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REVIEW ARTICLE

Neuromodulation in Bipolar Disorder: Diversity of Evidences and Practice Recommendations

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Abstract

Neuromodulation is increasingly being used in the management of the bipolar disorder. Moving beyond electroconvulsive therapy, research evidence on the use of neuromodulation techniques such as transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, magnetic seizure therapy and deep brain stimulation in bipolar disorder has surged in past few decades. This review summarizes the evidence on the role of various neuromodulation strategies in the management of bipolar affective disorder.

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Introduction

Bipolar affective disorder is among the leading contributors to the global burden attributable to mental disorders. Its global age-standardised prevalence is 489·8 (95% CI, 407·5–580·6) per lakh population.[1] The common intervention approaches for bipolar disorder, include pharmacological, psychosocial and neuromodulation. These interventions are targeted at achieving acute control of symptoms, early illness remission and resumption of work, preventing suicide, preventing illness relapse, minimize disability and improve the functioning and quality of life. Pharmacological treatments like– mood stabilizers, atypical antipsychotic drugs form the mainstay of management of bipolar disorder and psychotherapy and neuromodulation are often used as augmenting strategy in the clinical practice.

Neuromodulation techniques are a group of invasive and non-invasive methods developed and used over past several decades for management of various psychiatric disorders, including bipolar affective disorder. Some of the neuromodulation techniques such as electroconvulsive therapy, have been on the horizon for quite some time and is well researched. However, in the past few decades research on the use of other neuromodulation interventions in the area of bipolar disorder management has also gained momentum. In this review, the emerging evidence regarding the role of various neuromodulation strategies in management of bipolar affective disorder has been summarized.

Role of Electroconvulsive Therapy in Bipolar Affective Disorder

As per the CANMAT guideline, electroconvulsive therapy (ECT) augmentation is considered a second-line management option for type II bipolar depression.[2] Mood stabilizers are the mainstay of treatment in bipolar affective disorder. Most medications that stabilize the depressive episode can cause mania and those controlling the manic episode may induce depressive symptoms.[3] In this regard electroconvulsive therapy is an effective treatment modality for both manic episode and depressive episode management; however, an important limitation is the short-lasting effect of ECT. Hence, maintenance ECT may be alternative option for relapse prevention in bipolar affective disorder (Perugi et al., 2015).

Researchers evaluated the short term outcome with response to ECT in patients with severe drug resistant mixed affective episodes of patients with bipolar affective disorder.[4] At the end of ECT sessions, 41.6% patients responded and 30.5% patients achieved remission. It has been identified that patients with lifetime co-morbidity of obsessive compulsive disorder, higher baseline score on young mania rating scale, and longer length of current affective episode determine non response to ECT.[4,5]

Studies compared the efficacy of ECT in patients with unipolar and bipolar depression.[6-8] Sienaert et al., in their study reported that response rate to ECT in unipolar and bipolar depression are equal, though the patients with bipolar depression show the response bit earlier.[8] In a study, 220 patients with unipolar or bipolar depression were enrolled for ECT. The remission rate in both groups was not significantly different, nor were the number of sessions of ECT required to achieve remission.[6] However, similar studies reported that patients with unipolar depression require more number of sessions of ECT than those with bipolar depression.[9,10] An Indian study, also evaluated 150 patients with unipolar or bipolar depression after ECT in real life setting and it was found that the responses between unipolar and bipolar depression are not different.[7] A meta-analysis that included six studies (unipolar depression = 790 patients; bipolar depression=316 patients), revealed that the response rate in unipolar depression (50.9%) and bipolar depression (53.2%) are similar.[11] It indicates that ECT is a useful treatment strategy for management of unipolar and bipolar depression with equal effectiveness.

