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Treatment resistant depression: the emergence of deep brain stimulation

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The multiple phase Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trials have confirmed the clinical reality that among «real world» depressed patients, less than 30% achieved remission (defined as a final score of 7 or less on the Hamilton Rating Scale for Depression [HRSD])[1] after up to 14 weeks of treatment with adequate doses of citalopram[2]. Even after three levels of switching or augmentation strategies, the cumulative remission rate is just over 40%[3]. In reality, treatment resistant depression (TRD) is best considered as a relative concept with some patients achieving a partial response, others receiving a response (defined as a 50% reduction from baseline on a standard rating scale such as HRSD) and a minority achieving remission.

NEUROMODULATION THERAPIES

It is unfortunate that in recent years, electroconvulsive therapy (ECT) has rarely been compared to pharmacotherapy interventions under controlled conditions. On the other hand, significant advances in neurobiological psychiatry have been associated with new approaches to neuromodulation. A trio of neuromodulation interventions, supported by advances in neuroimaging and hypothesis driven models of depression neurocircuitry, are currently under investigation for the treatment of depression[4].

Repetitive transcranial magnetic stimulation (rTMS) involves the stimulation of cortical neurons by magnetic induction, using a brief high intensity magnetic field. While rTMS has the advantage of non-invasiveness, lack of anesthetic risk and flexible site selection, it has not proved to be as effective as ECT for severe or treatment resistant depression and much has still to be established in selecting optimal stimulation parameters and stimulator placements[5].

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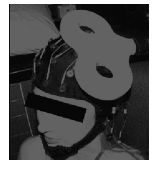
Advantages	Disadvantage
Non-invasive, non-convulsive stimulation of the brain Does not require general anaesthesia for its administration Ability to modifu the location and frequency of the stimulation applied to the brain Both stimulation and inhibition of neurons possible Effective in animal models of depression	Not as effective as ECT for severe/psychotic depression Limited data regarding long-term efficacy Unable to directly stimulate subcortical structures Uncertainty about optimal stimulation parameters 

Figura 1 *Repetitive transcranial magnetic stimulation.*

Vagus nerve simulation (VNS) is approved for the treatment of drug refractory epilepsy and recently received FDA approval in the United States for TRD, based largely on clinical evidence of safety and tolerability. While a surgical intervention is required to wrap the electrodes around the vagus nerve and subcutaneously connect them to the generator, this is a relatively minor procedure. A significant limitation to this treatment is the absence, to date, of established effi-

Advantages	Disadvantage
Large body of clinical evidence on safety and tolerability form use in epilepsy Growing literature regarding mode of action May have increasing benefit over time Well tolerated Effective in animal models	Requires surgical procedure for implantation Limited efficacy as an acute treatment for depression Less effective in patients with greater levels of resistance No acute double-blind evidence for efficacy in TRD

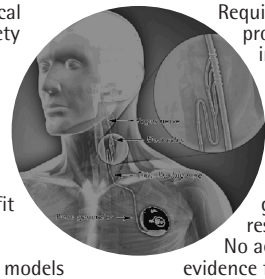
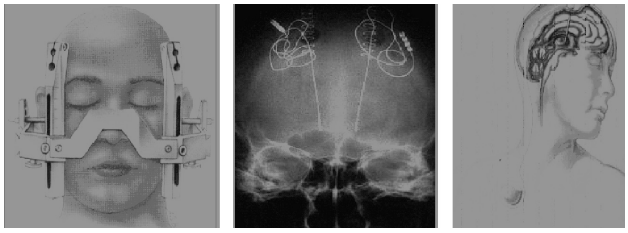


Figura 2 *Vagus nerve stimulation*



Local anaesthesia
Leksell frame
MRI targeting

Microelectrode mapping
Insertion bilateral electrodes
Turn on the devices/program

Figura 3 *Deep brain stimulation procedure.*

cacy data under acute double blind control conditions in TRD. The benefits of VNS appear to be gradual and more effective in patients with less severe treatment resistant depression[6].

Deep brain stimulation (DBS) represents a unique targeted approach to TRD. The emergence of DBS as an intervention for TRD occurs after its use for more than a decade in the treatment of Parkinson's Disease[7] and at a time when there is a hypothesis based rationale for target selection in TRD, in particular the subgenual cingulate cortex Brodmann (BA) 25[8]. Researchers in Toronto, Canada have initiated a large open study to evaluate the outcome of DBS to cingulate BA25 in severely treatment resistant depressed patients. Preliminary results from 6 patients were published in 2005 indicating that two thirds achieved significant response. This report included PET cerebral blood flow changes and supported the association between reduction in cingulate BA25 hyperactivity and favorable treatment outcome[9].

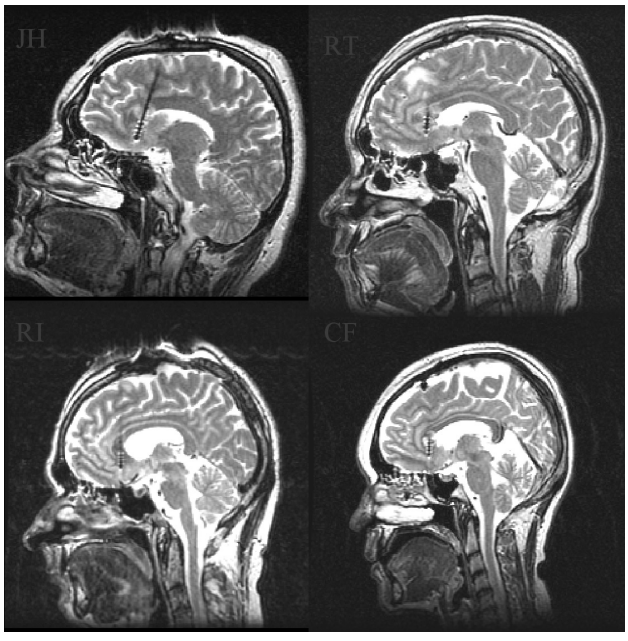


Figura 4 *DBS placement. Sagittal MIR (n = 4).*

While some patients have achieved a rapid, almost immediate effect in the operating room, this is not a sine qua non for treatment response and many subsequent patients in the expanded series have shown response or remission several months after the stimulator was turned on. Among responders, two clusters of symptoms on the 17-item HRSD were significantly improved following DBS in contrast to non-responders: melancholic (mood, work, guilt, retardation and suicide items) and sleep (initial, middle and late)[10]. The results of randomized sham versus active intervention studies will ultimately determine the future of DBS for TRD.

These neuromodulation therapies signal a new era for interventional psychiatry. Together with targeted drug developments, they contribute to the pursuit of selected interventions for specific subtypes of depression disorders.

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