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Review Article

Multiple Sclerosis and Introduction of Transcranial Direct Current Stimulation Technique in Pakistan

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EE collected the data and wrote the manuscript. GM designed and executed the study. FS collected the data and helped in writing. RS interpreted the data. SAM revised the manuscript critically. SB reviewed the manuscript critically.

Keywords
Multiple sclerosis (MS), Burden, Transcranial direct current stimulation (tDCS), Burden, Pakistan, Neuromodulation

Abstract | Multiple sclerosis (MS) is an autoimmune disease caused by demyelination of axons in the brain and spinal cord. The likelihood of MS is higher in an individual with a family history of disease and the degree of relationship. It is prevalent in females and adults of age between 20-40 years. Moreover, it is present in people living away from the equator. Symptoms of MS are optic neuritis, tremor and ataxic gait, weakness or numbness in limbs, double vision, fatigue, dysarthria, or dizziness. It may result in disability and quality of life of patients may also be affected. Furthermore, patients and their employers, families and caregivers as well as the entire healthcare system may bear considerable clinical and economic burdens linked with this disease. Currently, there is no specific treatment for MS, however, different medications have been approved to lessen the symptoms associated with MS to improve the living quality of patients. Transcranial direct current stimulation (tDCS) is a cheaper technique that has been proved beneficial in the improvement of various neurological conditions of MS such as reduction of pain, fatigue, depression and improvement of motor and cognitive performance. Treatment of MS is very expensive. Pakistan is a low-income country. Cases of MS are being reported in Pakistan. Thus, the timely introduction of tDCS in the healthcare system of Pakistan will improve the conditions of MS patients. Moreover, it will also decrease the economic burden on the health department and the government.

Novelty Statement | Multiple sclerosis (MS) disease is increasing in Pakistan with an estimated prevalence of 10 cases per 100,000 individuals. The introduction of transcranial direct current stimulation (tDCS) technique in Pakistan could help treat MS and reduce the burden of this disease on the healthcare system.

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Introduction

Multiple sclerosis (MS) is a long-lasting, progressive, and idiopathic disease caused by the demyelination of axons followed by axonal deterioration in various parts of the brain and spinal cord (Calabresi, 2004; Weinshenker,

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1996). The progression of this disease is difficult to predict. It is initially characterized by episodes of reversible neurological deficits that occur without a regular pattern often followed by a gradual decline in neurological function. People having MS can face disability and poor quality of life for a long time (Ransohoff and Engelhardt, 2012).

Despite intensive research work, the exact reason behind MS is still not clear. However, it seems that genetic and non-genetic factors, which include environmental factors, viruses, and metabolic disorders, are responsible for the onset of MS (Bermel and Cohen, 2011; Loma and Heyman, 2011). The most acknowledged explanation suggests that auto-aggressive T-cells traverse the blood-brain barrier causing the demyelination of axons. Recent histopathological studies have reported abnormalities in this barrier (Ransohoff and Engelhardt, 2012). Presently, no specific cure is available for MS, however different kinds of treatments are recommended to improve the symptoms associated with the disease after an attack and prevent new attacks (La Mantia *et al.*, 1994).

The prevalence of MS has increased since 2013. At present, an estimated 2.8 million people are living with MS throughout the world and the mean age of MS diagnosis is 32 years. According to MS data from 75 countries, the pooled incidence rate is 2.1 per 100,000 persons/year (Walton *et al.*, 2020). The number of MS patients was 2.1 million and 2.3 million in 2008 and 2013, respectively. MS prevalence varies in different parts of the world. The likelihood of MS is higher in an individual having a family history of disease and the degree of relationship, indicating genetic susceptibility as a risk factor (Hollenbach and Oksenberg, 2015). First-degree relatives have a 3% risk for MS, which is 2% for parents, 2% for children, and 4% for siblings (Patsopoulos, 2018). However, MS affects more young adults of age 20-40 years (Browne *et al.*, 2014). In the United States (US), the MS occurrence in 2012 was 149.2 per 100,000 people. The probability of having MS was higher in women compared to men (Dilokthornsakul *et al.*, 2016). Moreover, its signs were also observed in children. In Germany, the MS onset rate in paediatrics was 0.3 per 100,000 (Pohl, 2008). In Canada, in children below 18 years of age, the incidence of demyelinating disorders was 0.9 per 100,000 individuals (Banwell *et al.*, 2009).

