NON PHARMACOLOGICAL TREATMENTS FOR DIFFICULT TO TREAT DEPRESSION by J E Eastham

ELECTROCONVULSIVE THERAPY

ECT was first introduced to treat depression in 1938. The stigma attached to ECT is based on early treatments when the patients were awake when relatively high doses of electricity were administered. They experienced pain and sometimes bone fractures during the seizure that was induced. It remains a controversial treatment- although now-a-days it is a much safer treatment performed under general anaesthesia with a muscle relaxant. Doctors monitor the heart rate, blood pressure and breathing.

Electrodes are positioned on the patient's head and an electric current crosses the brain tissue causing a seizure. As the patient is asleep and muscles are relaxed, there is very little movement. A course of ECT is typically 2-3 x a week for 6-12 treatments with the average number of treatments being 8.

ECT has a rapid onset of action- faster than antidepressant medication (Lisanby 2007). It is useful in suicidal patients, in a patient who is refusing to eat/drink, patients who are not moving or speaking (catatonic) and in patients with 'psychotic' symptoms ('hallucinations' – e.g. hearing or seeing things that are not there or 'delusions' – fixed firmly held beliefs that are not supported by facts). It can also be used for patients who have not responded to a number of other treatments. 70-90% of patients with depression respond to ECT (Sackeim *et al.* 2000, Petrides *et al.* 2001) – this is a higher rate than any other current treatment for depression. The relapse rate however is high with over 50% of patients relapsing if maintenance treatment with ECT or antidepressants and/or therapy is not carried out (Sackeim *et al.* 2001). Maintenance ECT is when it is given every 1-4 weeks for several months (maybe years in some patients).

Side effects include headache, muscle pain, nausea and memory impairment. Following acute ECT the ability to form new memories is impaired. This usually improves over days/weeks. 30% of patients have problems recalling past memories pre-ECT and some of these patients are left with permanent gaps in their memory.

It is uncertain how ECT works. It changes patterns of blood flow in the brain (Mervaala *et al.* 2001). It may stimulate the development of new brain cells

(neurons) and promote changes in how brain cells communicate with each other. ECT floods the brain with chemicals (neurotransmitters) such as serotonin and dopamine, which are known to be involved in depression (Wahlund *et al.* 2003).

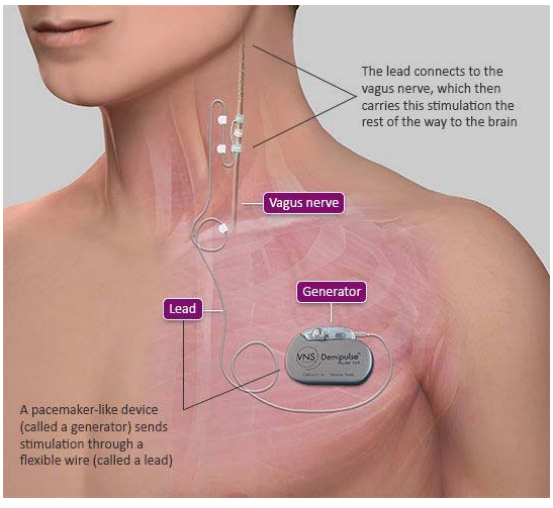
ECT is safe and effective, however it requires repeated anaesthetics and patients often relapse fairly quickly. It is a treatment that is currently underused.

VAGUS NERVE STIMULATION

VNS was introduced in the 1990's to treat treatment resistant epilepsy and scientists noticed there was a favourable effect on depressive symptoms. Since 2005 it has been approved to treat chronic recurrent depression. The patient must be >18years and have been ill for longer than 2 years, failing to respond to 4 adequate drug treatments.

It is an invasive technique and with local or general anaesthesia a pulse generator or 'stimulator' (a bit like a pace maker) is implanted under the skin in the upper left hand chest wall. A lead is passed from the stimulator under the skin and attached to the left vagus nerve in the neck. The stimulator is able to be adjusted using a 'wand' connected to a computer.

Usually, 2 weeks following implantation, the device is turned on. Most commonly, the stimulator is on for 30 secs every 5 mins (Mohr *et al.* 2011). Depending on its settings, the battery life of the stimulator is 6-10 years. Once the battery has failed, surgery is required to replace the stimulator.



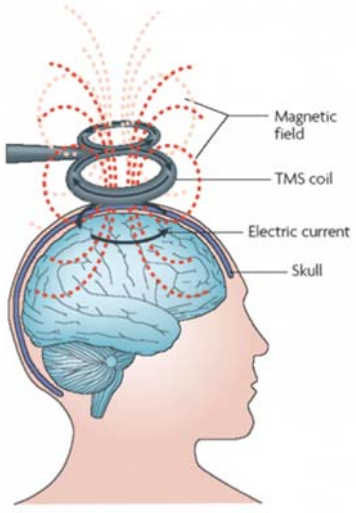
Generally VNS is well tolerated. It does not cause a seizure and is free from cognitive side effects. Surgical side effects that occur include: painful scar, wound infection, paralysis of left vocal cord, a loose device or device malfunction. Stimulation side effects decline over time and include: voice alterations (60%), cough (38%), breathlessness (21%), paraesthesia (21%). If the side effects are going to be problematic eg public speaking, exercising- the patient can switch the stimulation off using a hand held magnet.

