An Evaluation of the Comparative Effectiveness of tDCS Treatments for Depression in Saudi Arabia

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Abstract Depression is a common psychiatric illness occurs globally in general public with a lifetime frequency of 15-20%. A recent survey revealed that 6-7% people of Kingdom of Saudi Arabia (KSA) suffer from depression every year. Depressed persons show symptoms like low mood, suicidal thoughts, impaired sleep, reduced appetite, low energy and cognitive dysfunction. Other major impairments include the deterioration of physical and mental abilities. They not only cause substantial impacts on careers; but also lead to a profound economic cost. The annual estimated economic loss due to depression in KSA is approximately $4.3 billion in terms of low or lost productivity and 6 million lost working days. Psychotherapy or antidepressant medications are the standard treatment for depression. The medication is however recommended to the patients, having severe illness or who are not suitable for engagement in psychological treatment. Antidepressant medications are becoming common and enormously being utilized by such patients. As a result, lower response rates and significant long-term side effects are seen in these patients. Transcranial direct current stimulation (tDCS) is rapidly emerging as a standard alternative treatment intervention in depression all over the world. tDCS is currently employed on “the treatment resistant patient.” These are those patients who have failed to respond to one or more medication trials. This review reveals the scope and superiority of tDCS over other therapeutic methods and its adaptability and durability in the treatment of depression.

Keywords Depression, Economic Losses, KSA, Treatments, tDCS

1. Introduction

The recent report of World Health Organization (WHO) revealed the fact that depression is affecting more than 350 million people of all ages. This common mental health disorder is fourth leading cause of disability and premature death around the world [1, 2]. If it continues to be rising at the same pace it would be a disease cluster. In 2030, depression will be the leading cause of burden of disease exhibiting a mixture of primary symptoms including low mood, suicidal thoughts, impaired sleep, reduced appetite, low energy and cognitive dysfunction. Depression also causes some secondary effects. This leads to producing great individual suffering and substantial impacts on careers. It not only becomes a key factor in efficiency loss but also a profound economic loss as well. The economic cost of depression is rising all over the world and its annual estimated loss in KSA is approximately $4.3 billion in terms of lost productivity and 6 million lost working days [1].

Depression is a severe and common psychiatric illness with a lifetime prevalence of 15-20%. Like other developed countries, depression also affects 7-8% population of KSA each year (at least 17% across the life span) (National survey of mental health 2009). The standard treatment for depression is determined by the level of disorder severity. Psychological interventions such as cognitive behavioural therapy (CBT) manage the severity of depression, from mild to acute. Medication is frequently recommended to the patients, having severe depression. These patients can’t be engaged in psychological treatments. The medication in this case is recommended alone or in combination with psychological treatments. Antidepressants are commonly used all around the globe including KSA. In 2009-2010, there were 12.3 million prescriptions provided for antidepressants (National survey of mental health 2009). The selective serotonin reuptake inhibitors (SSRIs) are the most common first line antidepressants used in KSA. Unlike in KSA, most of the other countries dealing depression on a professional scale, recommend serotonin noradrenaline
reuptake inhibitors (SNRIs) to combat this serious disease [4-6].

There are significant unpleasant treatment needs in the management of patients with depression. Despite being a widely utilized first line treatment, there are substantial problems with the use of antidepressant medications. They are of moderate efficacy and are associated with a substantial rate of short-term and long-term side effects. This leads to the high rates of treatment discontinuation. The choice of treatment suggested to the depression patients varies. 7.3% of patients prefer antidepressant medications unlike 92.7%, who prefer non medication approaches [7-9]. Such convictions strongly support local demand for an expanded array of non-medication depression treatments to be made available to consumers [10].

Transcranial direct current stimulation (tDCS) is a promising new antidepressant intervention. It has been employed on patients with treatment resistant depression. It displays an enormously low rate of side effects, excellent safety profile and no discontinuation problems. Moreover, it is provided as a treatment for a defined episode of depression. This substantially overcomes issues associated with chronic treatment acceptability and tolerability. Patients having responded to tDCS exhibit less or no side effects as compared to medication treatment. tDCS treatment could also be employed as prevention strategies to avoid depression [11, 12]. Importantly, less treatment resistant patients are more likely to respond to tDCS suggesting that it may be most effective in untreated patients and such question will also be discussed in this current review report.