Types of MS

In 1996, an advisory committee on clinical trials in MS established by the U.S. National Multiple Sclerosis Society (NMSS) defined MS subtypes based on expert consensus clinical observation. These subtypes included primary progressive MS (PPMS), relapsing-remitting MS (RRMS), progressive relapsing MS (PRMS), and secondary progressive MS (SPMS) (Klineova and Lublin, 2018; Lublin and Reingold, 1996). Later, two more phenotypes, radiologically related syndrome (RIS) and clinically isolated syndrome (CIS), were proposed (Klineova and Lublin, 2018; Lublin *et al.*, 2014). The main clinical course of MS at onset is RRMS in 85% of patients with episodic neurological dysfunction (relapses) followed by completed or partial remissions, which gradually advanced into neurological impairment or SPMS in 10-15% without any relapses (Ford, 2020; Ömerhoca *et al.*, 2018). The MS, due to its fluctuating and progressive course, can complicate its management by the neurologists. Thus, diagnosing MS at early stages could be crucial for possible early treatment and preventing irreversible neurological impairment.

Risk factors of MS

MS afflicts people belonging to all age groups across the world. It often affects adults between 20 and 40 years of age and is rarely found in children and teenagers (Banwell *et al.*, 2009). It is 2 to 3 times more likely to affect women than men (Loma and Heyman, 2011). Moreover, the ratio of men to women having MS is different in different parts of the world. For instance, in the US, female to male ratio is 2.6:1, in the East Asia, ratio is estimated to be 2.6:1, and in some countries such as Iran, this ratio is 2.8:1 with MS. It is demonstrated that this ratio has elevated over recent decades greatly (Harbo *et al.*, 2013; Magyari, 2016). MS tends to occur slightly in families. If the parent is suffering from MS then it is estimated that there are 1-5% chances of developing this disease in the children (Hemminki *et al.*, 2006; Nielsen *et al.*, 2005).

MS has been reported to be higher among people living farther away from the equator, which suggests the impact of sunlight exposure on MS risk (O'Gorman *et al.*, 2012). According to one study, Caucasians, particularly those of Northern European descent, are at risk of developing MS (Avasarala, 2015; Khan *et al.*, 2015). Canada was reported to have the highest rate of MS in the world in 2011 (Amankwah *et al.*, 2017). In European countries, over the past three decades, 83 cases per 100,000 are estimated (Koutsouraki *et al.*, 2010). According to a report of the Pakistan Society of Neurology (PSN) (Wasay *et al.*, 2007, 2013), about 5% of the population in Pakistan is affected by MS and approximately 400 new cases of MS emerge every year. The retrospective data from a research conducted on the largest series of MS patients in Pakistan concludes that the mean age of MS patients is 27 years with a woman to man ratio of 1.45:1. Seventy five percent patients are diagnosed with multiple symptoms. The most common symptom of MS is motor weakness, which is present in 70% patients followed by sensory symptoms, which are present in 45% patients. The most prevalent form of MS present in 81% patients is RR-MS followed by PP-MS present in 21% patients and SP-MS present in 4% patients. Opticospinal MS is verified in only 3% of patients. Forty five percent and 31% patients are temperately and severely disabled at the time of assessment, respectively. It takes 5.2

years after an MS attack with severe disability to achieve recovery (Wasay *et al*., 2007, 2011).

Symptoms of MS

MS is the main cause of non-traumatic neurological disability among young adults, which affects approximately 2.8 million people across the world (Walton *et al*., 2020). It is characterized by demyelination of neurons leading to altered nerve impulses, destruction of nerve fibers, variable axonal and neuronal loss, gliosis, formation of white matter lesions, diffuse atrophy in the non-demyelinated white matter, and damage to grey matter (Chard *et al*., 2021; Mortazavi *et al*., 2021). The immune cells attack myelinated axons causing demyelination during MS lesions and dysregulate PPARγ and WNT/β-catenin pathways (Bando, 2020). However, while many studies recognized that the symptoms of MS are typically linked with the disruption of myelinated axons of the CNS (Stadelmann *et al*., 2019), recent studies have shown that a certain proportion of neurodegeneration is independent of demyelination (Correale *et al*., 2019). Furthermore, a recent study also suggests that the entire CNS and PNS (peripheral nervous system) appear to be involved in the disease (Oudejans *et al*., 2021).

