Is Transcranial Magnetic Stimulation Appropriate For Treating Adolescents with Depression?

ABSTRACT

Children who are inadequately treated for depression often experience greater dysfunction. Problems can include conduct disorders, substance abuse, physical illness, and poor performance at school, work, or in psychosocial contexts. Depression can lead to a greater risk of suicide. Suicide is the third most common cause of death among adolescents, with more than 500,000 attempts made by children each year. Suicide is the third most frequent cause of death among young people ages 10 to 19 years old. Thus, proper treatment is important. Major depressive disorder in adolescents is often followed by frequent recurrences in adulthood. Imaging studies document underactivity in the left dorsolateral prefrontal cortex in subjects suffering from depression. Activation of the brain with high-frequency transcranial magnetic stimulation increases neuronal excitability and induces the growth of new connections. Though larger, randomized, controlled trials with more patients and longer follow-up are needed, the favorable side effect profile and efficacy of TMS seen so far in the literature support the use of TMS as a therapeutic intervention in children and adolescents with depression.

KEYWORDS: Adolescent depression, affective illness, depression, neurostimulation, transcranial magnetic stimulation

by PUNEET NARANG, MD; KATELYN MADIGAN, BS; SIMRAT SARAI, MD; and STEVEN LIPPMANN, MD

Dr. Narang is with the University of Minnesota and Regions Hospital, Minneapolis–St. Paul in Minneapolis, Minnesota. Ms. Madigan is with the University of Minnesota, Minneapolis–St. Paul in Minneapolis, Minnesota. Drs. Sarai and Lippmann are with the University of Louisville School of Medicine in Louisville, Kentucky.

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In 2003, the Food and Drug Administration issued black box warnings about antidepressant drugs stating that such medicines can induce suicide among adolescent patients, which resulted in fewer physicians prescribing these medications to children and adolescents who were depressed.[1,2] Selective serotonin reuptake inhibitor (SSRI) prescriptions decreased from the years2002 to 2005; however, there was little change in the prevalence of adolescent depression.[3] Since SSRI medications are the most commonly prescribed pharmacotherapeutics for depressive symptoms, some teenagers with depression might have been inadequately treated out of fear that they might become suicidal. The suboptimal intervention of depression in children yields more recurrences of depression in adulthood. Antidepressant drug prescribing for adults increased over this same period of time.[4]

About 1 to 2 percent of children aged 6 to 12 years and 4 to 8 percent of adolescents aged 13 to 19 years suffer from depression.[5] Suicide is the third most common cause of death among adolescents, with more than 500,000 attempts made by children each year. One report in 2016 concluded that antidepressant pharmacotherapy has little advantage over placebo treatment in depressed children and adolescents.[6] Pharmacotherapy combined with psychotherapy has been reported to be no better than medication alone for such adolescent patients.[7]

TRANSCRANIAL MAGNETIC STIMULATION (TMS) AND DEPRESSION

Imaging studies demonstrate underactivity in the left dorsolateral prefrontal cortex (DLPFC) of patients with depression. Activation of this area of the brain with high-frequency transcranial magnetic stimulation (TMS) has been shown to increase neuronal excitability and induce growth of new connections.[8] TMS has also been shown to have an antidepressant effect in patients with unipolar depression, following high-frequency repetitive stimulation directed to the DLPFC.[9] Repetitive TMS (rTMS) is the most common form of this intervention, typically involving 4 to 8 weeks of high-frequency pulses directed daily to the DLPFC. The standard of care is 30 TMS sessions over six weeks, followed by a three-week taper. Research has shown that patients who have undergone this treatment maintained a reduction in affective symptoms for up to one

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CORRESPONDENCE: Puneet Narang, MD; Email: puneet.d.narang@healthpartners.com

year.[10] A 60-percent response rate at 12 months yields remission rates at 30 percent; about 84 percent of patients have reported benefit after a course of TMS treatment.[10] Based on its limited research, TMS appears to be safe for use as a treatment for depression in adolescents.[11]

TMS was introduced in 1985 to study motor pathways in patients during normal development and in patients with neurological disorders.[12] TMS can be applied in either a single-pulse or a paired-pulse manner following a preceding test stimulus. TMS research has facilitated a better level of understanding of cortical motor pathways in the human brain during early development; for the first three months of life, motor thresholds increase and remain high until around 10 years of age. Size differences exist between the brains of young children and those of adults. Motor thresholds decrease to adult levels by mid-adolescence but display great variability in latency-age children.[13] Inhibitory interneurons within the motor cortex are mediated by gamma-aminobutyric acid (GABA), ,which might explain this finding.