2. Stimulation Location

The dorsolateral prefrontal cortex (DLPFC) in the brain is the prime region of interest for tDCS application for depression (see Figure 1) on the basis of imaging studies [13, 14]. The anatomic target of tDCS is also DLPFC similar to repetitive TMS. It is noteworthy to mention the main pathophysiological models linking a “dorsal” and “ventral” network – account for the formation and modulation of the varied symptoms of depression states [13,14]. Within this theoretical framework, depression is hypothesized to involve concomitant hypoactivation of dorsal prefrontal regions and hyperactivation of ventral prefrontal regions, particularly in the left hemisphere. Therefore, remission of symptoms may require facilitation of hypoactive dorsal (HF-Anodal tDCS) brain regions and inhibition of hyperactive ventral areas (HF-cathodal tDCS) [13-16].

Most of the studies demonstrated positive effects of tDCS in depressed patients [17-25]. tDCS showed positive effect on dysphoria and retardation, while no change has been observed on vegetative symptoms (e.g. weight loss, loss of appetite) after treatment with tDCS (Table 1). Dorsolateral prefrontal cortex was the area of stimulation in most of studies [17-23].

Mild local adverse events such as transient skin redness, itching, or skin lesions were reported both after active and sham tDCS treatment. The frequency of adverse events or the effects on cognitive capabilities did not differ between the different treatment groups in the randomized control trial (RCT) of 120 patients [11]. However, Brunoni, 2013 reported six episodes of hypomania or clinical mania: five in the combined treatment group and one in the active tDCS + placebo group [18]. Accordingly, the risk of switching to mania should be considered when using tDCS in depressed patients.
### Table 1. The most recent studies of tDCS

| n. | Study name | Type of stimulation | Stimulation intensity | Type of depression | Number of subject | Outcome |
|----|------------|---------------------|-----------------------|--------------------|-------------------|---------|
| 1  | Brunoni AR1. 2013 | Anodal left/cathodal right prefrontal tDCS | 2-mA | Moderate to severe, nonpsychotic, unipolar MDD | Active= 120 | Significant difference in Montgomery-Asberg depression rating scale scores when comparing the combined treatment group (sertraline/active tDCS) VS sertraline only |
| 2  | Brunoni AR. 2014 | tDCS to dorsolateral prefrontal cortical (DLPFC) | ---- | MDD | Sham = 17 Active = 20 | Cognitive control therapy and tDCS combined might be beneficial for older depressed patients, particularly for those who have cognitive resources to adequately learn and improve task performance over time. |
| 3  | Alonzo A. 2013 | tDCS | ---- | MDD | 64 | tDCS appears to be particularly effective in treating dysphoria and retardation, but not vegetative symptoms of depression. This may have implications for selection of types of depression most likely to respond to this treatment. |
| 4  | Wolkenstein L. 2014 | Anodal tDCS to the left DLPFC | ---- | MDD | Active = 22 Sham = 22 | Anodal tDCS applied to the left DLPFC improves deficient cognitive control in MDD |
| 5  | Loo CK. 2012 | Anodal tDCS to the left prefrontal cortex | 2-mA | MDD | 64 | Significantly greater improvement in mood after active than after sham treatment (P<0.05). Attention and working memory improved after a single session of active but not sham tDCS (P<0.05). |
| 6  | Brunoni AR1. 2014 | Anode and cathode tDCS to left and right DLPFC | ---- | MDD | 24 | Active but not sham tDCS significantly modified the negative attentional bias. |
| 7  | Oliveira JF1. 2013 | Anode over the left and the cathode over the right DLPFC. | ---- | MDD | 28 | One session of tDCS acutely enhanced working memory in depressed subjects |
| 8  | Palm U. 2012 | Anodal tDCS | ---- | MDD | 22 | No significant difference in depression scores after 2 weeks of real compared with 2 weeks of sham tDCS. There is an increase in positive emotions after real tDCS compared with sham tDCS. |
| 9  | Brunoni AR. 2013 | Bifrontal setup anode and cathode over the left and the right | ---- | MDD | 28 | Active bifrontal tDCS prevented implicit learning in depressive patients |
| 10 | Martin DM. 2013 | tDCS | ---- | MDD | 26 | The cumulative probability of surviving without relapse was 83.7% at 3 months and 51.1% at 6 months. Medication resistance was found to be a predictor of relapse during continuation tDCS. |

### 3. Conclusions

Depression is a common disastrous disease worldwide and is rising at a rapid pace in all communities. Lack of focus on this disease could cause a major risk on the physical and mental health of a person. Many of such patients prefer non-medication therapy. tDCS is an appropriate alternative therapy for depression. It has also wide safe margins and shows no major side effects or dependence. Moreover, it is easy to operate and cost effective to the patients which enhances its durability towards the treatment of depression [26, 27]. tDCS is now emerging as novel technique in dealing neuropsychiatric diseases and requires further advance studies in larger sample size to deeply evaluate its mechanistic and rehabilitative effects on the patients.