The symptoms and presentations of MS are very diverse. However, the primary symptoms of the disease are gait tremor, double vision, weakness in limbs, optic neuritis (painful monocular visual loss), and faintness or dysarthria. Symptoms, which result directly from the injured neurons (grey matter symptoms) appear seldom so that their occurrence makes the diagnosis of MS doubtful. Few examples of these symptoms are aphasia, dementia, seizures of syncope, loss of consciousness, and muscle atrophy (Patti *et al*., 2003). Most of the symptoms of MS occur within hours or days. Attacks reach their maximum within a few days. These are then resolved completely within the next few days or weeks so that from the onset to recovery, a typical attack is symptomatic for about 8 weeks (Gajofatto and Benedetti, 2015; Lo Re *et al*., 2015).

RR-MS affects about 85% of MS patients. In this most common pattern, relapses strike approximately every 12-18 months. With the passage of time many patients enter into a phase of SP-MS. The attacks get more chronic and lethargic and ultimately convert into a continual degradation rather than episodic relapses. Another group of MS includes PP-MS, which affects about 10% of the MS patients. Symptoms of this pattern continue to become more worsen without any remissions/relapses (Gajofatto and Benedetti, 2015; Patti *et al*., 2003).

Consequences of MS

MS is a lethal disease. The life expectancy of MS patients is shortened over a period of a few months. Most physicians and patients consider MS to be a steadily worsening and disabling disease, however, this concept lacks supporting evidence. In actuality, 15 years after the onset of MS, about 20% patients become paralysed or institutionalized. Sixty percent patients can move independently without any assistance, and 20% patients spend their lives without any disability, however they face discontinuous and short episodes of symptoms (Goksel Karatepe *et al*., 2011).

Diagnosis of MS

It is difficult to diagnose MS as many confusing symptoms are associated with it. Moreover, these symptoms appear in diverse ways. The diagnosis can be difficult or sometimes impossible, particularly in the case of old patients. The symptoms are progressive; however, sometimes neurological impairment may occur in one episode. MS can be diagnosed by clinical tests, however they have limitations. MRI of the head region is suggested as the first test to examine the inflammatory scratches, which are visible in the white matter, particularly around the ventricles. Almost 90% of the MS patients do not have normal MRI scans (Bermel and Cohen, 2011; Ontaneda *et al*., 2015). Moreover, MRI of the spinal cord can also be employed to diagnose MS, as MS patients with spinal cord lesions (SCL) exhibited higher levels of disability (Saini *et al*., 2021).

Treatment and rehabilitation

Currently, no cure is available for MS. However, different medications and therapies have been permitted by the Food and Drug Administration (FDA) for RRMS, which are used to decrease the frequency of relapses and the development of new scratches in the brain. Five injectable drugs including betaseron, 4 beta- interferons *viz*. avonex, extavia and rebif and the co-polymer polypeptide mixture, glatiramer acetate are mainly the first-line considerations for the treatment of MS. The treatment is recommended to start with one of these drugs as soon as the RR-MS has been diagnosed. Several other drug therapies, which are considered as the potential medications and currently are in the research pipeline include therapeutic agents viz. natalizumab, ocrelizumab, mitoxantrone (novantrone), alemtuzumab (campath), daclizumab (zenapax), BG-12 (dimethyl fumarate), and teriflunomide (Damal *et al*., 2013).

Besides these DMTs, rehabilitation is also provided to people suffering from MS. Unfortunately, little attention is paid towards the planning for the rehabilitation of MS patients due to the progressive nature of this disease. Different methods of non-invasive stimulation of the brain, which include transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (rTMS, iTBS), have recently been utilized in the rehabilitation of various neurological diseases including MS (Palm *et al*., 2014; Schlaug *et al*., 2008).

Transcranial direct current stimulation (tDCS)

In this method, the cortical area of the brain is stimulated non-invasively, which can significantly alter the functioning of the brain. It is well tolerated with negligible side effects. Its initial administration does not provoke any type of auditory or somatosensory perceptions. Moreover, it facilitates learning processes in healthy subjects (Nitsche *et al.*, 2003; Nitsche and Paulus, 2000). The clinical application of tDCS was first reported in 2005 (Hummel *et al.*, 2005). This report comprises about 340 articles in which the effects of tDCS were evaluated in neuropsychiatric conditions (Patti *et al.*, 2003).