VNS increases neurotransmitters and neurotrophic factors. It effects various regions of the brain and alters the functional activity of brain areas that are dysregulated in depression.

Response to VNS can take 6-12 months- so it is not an acute treatment. Although responses takes longer than ECT, it is a more sustained response. Patients who respond best are those who have a shorter duration of their current episode of depression, who have failed to respond to fewer antidepressants and who have responded to ECT. VNS with treatment as usual (TAU) is more effective than TAU alone- with up to 68% of patients responding over 5 years (Aaronson *et al.* 2017).

A non-invasive form of VNS referred to transcutaneous VNS (tVNS), requires further research. It is non- surgical technique using an ear clip to stimulate the auricular branch of the vagus nerve (Hein *et al.* 2013, Kong *et al.* 2018).

TRANSCRANIAL MAGNETIC STIMULATION



Repetitive TMS (rTMS) was approved in USA in 2008 to treat moderate treatment resistant depression. rTMS uses a magnet to activate the brain. The treatment is carried out in a clinical setting whilst the patient is awake and alert. The patient wears earplugs to protect them from the clicking sounds. A magnetic coil is held against the skull near an area of brain involved in mood regulation. A magnetic field induces an electric current which passes through the scalp and skull targeting a small area of the brain. TMS, unlike ECT, targets a specific site. Not all scientists agree on the best way to position the magnet or give the electromagnetic pulses.

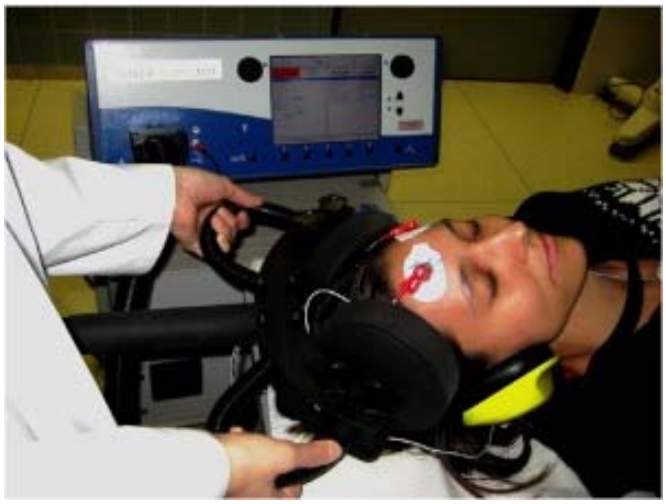
Side effects include mild scalp discomfort and headaches. The risk of a seizure is very small. It has no negative effect on cognitive function/memory. A typical treatment lasts 20-45mins and is given 5 days a week for 3-6 weeks. It is not as effective as ECT when treating depression. It may be used to enhance antidepressant medication or psychotherapy. Patients that are less treatment resistant respond better to TMS than patients who are highly treatment resistant.

The exact mechanisms of TMS therapy are unclear. There is an increase of blood flow to the brain. The electric current activates cells within the brain which release neurotransmitters such as serotonin and dopamine. The current stimulates the inactive or disrupted area of the brain or suppresses the overactive area- reducing the symptoms of depression. It may result in the increase in the production of brain cells (neurons) and an activation of brain cells causing them to rewire.

TMS has been shown to be effective in the treatment of depression (O'Reardon *et al.* 2007, Janicak *et al.* 2010, Bakker *et al.* 2015, Berlim *et al.* 2017). It is perhaps of most use for patients with more mild depression than those for whom ECT may be used and for patients that can't take medication.

In the UK TMS is currently an experimental procedure used in the context of research, though there are an increasing number of NHS clinics being set up.