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### Conflict of Interest

The authors disclose having no conflicts of interest.

### Reference

[1] Kingdom of Saudi Arabia Bureau of Statistics 2007 National Survey of Mental Health and Wellbeing: Summary of Results, 2008.
[2] DSM-- IV (1994). DSM--IV: Diagnostic and statistical manual of mental disorders.

[3] Fava, M., Diagnosis and definition of treatment-resistant depression. Biol Psychiatry, 2003. 53(8): p. 649-59.

[4] Fava, M. and K.G. Davidson, Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am, 1996. 19(2): p. 179-200.

[5] Kikuchi, T., T. Suzuki, H. Uchida, et al., Subjective recognition of adverse events with antidepressant in people with depression: a prospective study. J Affect Disord, 2011. 135(1-3): p. 347-53.

[6] Cascade, E., A.H. Kalali, and S.H. Kennedy, Real-World Data on SSRI Antidepressant Side Effects. Psychiatry (Edgmont), 2009. 6(2): p. 16-8.

[7] Katz, A.J., S.B. Dusetzina, J.F. Farley, et al., Distressing Adverse Events After Antidepressant Switch in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial: Influence of Adverse Events During Initial Treatment with Citalopram on Development of Subsequent Adverse Events with an Alternative Antidepressant. Pharmacotherapy, 2012.

[8] Sansone, R.A. and L.A. Sansone, Antidepressant adherence: are patients taking their medications? Innov Clin Neurosci, 2012. 9(5-6): p. 41-6.

[9] National Institute for Health and Care Excellence (United Kingdom). Interventional procedure overview of transcranial direct current stimulation (tDCS) for depression. NICE Interv. Proced. Program. 1-42 (2015).

[10] Tortella, G. et al. Transcranial direct current stimulation in psychiatric disorders. World J Psychiatry 5, 88–102 (2015).

[11] Segrave, R. et al. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul. 7, 325–31 (2014).

[12] Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci 1997;9:471-481.

[13] Davidson RJ. Anterior electrophysiological asymmetries, emotion, and depression: conceptual and methodological conundrums. Psychophysiology 1998;35:607-14.

[14] Fitzgerald, P. et al. An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. Psychiatry Res. 148, 33–45 (2006).

[15] Grimm, S. et al. Imbalance between Left and Right Dorsolateral Prefrontal Cortex in Major Depression Is Linked to Negative Emotional Judgment: An fMRI Study in Severe Major Depressive Disorder. Biol. Psychiatry 63, 369–376 (2008).

[16] Brunoni, A. et al. The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study. JAMA Psychiatry 70, 383 (2013).

[17] Alonzo A, Chan G, Martin D, Mitchell PB, Loo C. Transcranial direct current stimulation (tDCS) for depression: analysis of response using a three-factor structure of the Montgomery-Åsberg depression rating scale. J Affect Disord. 2013;150(1):91–95.

[18] Wolkenstein L., Zeiller M., Kanske P. & Plewnia C. Induction of a depression-like negativity bias by cathodal transcranial direct current stimulation. Cortex. 59, 103–112 (2014).

[19] Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry 2012; 200: 52–9.

[20] Brunoni AR, Schestatsky P, Lotufo PA, Bensenor IM, Fregni F. Comparison of binding effectiveness between sham tDCS and placebo sertraline in a 6-week major depression randomized clinical trial. Clinical Neurophysiology 2014; 125: 298–305.

[21] Oliveira J. F., Zanão T. A., Valiengo L., Lotufo P. A., Benseñor I. M., Fregni F., et al. (2013). Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder. Neurosci. Lett. 537 60–64. 10.1016/j.neulet.2013.01.023

[22] Palm U, Schiller C, Fintescu Z, Obermeier M, Keeser D, Reisinger E et al. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. Brain Stimul. 2012. July;5(3):242–51.

[23] Brunoni AR, Boggio PS, De Raedt R, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J Affect Disord. 2014;162:43–49.

[24] Martin, D. et al. Continuation transcranial direct current stimulation for the prevention of relapse in major depression. J. Affect. Disord. 144, 274–278 (2013).

[25] Milev, R. V. et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder Section 4. Neurostimulation Treatments. The Canadian Journal of Psychiatry, 61, 561-575, (2016).

[26] Brunoni, A. R. et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. The British Journal of Psychiatry, 208(6), 522-531, (2016).