonstrated to be associated with greater response; these include younger age, diminished resistance to antidepressants, and an absence of psychotic features. The first double-blind, placebo-controlled (i.e. sham treatment) began in 1997 and FDA approval of the use of TMS for the treatment of major depressive disorder was secured in 2008 (George, 2011).

**Using TMS**

Patients are expected to tolerate TMS well and report few side effects. A TMS session begins with the coil being placed over the motor cortex, a part of the brain that lies on the left side of the patient’s head. The amount of energy necessary to cause depolarization of motor neurons and cause the thumb to twitch determines the patient’s motor threshold (MT). Depending on the treatment protocol employed, the coil is then moved 7 cm forward, laying over the prefrontal cortex. The percentage of MT energy employed per pulse is a function of age (i.e. normal aging causes the brain to shrink, increasing its distance from the coil) and the patient’s ability to tolerate the local effects of the energy pulse.

Patients report a wide variety of experiences during the TMS sessions. Some experience no sensation at all, while others experience a tingling sensation, local muscle tension, or headache. The typical TMS treatment of depression consists of a 37-minute session delivering between three thousand to six thousand pulses, five days a week for four to eight weeks. As accuracy of the magnetic field and associated electrical stimulus is of paramount importance, the patient lies in a reclined position with the coil held securely against the head over the left prefrontal cortex in the treatment of major depressive disorder.
Efficacy of TMS

To date, there have been three large multisite trials of TMS for the treatment of major depressive disorder. A European trial of 127 patients used TMS versus sham for the augmentation of medication startup. This trial failed to find any augmenting effect of TMS (Avery, 2008). A TMS manufacturer in the United States randomly assigned 301 medication-free patients with major depression to receive either active TMS or sham treatment for four to six weeks (O’Reardon, 2008). In this trial, effect size was observed to be larger in those patients whose depression was historically less resistant to treatment with medications. This explains the FDA approval of TMS in 2008 for the treatment of major depressive disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant trial at or above the minimal effective dosage and duration in the current episode.

Significant controversy exists over the relative utility of TMS compared with ECT. An initial study by Eranti et al published in 2007 found that TMS was inferior to ECT, although the side effect profile was found to be significantly better than ECT (Eranti, 2007). However, this study suffered from a number of significant design flaws, most significant among these being that patients assigned to the TMS group received only 15,000 total pulses, far less than the typical total amount of energy now employed in TMS therapy (Janicak, 2007). STAR-D remains the largest study to date of pharmacologic and psychotherapeutic (i.e. CBT only) modalities for the treatment of major depressive disorder. The STAR-D study, while not naturalistic, followed a protocol that was devised to simulate the manner in which a psychiatrist might recommend serial therapies for patients who have not responded to early treatment. The three large, multicenter TMS trials have shown a placebo (i.e. sham) effect of 5% to 8%, compared to efficacy of TMS rates of between 15% and 48%. The STAR-D study helps to put these numbers into context. The initial therapy used in the STAR-D protocol, citalopram, showed efficacy of approximately 33%, with the following round of treatments dropping to approximately 20%. By the third and fourth rounds, only 6-7% of patients responded (Rush, 2006). Compared to these numbers, efficacy rates between 15% and 48% for TMS become attractive, especially when compounded with the relative absence of side effects and long-term complications.

Conclusion

It is proposed that emerging adulthood is a developmental epoch particularly positioned to take advantage of the use of TMS for depression in difficult-to-treat emerging adults, ages 18 to 29. Young people in this age range may be especially likely to benefit from TMS because this is a sensitive period of post-pediatric neuroplasticity. With the 2008 FDA-approval, TMS has left the laboratory and entered clinical use. TMS currently offers us a chance to help emerging adults that might otherwise not receive optimal therapy or relief from their symptoms at a time that is so crucial to the makeup of the rest of their lives. Researchers are already at work on future generations of TMS that will allow for deeper and more specific brain structures to be reached and treated. Until then, the current iteration of TMS technology will bring hope to patients that might have seen their treatment options dwindling. Research is underway exploring the role that TMS might play in the treatment of a wide variety of disorders, from post-traumatic stress disorder to obsessive-compulsive disorder, bipolar depression to chronic anxiety. Outside of the psychiatric realm, TMS is utilized for such disparate conditions as chronic pain, cortical blindness, and beyond. The expansion of the psychiatric armamentarium by the addition of TMS represents a change in the way that we view the treatment of depression, and a change in the patients we believe are “difficult to treat.” The application of thistechology to emerging adults is another tool that improves our chances of giving these patients the best chance for optimal functioning during the time of life that is so crucial in defining personal identity and one’s identity in the world.

References