In a randomized controlled trial including patients with treatment resistant depression, enrollment of patients was done to unilateral brief pulse ECT or algorithm based pharmacotherapy and the acute response was monitored till 6 weeks.[12,13] The remission rate in both the treatment groups were not significantly different; however, the response rate in the ECT intervention group (73.9%) was significantly higher than the pharmacotherapy group (35.0%).[12,13]

ECT has been used in elderly population (age >65 years) with bipolar depression.[14] There is significant reduction of depressive symptoms and improvement in cognitive functioning. Patients also tolerated the therapy well, with no noticeable side effects.[14] ECT is also considered a safer option for treating severe episodes of mania and bipolar depression in pregnant women, though there is a need for interdisciplinary coordination.[15] A systematic review and network meta-analysis of trials using non-surgical brain stimulation for the acute treatment of major depressive episodes (unipolar and bipolar depression) in adults revealed that bitemporal ECT and high dose right unilateral ECT are associated with higher response rate than any other brain stimulation techniques.[16]

Role of Transcranial Magnetic Stimulation in Bipolar Affective Disorder

It has been reported that there is significant variation in cortical excitability (which is mediated by the interplay of GABA and glutamate) in patients with symptomatic bipolar affective disorder (manic episode), recently remitted patients with bipolar affective disorder and healthy subjects.[17] The variation of cortical excitability was elicited by measuring the electro-neurophysiological parameters like resting motor threshold (RMT), motor evoked potential (MEP), short-interval (SICI) and long-interval intracortical inhibition (LICI).[17] Evidence suggests that patients on remission have lower RMT compared to symptomatic manic patients and healthy controls, which might be due to the

effect of medication.[17] Similarly, inter-hemispheric asymmetry in cortical excitability is evident in mood disorders like bipolar affective disorde.[18] Repetitive transcranial magnetic stimulation (rTMS) modulates neuronal physiology, thereby helps in normalizing the cortical excitability variations.

Repetitive transcranial magnetic stimulation has been used in the treatment of various psychiatric disorders, including bipolar affective disorder.[2] A retrospective analysis, included patients with bipolar depression (bipolar disorder type I and type II), and the patients had received high frequency (10Hz) rTMS at 120% RMT over left dorsolateral prefrontal cortex (3000 pulses per session daily for 30 sessions).[19] Patients enrolled in the study were having two past failed treatment attempts for depression and were receiving one or mood stabilizer without any antidepressant at the time of rTMS therapy. It was found that at the end of 25 sessions of rTMS 41% participants met response criteria and by the end of 30 sessions 77% patients met response criteria.[19] Patients with type I bipolar affective disorder had better response, remission rate, and more adverse effects to rTMS than those with type II bipolar affective disorder.[19] A randomized control trial evaluated the safety and efficacy of deep TMS (dTMS) in treatment resistant cases of bipolar affective disorder.[20] At the end of therapy (four weeks from baseline), the patients who received active TMS show significant reduction of depressive symptoms than the sham group; however, following subsequent follow-up visits over another four weeks the improvement in both groups were not significantly different.[20] Patients, who received active TMS have higher response rate (48%), then those who received sham TMS (24%).[20] Most studies using rTMS for treating manic episode, targeted right dorsolateral prefrontal cortex.[21] Patients receiving high frequency rTMS over right dorsolateral prefrontal cortex show reduction in manic symptoms at the end of therapy.[21]

A systematic review and meta-analysis, that included 56 randomized controlled trials (n=3058 adults with unipolar or bipolar depression) evaluated the efficacy and acceptability of various non-invasive brain stimulation techniques (transcranial direct current stimulation, transcranial magnetic stimulation and theta-burst stimulation).[22] High frequency rTMS over left dorsolateral prefrontal cortex is found to have highest level of evidence in terms of efficacy. Similarly, intermittent theta burst stimulation (iTBS) helps in reducing treatment duration. Continuous TBS and bilateral TBS are not much efficacious in the treatment as found in this study.[22] However, these conclusions are preliminary and there is need of robust evidence to have better insight regarding the efficacy of various non-invasive brain stimulation techniques in the management of unipolar or bipolar depression.[22,23] The safety and efficacy of accelerated rTMS protocol (total of 30 sessions over 15 days) was assessed in a study that included both unipolar and bipolar depression patients.[24] The patients had received high frequency rTMS (20Hz) over left dorsolateral prefrontal cortex. Patients with more than 60 years of age had significantly higher rate of remission and response than those with age less than 60 years. Similarly, the older population also reported significantly greater improvement in anxiety and depressive symptoms than the population with age less than 60 years.[24]