Short interval intracortical inhibition (SICI) levels in children around the age of 10 years is 25 percent less than levels found in adults;[14] this decreased SICI is attributed to neuroplasticity. TMS measures of cortical inhibition and excitability might serve as biomarkers for psychiatric illness in adults, but are less indicative of illness severity in children. The relationship between depression severity and TMS measures of cortical inhibition or excitability in children is not well-understood; yet, there appears to be an association between GABAergic and glutaminergic cortical processes and affective illness severity.[15] Most studies have utilized high-frequency TMS directed toward the left DLPFC due to its enhancing effects on cortical excitability. Other studies have targeted the right DLPFC due to the overactivity seen in patients with depression, It is theorized that this might normalize following TMS.[16]

Single-pulse TMS induces a resting motor threshold, applying the lowest stimulus intensity required to generate a target muscle, motor-evoked potential in the contralateral motor cortex. Motor thresholds offer an individualized reference for setting TMS stimulation parameters. Active central motor conduction times in humans mature at 3 to 5 years of age, while resting central motor conduction times approach adult values during adolescence. This "latency jump" is hypothesized to be caused by central motor neuron recruitment, synaptic maturation, central myelination that occurs at 5 to 10 years of age, and increased neuroplasticity.[17]

It remains unclear if TMS enhances neuroplasticity. Electroencephalography promotes the measurement of cortical inhibition in the motor and DLPFC by paired-pulse TMS.[17] Cortical activity suppression correlates with TMS applications.[17] This mediates GABAB-receptor inhibitory neurotransmission after TMS treatment.[17]

Some analyses evaluating rTMS efficacy are of suboptimal duration.[18] Clinical improvements in two subjects were documented without adverse effects or dysfunction.[18] Demonstrating the superiority of rTMS over a sham control requires more study.[19] Longer treatment courses are required, and further refinement of rTMS antidepressant therapy is ongoing.[20]

TMS intervention has shown good clinical efficacy and safety in adolescent patients with depression,[9,13,17] and has shown a favorable side effect profile, compared to antidepressant medications. Headache was the most common complaint.[4] Other adverse events included seizures, hearing loss, and/or scalp pain. TMS-precipitated convulsions occurred in less than one percent of healthy subjects.[4] Neurological morbidities including stroke, cortical lesions, and/or epilepsy are reported, but not always with sequelae.[20] Cognition was unaffected. There was no injury to brain maturation, neurophysiologic parameters, or motor development in 75 TMS studies involving children. Because of hearing impairment concerns, earplugs are provided during treatments;[21] TMS exposure did not cause hearing loss in adults when earplugs were utilized.[4] Scalp pain is diminished by cleaning of the area of electrode proximity.[4]

The magnetic field strength of TMS at 1.5 to 2 Tesla is comparable to being scanned by magnetic resonance imaging.[15] Additionally, the magnetic field volume is small. Tissue only a few centimeters beyond the coil is unaffected since the magnetic field intensity decreases exponentially with distance. Cortical damage has been documented in animals at 100μJ/cm^3 and 50 Hz of charge density after seven hours of continuous simulation. TMS energy exposure is only half that delivered by electroconvulsive therapy.[22]

CONCLUSION

The favorable side effect profile and efficacy of TMS support the use of TMS as a therapeutic intervention in children and adolescents with depression.[9,13,17] The American Academy of Child Adolescent Psychiatry recommends that TMS intervention in children and adolescents with depression should continue for six months to a year; longer durations may be considered for those who suffer more than one depressive episode.[23] Patients who have received TMS usually describe it as having been "helpful."[19] TMS is generally well-tolerated when proper application protocol is followed. There are few safety concerns and no evidence of resultant brain injury. Psychoeducation that includes coping skills, guidance, and family therapy, along with regular clinical follow-up, is indicated for all young patients with depression and their families as part of their treatment plan for optimal outcomes.

The frequency and severity of depression among children and adolescents merit additional investigation into the safety and effiectiveness of TMS intervention for depression in this patient population. Larger, randomized, controlled studies with longer follow-up are required to better understand the potential role TMS intervention can play in the therapeutic management of depression in children and adolescents.

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