MAGNETIC SEIZURE THERAPY

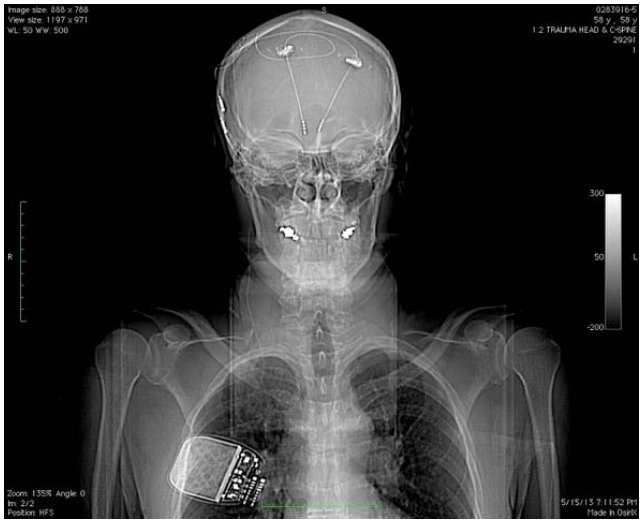


MST is a novel therapeutic intervention (Cretaz *et al.* 2015) combining the efficacy of ECT with the minimal cognitive side effect profile of rTMS. Unlike ECT, the seizure is a focussed seizure, the target being the part of the brain called the prefrontal cortex. There is little spread of the seizure to deeper brain structures and the areas involved in memory are not affected.

The patient is given a general anaesthetic and a muscle relaxant. A high strength magnetic field is used. Recovery time for MST is shorter than for ECT and there is less confusion. Response rates vary between 40-70% and remission rates 15-46%.

Study sizes to date have been small. Larger sample sizes are required to definitively demonstrate therapeutic equivalence between MST and ECT. There is very little data supporting its use as yet. Currently there are only a few study centres worldwide providing MST (Bewernick *et al.* 2015).

DEEP BRAIN STIMULATION



DBS has been used to treat Parkinson's disease since 1987. In psychiatry, it is still in an investigational stage; but has been approved in USA to treat obsessive compulsive disorder. It is a refined alternative to psychosurgery and involves the use of an electrical stimulus on a specific target in the brain (Schlapfer *et al.* 2009). Its superiority to psychosurgery remains to be scientifically proven.

The structures targeted in DBS vary- depending on the psychiatric condition to be treated. An area of the brain called the subgenual cingulate cortex is believed to be overactive in depression. DBS to this area can reduce the elevated activity (Conen *et al.* 2017). Additional targets are continuously being developed and the optimum site for stimulation remains unclear.

DBS is invasive; but reversible. Under local anaesthetic holes are drilled in the skull. The brain itself has no pain receptors and so does not feel pain. A special framework is placed on the head. Guided by the framework and using MRI scanning, the electrodes are surgically implanted in the brain. The patient is awake and can provide feedback to the surgeon. Once the electrodes are implanted, the patient is given a general anaesthetic. A stimulator (similar to the ones used for VNS) is then implanted in the chest and this is connected by leads to the electrodes in the brain. The stimulator has a life span of up to 4-5 years. The stimulation perameters are customised to the patient- adjusted by a clinician using a hand held device. Stimulation is constant.

The patient must be capable of giving informed consent for DBS to be carried out. A multidisciplinary team is essential, as is long term follow up. Although the mechanism of action of DBS is unclear- it is believed that electric pulses

reset the area of brain that is malfunctioning. Various chemicals (neurotransmitters) are released and DBS alters the blood flow to the brain.

Surgical side effects (Wang *et al.* 2018) include: infection, bleeding in the brain, stroke and electrode damage. Stimulation side effects include: movement disorders, numbness and tingling sensations in parts of the body, difficulty with speech, visual disturbances, fear, agitation, over-elated mood and the risk of suicide. More studies are needed to determine if personality and cognitive function are affected. If the side effects become severe- the electrodes can be blocked to cease treatment and the hardware can be removed.

Several small scale studies on DBS have been carried out. Only a few have been of a high quality including a treatment group and a control group which did not receive DBS. Two randomised control trials have failed (Morishita *et al.* 2014, Dougherty *et al.* 2015). More trials and further research is essential.