A retrospective chart review compared the effectiveness of rTMS in the management of unipolar depression versus bipolar depressio.[25] Patients, who received rTMS were mostly received the treatment after at least one failed treatment response to antidepressants. rTMS was used as an augmenting treatment modality to the ongoing pharmacological treatment. The response rate to rTMS in bipolar depression is significantly lower (7.7%) than that with unipolar depression (39.3%).[25] The patients received high frequency (10Hz) rTMS at 120% of RMT over left dorsolateral prefrontal cortex on daily basis (3000 pulses per session). Outcome was measured by periodic monitoring on Hamilton depression rating scale.[25] However, this study has a limitation due to having fewer number of patients with bipolar disorder (n = 13) than unipolar depression (n = 63).[25] Another recent study, in a relatively larger sample (Bipolar depression=34; Unipolar depression = 283), compared the response and remission rate between unipolar and bipolar depression with response to rTMS augmentation.[26] Patients with bipolar depression receiving unilateral rTMS (either over right dorsolateral prefrontal cortex or left dorsolateral prefrontal cortex) have 45% remission

rate and 80% response rate, whereas for patients with unipolar depression receiving unilateral rTMS, have 15% remission rate and 39% response rate.[26]

Non-invasive neuromodulation techniques like rTMS and tDCS are commonly used as an augmentation strategy in the management of bipolar disorder (mostly depression) with a minimum switch risk to mania.[27] Hence, rTMS and tDCS may be considered as safe and effective augmenting methods in the treatment of bipolar depression. Some innovations in the protocol are also done to potentiate the therapeutic effects of rTMS. To boost the therapeutic effect, priming of the target area (to augment the low frequency rTMS effect, high-frequency rTMS is given, before low-frequency rTMS).[28] A meta-analysis reports that patients with acute bipolar depression receiving low frequency rTMS or continuous TBS over right dorsolateral prefrontal cortex, is more efficacious than high frequency rTMS over left dorsolateral prefrontal cortex.[28,29] Affective switch (switch to mania) is a rare phenomenon with rTMS trials.[29.30] Interestingly the risk of switch to mania or hypomania with rTMS treatment is not significantly different between patients receiving active rTMS and sham rTMS.[30]

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) recommend the use of rTMS in the management of type I bipolar affective disorder (both depression and manic episode) as an augmenting agent to pharmacotherapy.[2,31,32] There is no recommendation for type II bipolar affective disorder in these guidelines.[2,31] As per the CANMAT guideline, rTMS augmentation is considered as a third line management option for acute manic episode along with the ongoing pharmacological treatment.[2] Similarly, for the management of depressive episode, rTMS is also considered as an third line management strategy (as an add on treatment to pharmacotherapy).[2]

Cognitive impairment is a well-known phenomenon in bipolar affective disorder. Researchers attempted to investigate the possible pro-cognitive effect of high frequency (18Hz) repetitive transcranial magnetic stimulation using H-coil (deep TMS) at 120% of the RMT in patients with bipolar depression in a double blind randomized controlled trial.[33] The result is suggestive of improvement in cognition in both active rTMS and sham rTMS group, which is irrespective of the improvement of depressive symptoms. It indicates questionable superiority of active deep TMS over sham TMS.[33] Another recent double blind randomized controlled trial, that used high speed and high frequency (10Hz) rTMS over left dorsolateral prefrontal cortex for 10 consecutive days at 110% of RMT.[34] This study suggests about the superior efficacy of rTMS in improving the cognitive symptoms in bipolar disorder.[34] May be a larger sample population, some newer protocols and new target areas give better insight to the effectiveness of TMS on cognitive deficits in bipolar disorder. Accelerated intermittent theta burst stimulation was used for the treatment of binge eating disorder comorbid with type II bipolar depression targeting the left dorsolateral prefrontal cortex.[35] There was significant improvement in binge eating psychopathology, though the improvement of depressive symptoms are not remarkable.[35] Researchers attempted to use deep TMS as a maintenance treatment of unipolar and bipolar depression. It was found that patients receiving maintenance deep TMS have no worsening of depressive symptoms; however, those who had not received maintenance TMS, reported symptom worsening in 6 to 12 months follow up.[36]

