REVIEW ARTICLE

Novel strategies in the management of treatment resistant depression: a brief update

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ABSTRACT

Treatment resistant depression is a common clinical entity. Management of such patients is difficult in face of failure of repeated trials of medications. Accordingly, newer novel strategies like repetitive transcranial magnetic stimulation or vagus nerve stimulation therapy can play have an important role in the condition. These treatments are still in experimental phases with well-validated controlled trials still lacking. However, results till date are encouraging enough to suggest that these treatment modalities are worth studying further. The paper gives a short overview of the novel strategies in treatment resistant depression.

Key words : *Treatment resistant depression, management*

INTRODUCTION

Major depressive disorder is a costly and disabling condition with a prevalence of 34/1000 population[1] and about 5% to 25% in primary health care settings.[1,2] Various studies have estimated that approximately 30% to 45% of these patients do not have an adequate response and 19% to 34% do not respond to the first antidepressant trial.[3] This group has been variously described as resistant, refractory, or intractable. These patients are twice as likely to be hospitalized, make 41% more OPD visits compared to non-resistant major depression and receive two to three times more psychotropic prescriptions with higher total health care costs.[3] Selecting proper treatments for these patients of refractory depression is a difficult proposition, especially as little is available by way of controlled trial evidence to determine best possible treatment options. Faced with such immense challenge to decide the next best treatment for such patients more and more clinicians are looking towards novel treatment strategies. All these strategies have been borrowed from neurological applications emphasizing the involvement of complex neuro-circuitry in manifestation of depressive syndromes. The paper intends to give an account of novel treatment options available with special reference to treatment-resistant depression.

Repetitive transcranial magnetic stimulation (rTMS)

An investigative tool in hands of neurologist to map cortical function for over a decade, transcranial magnetic stimulation (TMS) was found to enhance mood in patients undergoing this procedure. It is a noninvasive technique for stimulating the cerebral cortex and altering cortical and sub cortical function. It involves focal electromagnetic induction of 1.5 to 2.0 Tesla with the help of an insulated coil placed on the surface of the scalp and changing the direction of the current through the coil. Electric currents thus generated within the cortex up to depths of 2 cms interrupt or facilitate neuronal function. Low frequencies (less than 1 Hz) are inhibitory and have been used in overactive epileptogenic focus whereas higher frequencies improve reaction time

for specific motor tasks in patients with parkinsonism. Higher frequencies have been used in patients of depression with varying responses. Left dorsolateral prefrontal cortex is the preferred site. The scalp location is determined by assessing the optimal stimulation point of the right first dorsal interosseous muscle and the treatment stimulation point is fixed at 5 cm anterior in a parasagittal line on a Lycra swim cap. This facilitates location of the motor cortex and the site of stimulation in subsequent sessions.[4] The procedure entails the patient to be seated comfortably, conscious and wearing a specially designed cap with marking of coil position on the surface. Concurrent monitoring of motor evoked potential and EEG are done with electrodes over the first dorsal interosseus. Studies have varied with regard to stimulation strengths and interval.[4]

TMS has been established as a safe procedure when performed within guidelines of maximum stimulus frequency, intensity and duration. Few individuals complain of scalp pain, headache. Serious side-effects such as treatment emergent seizures have been reported only in a few individuals with single intense stimulation or multiple stimuli with short inter-train interval. No harmful cognitive, neurophysiological and endocrine disturbances have been reported till date.[4]

rTMS is an experimental technique and has not been approved for treatment of depression. The effectiveness of rTMS has been studied as a potential treatment for depression. To date, much of the literature has focussed on comparison of rTMS to sham rTMS. The results of such research are equivocal with some open reviews [5,6] suggesting that rTMS has proven efficacy in depression, while meta-analytic reviews have not found good evidence for the same.[7,8] At the same time there are several randomized-controlled trials in of rTMS in treatment-resistant depression which conclude that it is an efficacious treatment in these circumstances.[9-12] Obviously, much more research will be required before deciding on the efficacy of rTMS in refractory depression.

Certain clinical variables seem to predict response to rTMS including short duration of episode and low level of treatment-resistance. More specific clinical variables such as high level of sleep disturbances also showed significant differences between responders and non-responders.[13]

rTMS is thus a promising procedure but is constrained by availability, cost consideration and paucity of well controlled parallel design studies.

Magnetic Seizure Therapy (MST)

MST entails the use of rTMS to trigger a seizure from superficial cortex under general anaesthesia. The advantage of MST over ECT is that the electrical field generated by MST is far more focal. Like ECT it is presently given once a day three times a week with a modified rTMS machine with extended parameter range to overcome the anticonvulsant effect of anaesthesia. Preliminary work is still in progress with small studies in depression showing some efficacy with reduced cognitive deficits.[14]

Vagus Nerve Stimulation (VNS) Therapy

Vagus nerve stimulation therapy was initially found to reduce the frequency of seizures among patients with resistant partial epilepsy. Experience from this use also showed improvement in mood and well being in participants.