A continuous current stimulator and saline-soaked surface electrodes are employed in tDCS. The current stimulator generates a current flow of 0-4 mA DC. The surface electrodes control the neuronal excitability where they are placed. Placement of the anode over the right prefrontal cortex increases excitability, whereas the cathode placed over the left prefrontal cortex decreases excitability. The electrodes are applied onto the chosen areas of the scalp, which makes the currents flow through the brain tissue present beneath. Initially, when current is applied, it produces a transitory itching sensation in the area where the electrode lies. This effect lasts between 30 s to 1 min. In a previous study (McCreery *et al.*, 1990), it is reported that the current with a density < 25 mA/cm^2 does not damage the brain. Therefore, administration of 1-2 mA/cm^2 current is considered completely safe (Nitsche *et al.*, 2008). Moreover, application of this low-density current is sufficient to excite neurons (Woods *et al.*, 2016).

The employment of tDCS is expedient over the other stimulation techniques being safe, painless (Clemens *et al.*, 2014), easy to use, and having portable sized electrodes. Due to its portability and small size, it can be administered whenever needed. Controlled sham experiments can also be conducted for precise and randomized scientific investigation. Moreover, it is a cheaper technique and its administration is becoming common for the treatment of many diseases. Though, tDCS is an easy and user-friendly technique yet it has some limitations including the placement of electrodes on the brain area and the variation of hair and anatomical features of head of different individuals, which are likely to delay current transmission to the brain (Antal *et al.*, 2017).

For safe and proper tDCS administration, certain conditions are mandatory for its beneficial effects. For instance, electrodes should be placed properly on specific brain regions to avoid any kind of skin damage. Duration of the current supply and the strength of the current applied should be under controlled conditions. To achieve beneficial and prolonged effects of tDCS, it should be used with an interval of 30 min (Antal *et al.*, 2017; Woods *et al.*, 2016). People who are administered with tDCS may face tiredness, headache, and itching and tingling sensations under the electrodes. To avoid irritating effects, it is suggested to prepare electrodes with saline solution and treat the skin with electrode cream. Moreover, these effects can be reduced when current intensity is increased gradually (Poreisz *et al.*, 2007).

Effects of tDCS on MS patients

Studies in which tDCS is involved promise its employment for the improvement of decision-making ability and control of emotion in human beings (Lefaucheur, 2016). tDCS technique has been proved helpful in the improvement of various conditions of MS such as fatigue score decreases in the different phases of MS such as PP-MS, RR-MS, and SP-MS (Tecchio *et al.*, 2014). Anodal tDCS applied on the somatosensory cortex for 5 days ameliorated tactile sensory loss (Mori *et al.*, 2013). Recently, in a randomised sham-controlled study, tDCS administration not only modulated fatigue but also improved anxiety symptoms in MS patients (Chalah *et al.*, 2020). In a recent study, gait spatiotemporal parameters were evaluated in MS patients. Active tDCS sessions over the left M1 cortex resulted in a significant increase in distance covered in a 2-minute walking test and gait speed (Pilloni *et al.*, 2020). MS patients face cognitive problems, which are predicted by atrophy and cortical lesions (Langdon, 2011). Application of anodal tDCS sessions on the left DLPFC significantly improved reasoning and executive functions of MS patients (Gholami *et al.*, 2021). In a cognitive training of RR-MS patients having impaired attention or information processing, anodal tDCS application over the left DLPFC resulted in improvement of attention and executive functions (Mattioli *et al.*, 2016). Various studies have also described the efficacy of tDCS concerning the reduction of fatigue (Ferrucci *et al.*, 2014; Tecchio *et al.*, 2015; Workman *et al.*, 2020) and pain (Ayache *et al.*, 2016; Mori *et al.*, 2010; Young *et al.*, 2020) in MS patients. Motor problems such as impaired voluntary control and exaggerated responses to lengthening of passive muscles are also reported by MS patients (Benecke and Conrad, 1980). MS patients with dysphagia who received 5 sessions of anodal tDCS over the pharyngeal motor cortex for one month exhibited beneficial effects (Restivo *et al.*, 2019). A previous pilot study conducted by recruiting MS patients with swallowing problems demonstrated mild improvement of dysphagia by stimulating the right motor cortex with anodal tDCS (Cosentino *et al.*, 2018). However, stimulation of the primary motor cortex by anodal tDCS could not improve spasticity and walking score in RR-MS patients (Iodice *et al.*, 2015). In another study (Meesen *et al.*, 2014), a single session of M1 tDCS could not improve motor performance (finger tapping) in RR-MS, SP-MS, and PP-MS patients (Table 1).