Several existing evidences are contradicting and are mostly limited by small sample size or study design. There are potential areas that are under-evaluated and need to be evaluated more intensely in future research, which are role of rTMS in mixed episodes, rapid cycling bipolar disorder, maintenance phase of bipolar affective disorders, and organic bipolar affective disorder. Similarly, various target brain areas, protocols of TMS (accelerated protocol, extended protocol and combination of both), parameters of TMS (pulses/train, frequency, trains, pulses per session) and coils (figure eight angular coil, H-coil) need to be evaluated for their safety and efficacy in larger samples to have better insight to the utility of rTMS in management of bipolar affective disorders.

Role of Transcranial Direct Current Stimulation in Bipolar Affective Disorder

A systematic review and meta-analysis of randomized controlled trials, suggest that tDCS has potential

role in the treatment of non-treatment resistant depression (unipolar and bipolar).[22]

In a randomized controlled trial (RCT), tDCS was given along with medication (mood stabilizer) in group and the other group was receiving medications alone.[37] It was found that patients of bipolar depression receiving the combination of tDCS and medication responded well and had significant higher reduction of depressive symptoms in comparison to those receiving medication alone.[37] However, at three month follow up the benefits are not sustained. Similarly, patients receiving combination of tDCS and medication, have less cognitive deficits than those on medication only.[37] This study is limited by very small sample size (n=15 in each group) and shorter duration of intervention (total of 10 sessions over five days. Bipolar depression electrical treatment trial (BETTER) used, active tDCS and sham tDCS along with ongoing pharmacotherapy in the case group and control group, respectively. A total of 10 daily sessions of tDCS were delivered with anode over left dorsolateral prefrontal cortex and cathode over right dorsolateral prefrontal cortex. Subsequently, one session every two weekly, delivered for next four weeks using the same protocol. The result suggests that there is significant improvement in depressive symptoms in the group receiving active tDCS in comparison to the group receiving sham tDCS.[38]

The side effects associated with tDCS are well tolerable and risk of switch to mania is rare.[38]

In an open label study, patients with unipolar and bipolar depression with one or failed medication trial were enrolled for tDCS (10 sessions over five days with anode over F3 and cathode over F4). At the end of therapy, both the patient groups reported improvement of cognition, depressive and anxiety symptoms, equally.[39] A study pooled data from three studies that evaluated the efficacy of tDCS in major depression (both unipolar and bipolar depression) and found that the improvement in depressive symptoms in unipolar and bipolar depression are comparable.[40] This study identified that the patients with cognitive deficits, psychomotor retardation, anxiety and somatization are important clinical predictors of response to tDCS treatment.[40] Researchers in BETTER trial also investigated the possible association of inflammatory biomarkers with response to tDCS in bipolar depression. It was found that with tDCS treatment the level of interleukin-6 level falls and baseline increased interleukin-6 level is found to be an important predictor of response to tDCS in bipolar depression.[41] Bipolar depression electrical treatment trial (BETTER) attempted to investigate the impact of tDCS in the cognitive parameters in patients with bipolar depression receiving tDCS (Tortella et al., 2021). The change in cognitive parameters was not significant both in the groups receiving active tDCS versus sham tDCS.[42]

A sham controlled RCT, used transcranial random noise stimulation (tRNS) in the treatment of depression (both unipolar and bipolar depression), where anode is placed over left dorsolateral prefrontal cortex and cathode is placed over right dorsolateral prefrontal cortex.[43] Both the groups received 20 sessions of tRNS over a period of four weeks. There is no significant difference in the response and remission rate in the active and sham tRNS groups.[43] Existing evidences are sparce and further research is required to establish the efficacy of tRNS in bipolar affective disorder.