The exact mechanism of action of this treatment is not known. The vagus nerve (cranial nerve X) carries afferent sensory information from the abdomen, thorax, neck, and head to the nodose ganglion in the brainstem. From here information is relayed to the nucleus tractus solitarius (NTS) and then to the locus ceruleus (LC), the parabrachial nucleus (PB), the reticular formation (RF), or the relevant autonomic feedback loops. The PB and LC have widespread

connections in the central nervous system (CNS), including the hypothalamus, amygdala, and bed nucleus of the stria terminalis, thalamus, with forward connection with orbitofrontal and prefrontal cortices. Studies have shown an increase in C-fos protein, a marker for cellular activity, in the LC, hypothalamus, amygdala, and cingulate of rats receiving VNS. Projections in the vagus nerve pathway from the NTS to the amygdala and hippocampus might also account for the enhanced neurocognitive performance in subjects receiving VNS for treatment-resistant depression.[15]

In a PET evaluation of 10 epilepsy patients undergoing VNS, increased blood flow in the rostral medulla, thalamus, hypothalamus, insula, and postcentral gyrus was noticed. In these regions the increase in blood flow was found to be greater on the right side (i.e., contralateral to the site of device implantation) than on the left side.[15]

In animal and human studies it has been found that VNS alters the cerebrospinal fluid (CSF) concentrations of neurotransmitters or their metabolites (e.g., increased gamma-aminobutyric acid (GABA), increased 5-hydroxyindoleacetic acid (5H1AA), increased homovanillic acid). VNS also alters the functional activity of CNS regions, (e.g., orbital frontai cortex, insula, thalamus, hypothalamus, cingulate, and hippocampus) dysregulated in mood disorders. Finally, epilepsy patients who have received VNS have shown improvement in depressive symptoms independent of the degree of seizure control.[15]

The actual procedure entails surgery for implantation of the device. This is done with the patient under either general anesthesia or regional cervical block. Since right vagus nerve stimulation produces bradycardia, implantation is limited to left-sided unilateral implantations. The carotid sheath is opened and 2 spiral electrodes are wrapped around the vagus and connected to an infraclavicular generator pack. In experienced hands, the entire procedure requires less than 2 hours. The programmable stimulator may be programmed in advance to stimulate at regular times or upon demand by patients or family by placing a magnet against the subclavicular implant site. Stimulator settings are programmed to deliver intermittent stimulation with current of 0.25–3.0 mA, frequency of 20–50 Hz, and pulse width of 500 nanoseconds for 30–90 seconds every 5–10 minutes.

Adverse effects, such as injuries to the vagus nerve, are rare. Hoarseness, throat pain, and cough are common during simulation, but are not life-threatening. Infection necessitating removal of the device was reported in 1% of investigational device exemption (IDE) clinical trials for epilepsy indication and has been reported in 1% of commercial implants (U.S. Food and Drug Administration Center for Devices and Radiological Health 2004). The most common nerve injuries are left vocal cord paralysis or left facial paralysis. The rate of nerve injuries reported in IDE clinical trials was 1% and 0.5% in commercial use. There was a 5% rate of mania or hypomania. Among subjects with a diagnosis of bipolar disorder, the rate of mania or hypomania was 22%.[16]

This modality of treatment has received post marketing approval from the FDA for "adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments" (U.S. Food and Drug Administration Center for Devices and Radiological Health 2005).[16]

Open studies report a 40% response in depression.[15] Three multi-centre studies, supported by the manufacturer of the implantable VNS device and conducted by the same research team, have now examined the

device's short- and longer-term efficacy in a group of 222 patients with clearly refractory depression.[17-19] All patients underwent surgery for device implantation. Results suggested that although adjunctive VNS was not particularly effective acutely, response might increase with continued treatment. Further such trials are awaited in this field.

A few patients who have not responded to other treatments might benefit from VNS. However, clinicians should avoid exposing large numbers of patients to this expensive treatment which requires surgical implantation — especially because many will not do well. Additional research will be required to determine specific predictors of benefit, any overlap between ECT non-response and VNS non-response, and any meaningful improvement in functioning

Deep Brain Stimulation (DBS)

This technique like VNS and TMS is borrowed from neurology. DBS as a technique has both diagnostic and therapeutic implications. Early researchers observed intense transient affective symptoms of tearfulness, sadness and despair with stimuation of subthalamic region near substantia nigra, with improvement of mood when the stimulator was moved away from the region. Others had observed that unilateral and bilateral DBS of the subthalamic region resulted in involuntary laughter, humorous triggered imaginative associations, and feelings of well-being lasting several minutes until the stimulus intensity was lowered or discontinued. Recent data indicates that other regions are similarly associated with intense affective symptoms such as the centro-median area of thalamus. Neuroanatomical studies in depression indicate involvement of anterior para-limbic structures (like amygdale, septum, anterior cingulated cortex, anterior temporal lobes and orbito-frontal cortex). Neurosurgical ablation of anterior cingulate gyrus and anterior limb of internal capsule has been used for treatment resistant depression for many years. These neurobiological correlates have lead researchers to study the technique of DBS in small samples of patients. The technique involves drilling a burr hole in the skull and implanting DBS quadripolar electrodes at the chosen site. Initialy electrodes are kept externalized to test for adverse effects and clinical benefits. After 5-7 days electrodes are connected to a pulse generator in the infraclavicular region through wire tunneled under the skin.[16]

In one open study involving stimulation of Broadman area 25 observed clinical benefits in the form of sustained remission in four out of six treatment resistant depression patients till 6 months.[20]

Adverse effects are those same for any surgical procedures entailing brain surgeries.

CONCLUSION

Treatment resistant depression is a common problem. The management of such patients is often difficult because of poor efficacy of several conventional or newer drugs. Thus there is much scope for utilization of newer techniques in such situations. The novel treatment modalities discussed above are still in the process of further evaluation and hence lack well-controlled data to support their present use in depression, particularly treatment-resistant patients. However, the data that is available shows enough promise to support further research in this area. Moreover, such studies might also help in uncovering the underlying neurobiological processes in depression including refractory depression. Then again, most of these techniques require either an invasive procedure or use of high cost equipment. Consequently, the present state of knowledge dictates that such procedures be recommended only when other conventional treatments fail, in settings where these are available, and in situations where patients are

highly motivated to undergo such experimental procedures.

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