Non-Pharmacological Approaches to the Treatment of Depression – Mechanisms and Future Prospects

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Introduction

There is growing awareness within the field of psychiatry of an urgent need for new therapeutic options for patients with treatment refractory severe depression. The recognition that psychiatric disorders such as depression and obsessive compulsive disorder are correlated with impaired function of circuits within specific brain regions, many of which are becoming well characterized, has led to the development of techniques for stimulation of these brain circuits. Novel methods of brain stimulation developed over the last decade include repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy (MST), vagus nerve stimulation (VNS) and deep brain stimulation (DBS).

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) employs a hand-held stimulating coil applied directly to the head to deliver very strong magnetic fields to the cerebral cortex in order to induce currents which are able to depolarize neurons [3]. Unlike vagus nerve stimulation, deep brain stimulation and magnetic seizure therapy, TMS requires neither an implanted prosthesis nor general anesthesia [2]. It has been demonstrated that a range of measures of brain function are influenced by TMS, including increased early gene expression (c-FOS) in the periventricular nucleus of the thalamus, dopamine release and changes in cortisol and prolactin levels.

Studies of TMS in depression have yielded inconclusive results. A systematic review of approximately 15 randomized, placebo-controlled clinical studies involving around 200 patients reached the conclusion that there is currently insufficient evidence to suggest that TMS is effective for this indication [9]. The authors did not rule out a beneficial effect from this intervention; however, they cited a number of methodological flaws in the evidence base, for example small sample size, concurrent use of psychotropic medication and failure to conceal the treatment group to which a patient was allocated [9].

Studies support a potential antidepressant effect from repetitive TMS (rTMS), with one study assessing rTMS to the left dorsal prefrontal cortex in seven children and adolescents with depression, reporting a response in five of the seven patients treated [13]. Significant adverse events, seizures or cognitive changes with TMS have not been reported [11, 13]. Today, rTMS presents an interesting and potentially promising technique.

Magnetic Seizure Treatment

While electroconvulsive treatment (ECT) has demonstrated unparalleled efficacy in severe depression, it is
associated with cognitive adverse events [15]. Improved understanding of the mechanisms underlying ECT has led to the development of magnetic seizure treatment (MST). The first use of therapeutic magnetic seizure induction in a psychiatric patient took place at the University Hospital in Bern, Switzerland, in May 2000. MST uses TMS to induce therapeutic seizures under general anesthesia in the same setting as for ECT [5]. The electrical field induced by MST for seizure induction is more focal and limited than that induced by ECT [6]. This enhanced control allows treatment to be focused on target cortical structures considered essential to the antidepressant response, while reducing spread to medial temporal regions, which are associated with the cognitive adverse events of ECT [7].

Although MST is at an early stage of development, preliminary data suggest advantages over ECT in terms of both subjective adverse events and acute cognitive function [7]. A recent randomized, within-patient, double-masked trial compared ECT and MST in 10 patients and indicated superiority with MST in terms of time to recovery of orientation, measures of attention, retrograde amnesia, category fluency and a reduced incidence of adverse events [8]. Studies are currently underway to address the antidepressant efficacy of MST [7].

**Vagus Nerve Stimulation**

Vagus nerve stimulation (VNS) is an established treatment for drug-resistant partial-onset seizures in epilepsy and is now approved by the FDA for the treatment of refractory depression.

During VNS, electrical signals are delivered to the left vagus nerve at the cervical level. The pulse generator is implanted in a subcutaneous chest pocket just below the clavicle, whereas the electrodes are attached to the vagus nerve through an incision at the neck [4].

This treatment appears to be well tolerated by and of benefit to patients with treatment-resistant depression. In a study of 30 patients, a response rate of 40% (12/30 patients) was seen after 12 months of VNS treatment, with a remission rate of 29% (8/28 patients). This result is supported by two recent 12-month studies [2, 14]; VNS demonstrated significantly greater antidepressant benefit than usual treatment procedures at 1 year [2].

Longer-term studies also support the use of VNS in the treatment of chronic or recurrent treatment-resistant depression. In 59 patients, a response rate of 42% (25/59) and a remission rate of 22% (13/29) were seen at 2 years of VNS treatment in one study [12].

**Deep Brain Stimulation**

Deep brain stimulation (DBS) is a particularly promising investigational treatment in neuropsychiatry and is conducted through the stereotactic placement of unilateral or bilateral electrodes connected to a permanently implanted neurostimulator [15].

Although its exact mode of action is unknown, the hypothesis is that chronic high frequency (130–185 Hz) stimulation reduces neural transmission through the inactivation of voltage-dependent ion channels. Recently, promising results have been seen in refractory depression with DBS close to the subgenual cingulated region cg25 (Brodmann area 25) [10]. This area is metabolically overactive in treatment-resistant depression and DBS may reduce the elevation in activity and produce benefit in patients with treatment-resistant depression.

After 2 months of chronic white matter tract stimulation, a striking response on depression was seen in five patients, of whom four maintained this response after 6 months. Antidepressant effects were