A recent study evaluated the possible role of tDCS on new target areas like left ventrolateral prefrontal cortex.[44] In patients with bipolar disorder, the left ventrolateral prefrontal cortex (vlPFC) shows unusually high activity during reward anticipation and cathodal tDCS over this site is effective in reducing the hyperactivity, which can have potential therapeutic role in the management of bipolar disorder.[44]

Researchers used tDCS as an augmentation strategy in a mixed population with unipolar or bipolar depression and the improvement in depressive symptoms were measured periodically in follow up till three months.[45] The reduction in depressive symptoms persisted in approximately 50% of the participants till three months of follow up.[45]

A systematic review, included 19 studies (n=170), where tDCS was used for the treatment of bipolar affective disorder. Ten studies reported that tDCS is effective in reducing the depressive symptoms. Four studies reported about beneficial role of tDCS in the neurocognitive performance in patients with bipolar disorder, who were euthymic and one case report revealed the

beneficial effect of tDCS on manic symptoms.[46] The side effects of tDCS reported were mild in severity and often short-lasting in nature. Another recent meta-analysis reported the evidence base for use of tDCS in various neuropsychiatric disorders.[47] Existing evidences reveal that most of the studies evaluating the effect of tDCS in depression, excluded bipolar depression from their study as a result of which effect of tDCS in bipolar depression is less studied. Whatever studies that included bipolar depression, report that tDCS is equally efficacious in bipolar depression like unipolar depression.[47]

Role of Other Neuromodulation Techniques in Bipolar Affective Disorder

Vagus nerve stimulation (VNS) is on of the invasive neuromodulation technique used in the treatment of resistant depression over past few decades. Researchers used VNS in the management of bipolar depression, the improvement in depressive symptoms in unipolar and bipolar depression, did not differ significantly.[48] In a study nine patients with rapid cycling bipolar affective disorder were treated with VNS for a year and it was found that there is more than 38% reduction of severity of depressive symptoms over the course of treatment with negligible side effects.[49] A study evaluated the efficacy of VNS in unipolar and bipolar depression over a period of two years and it was found that there is no noticeable difference in the efficacy of VNS between unipolar and bipolar depression.[50] In a study VNS is used in severe treatment resistant bipolar depression as an add on to the treatment as usual and it was found that there is reduction in depressive symptoms and reduction in suicidality.[51]

Magnetic seizure therapy (MST) is another neuromodulation technique that induces seizure

Table 1: Role of ECT in bipolar affective disorder: evidences and recommendations

1	ECT is the second line management for type II bipolar depression as per CANMAT guidelines
2	Effect is short lasting hence maintenance ECT may be required for relapse prevention.
3	Effectiveness of ECT in unipolar vs bipolar depression is similar.
4	ECT helps in improvement of depressive symptoms as well as cognitive functioning in elderly population with bipolar depression
5	It is safe in elderly population
6	ECT is a safer option for treatment of severe episodes of mania and bipolar depression in pregnant women, though interdisciplinary coordination is required
7	Response rate associated with ECT is higher in comparison to other brain stimulation techniques.

Table 2: Role of rTMS in bipolar affective disorder: evidences and recommendations

1	rTMS is the third line management as an augmentation strategy to ongoing pharmacotherapy for the acute management of depressive and manic episode in type I bipolar affective disorder
2	High frequency rTMS over Left dorsolateral prefrontal cortex or low frequency rTMS over right dorsolateral prefrontal cortex is recommended in the management of a depressive episode
3	High frequency rTMS over right dorsolateral prefrontal cortex is recommended in the management of a manic episode
4	rTMS is a safe modality of treatment and rTMS induced switch to mania or hypomania is a rare phenomenon
5	Preliminary evidences suggest that a greater number of sessions (extended protocol) and more frequent session (twice daily session; accelerated protocol) may be associated with higher remission and response rate
6	rTMS is beneficial in the treatment of bipolar affective disorder in elderly population (maybe with a better response and remission rate than adult population)
7	rTMS may cause improvement in cognitive symptoms in bipolar affective disorder; however, evidences are inconclusive
8	Contradicting evidences exist regarding superiority of rTMS in treating unipolar depression versus bipolar depression

Table 3: Role of transcranial direct current stimulation in bipolar affective disorder: evidences and recommendations