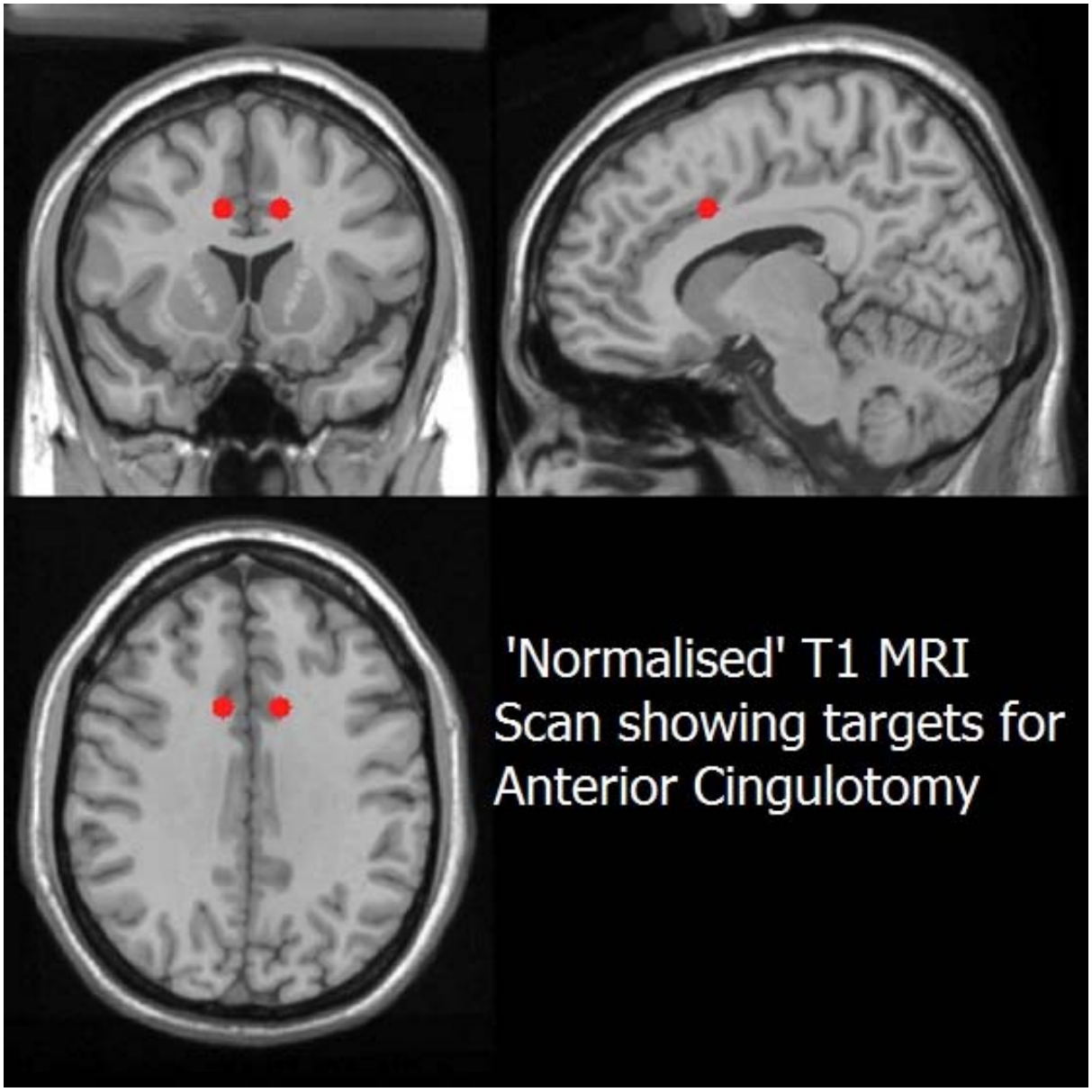
NEUROSURGERY FOR MENTAL DISORDERS

Brain surgery that promotes behavioural or affective changes in humans is controversial. 1935-1950 saw the use of “frontal lobotomies” to treat psychiatric disorders. This resulted in major personality changes. The surgery was often carried out by inadequately trained surgeons using a crude technique to blindly insert cutting instruments into the brain. There was a high incidence of complications and side effects.

Now-a-days, the technique is more refined and the term “psychosurgery” has been replaced by the term “neurosurgery for mental disorders”. The patient receives a general anaesthetic. Highly skilled surgeons use a special framework and MRI scans to accurately place the lesions in the brain. A probe tip is carefully positioned and heated to 70-80 degrees centigrade in order to create a lesion 8-10mm in diameter. Consent from the patient is essential and modern surgical intervention is for intractable mental disorders when all other treatment has failed.

There are different surgical procedures including an anterior capsulotomy, an anterior cingulotomy, a limbic leucotomy and a subcaudate tractotomy. Modern techniques ensure there is no deterioration in intelligence or change in personality or memory. The treatment is irreversible- so accurate placement of the lesions is essential. It is not a cure. It may take 9-12 months to see a

clinical improvement and if successful, the patient will need continuing psychiatric support. Approximately a third to a half of patients receiving psychosurgery achieve a response or remission (Volpini *et al.* 2017).



Side effects that are transient include: urinary incontinence, headache, nausea, confusion, tiredness, infection, agitation, seizures and weight gain. Sustained side effects include: urinary incontinence, headache, epilepsy, intracranial bleed/stroke, suicide.

If performed by experienced surgeons neurosurgery for mental disorders is safe, quick, involves no implants, requires no post -operative adjustment of

hardware (due to infection or battery replacement) and it is cheaper than DBS. It obviates the risks and expense of a lifelong implant.

CONCLUSIONS

- ECT is a highly effective treatment that is currently underused
- rTMS may be an alternative to ECT; but is not currently as effective
- VNS is not an alternative to acute ECT; but may be an alternative to maintenance ECT
- MST and DBS are not currently treatment options and more research is needed
- Psychosurgery is an “end stage” option for treatment resistant depression

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