Table 1: A multi study analysis of transcranial direct current stimulation for multiple sclerosis rehabilitation.

Study	Clinical condition	Results
Gholmai *et al.*, 2021	MS with cognitive dysfunction	Improvement in reasoning and executive functions
Pilloni *et al.*, 2020	RR-MS or SP-MS (EDSS 1.0-6.5)	Improvement in walking functions
Chalah *et al.*, 2020	MS with anxiety symptoms	Improvement in anxiety symptoms
Workman *et al.*, 2020	MS with fatigue	Reduction in fatigue
Young *et al.*, 2020	MS with chronic neuropathic pain	Reduction in pain intensity
Restivo *et al.*, 2019	MS with dysphagia	Improvement in the oro-pharyngeal components of swallowing
Cosentino *et al.*, 2018	MS with dysphagia	Mild improvement in dysphagia
Ayache *et al.*, 2016	MS patients with chronic neuropathic pain	Amelioration in pain
Mattioli *et al.*, 2016	RR-MS (mean EDSS 2.1/2.9) with impaired attention or information processing	Improvement in cognitive performance (attention and executive function)
Iodice *et al.*, 2015	PR-MS with spasticity	No improvement in spasticity and walking score
Tecchio *et al.*, 2015	RR-MS (EDSS 0-3.5, mean 1.5) with fatigue	Reduction in fatigue score
Ferrucci *et al.*, 2014	RR-MS (19) and SP-MS (4) (EDSS 0-6.5) with fatigue	Reduction in fatigue score
Meesen *et al.*, 2014	RR-MS (20), SP-MS (9) and PP-MS (2) (EDSS 1.5-6.5, mean 3.15)	No improvement in motor performance
Tecchio *et al.*, 2014	RR-MS (7), SP-MS (1), and PP-MS (2) (EDSS 0-3.5) with fatigue	Reduction in fatigue score
Mori *et al.*, 2013	RR-MS (EDSS 1-4) with hypoesthesia	Amelioration in tactile sensory loss
Mori *et al.*, 2010	MS with pain	Improvement in pain

Conclusion

MS, as an autoimmune disease, results in non-traumatic impairment in young people. MS patients have physiological disorders which may cause a number of physical, neurological, and medical disorders, for instance, degradation of the body composition, greater risk for cardiovascular disease, diabetes mellitus (non-insulin dependent), osteoporotic fractures, and disorders in lipid metabolism. Moreover, MS patients may also face changes in soft tissues and bones. Thus, MS patients should be aware of loss of soft tissues and bone mass (Evans *et al.*, 2013).

The best cure of this disease is the proper care along with proper medicine, healthy diet, exercise, rest, and some therapies may help relieve MS symptoms and enhance the quality of life for MS patients. tDCS has been proved significant in the improvement of various neurological conditions of MS such as reduction of pain, fatigue, depression and the improvement of motor and cognitive performance. Though its effect lasts for a limited duration yet it helps in improving the patient condition (Table 1).

Burden of tDCS

MS is treated with drugs and various therapies such as speech therapy, physical therapy, and the provision of mobility aids. However, the expenses of these cures are very high. It is very challenging for the poor patients and sometimes they have to skip doses (Adelman *et al.*, 2013; Owens, 2016). According to the World Bank, the per capita health spending of Pakistan is $36.2. This expenditure is less than the WHO low-income countries benchmark of $86. As ischemic heart attack, stroke, tuberculosis, hepatitis, cancer, etc. are common in Pakistan. These diseases are already posing a high economic burden on the government and in this scenario emergence of new MS cases can worsen the condition.

In Pakistan, where a single person has to feed a whole family and meet their expenses, the treatment of tDCS becomes a burden for the family because different DMTs required to treat MS are very expensive. Administration of tDCS is a comparatively better treatment method as it is a cheaper technique. Currently, though MS is not very common in Pakistan, however new cases are emerging every year and its prevalence is progressively increasing (Javid *et al.*, 2017; Wasay *et al.*, 2007, 2011, 2013). Thus, the timely implementation of tDCS in Pakistan will result in lessening the economic burden of MS on the government as well as individuals in the future.

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IRB approval

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Declaration of generative AI and AI-assisted technologies in the writing process

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Conflict of interest

The authors have declared no conflict of interest.

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