1	tDCS has potential role in the treatment of non-treatment resistant depression
2	In Bipolar depression, anode is placed over left dorsolateral prefrontal cortex and cathode over right dorsolateral prefrontal cortex with current intensity of 2 mA
3	The side effects with tDCS are minimal and risk of switch to mania is rare
4	Clinical predictors of response are cognitive deficits, psychomotor retardation, anxiety and somatization
5	Baseline increased level of Inflammatory biomarkers (interleukin-6) is an important predictor of response to tDCS in bipolar depression
6	Left ventrolateral prefrontal cortex can have potential therapeutic role requiring further research

Table 4: Role of other neuromodulation techniques in bipolar affective disorder: evidences and recommendations

1	Vagus nerve stimulation	Efficacy is equal for both unipolar and bipolar depression
2	Magnetic seizure herapy (MST)	Used for treatment refractory bipolar depression Evidences suggest improvement in depressive symptoms with relatively less side effects and better cognitive functioning in comparison to ECT, however, sample population was very small.
3	Deep brain stimulation (DBS)	Used for treatment resistant depression (both unipolar and bipolar) Potential targets are bilateral subcallosal cingulate cortex, superolateral branch of median forebrain bundle With co-morbid obsessive-compulsive disorder, DBS on ventral anterior limb of the internal capsule (vALIC) showed reduction in symptoms of OCD and depression

through high frequency repetitive magnetic stimulation and is considered an alternative to electroconvulsive therapy.[52] In an open label study, patients with treatment resistant bipolar depression were recruited for magnetic seizure therapy and it was found that the remission rate was 30% and response rate was 50%, who completed the protocol.[53] MST has been used for the treatment of refractory bipolar depression in an adolescent with significant reduction of depressive symptoms without any noticeable side effects.[54] A systematic review, that included eight studies using MST in the treatment of unipolar and bipolar depression revealed that the remission rate with MST ranges between 30 - 40% and it is a safe, well tolerated procedure with better cognitive functioning in comparison to ECT.[55] However, this systematic review also mentions that the number of patients with bipolar depression included in the studies are few, which is a major limitation and may be a potential bias. A recent study evaluated the possible role of MST as a maintenance treatment of treatment-resistant unipolar and bipolar depression.[56] A total of 12 booster sessions of MST were delivered over a period of six months follow up. About two-thirds of participants those who took part in the study, saw improvements in their depressed symptoms without any negative cognitive consequences.[56]

Deep brain stimulation (DBS) has been tried in patients with treatment resistant depression (which also included patients with bipolar depression).[57] Patients with bipolar depression report significant improvement in depressive symptoms with DBS. Switch to hypomania or mania is a rare phenomenon and which can be managed with adjustment of the stimulation parameters.[57] Several important deep seated brain areas (bilateral subcallosal cingulate cortex, superolateral branch of median forebrain bundle) have been identified as potential targets of deep brain stimulation for management of depression.[58,59] Efficacy of DBS in unipolar and bipolar depression are similar, as seen from some preliminary evidences.[59] A study, evaluated the safety and efficacy of DBS on ventral anterior limb of the internal capsule (vALIC) in five patients of obsessive compulsive disorder (OCD) with bipolar depression.[60] There is significant reduction in symptoms of OCD as well as depression; however, the risk of switching to hypomania/mania was high, though it was a transient phenomenon.[60]

Conclusion

The availability of neuromodulation techniques has increased the menu of options available for bipolar disorder management. These interventions may have potential benefits in terms of rapidity of response, low side effect profile, lesser potential for switch, and increased effectiveness. Research evidences suggest that the benefit resulted from most of the neuromodulation techniques (ECT, rTMS, tDCS, MST) are mostly acute responses and with time the benefits wear off. Hence, there is a need to explore the scope of maintenance treatment using these techniques in bipolar disorder. Despite an increase in research, this is an area where further research is needed to fill the current gaps in knowledge and understanding. Identification of safe and effective protocols and parameters may help improve the treatment outcomes. The Table 1-4 summarizes the evidences and recommendations of ECT, rTMS, tDCS and other neuromodulation techniques in the management of bipolar disorder, respectively.

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