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COMMENTARY

Vagus rules still apply

A commentary on 'Vagus nerve stimulation for depression: efficacy and safety in a European study' by Schlaepfer *et al*. (2008)

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Introduction

VNS has been proposed for treatment-resistant depression. A single, randomized controlled trial found no significant difference between real and sham VNS after 10 weeks. However, open studies suggest that prolonged treatment may be beneficial. Similar to other investigational neuromodulation techniques [e.g. transcranial magnetic stimulation (TMS), deep brain stimulation (DBS)], interpretation of these studies is limited by uncontrolled design and difficulties with suitable control conditions and blinding.

Vagus nerve stimulation for depression

Up to 20% of patients with depression fail to respond sufficiently to standard treatments and comprise a group who require other, and preferably better, therapies than currently available. Over the past 15 years there has been increasing therapeutic interest in using focal brain stimulation techniques for treatment-resistant depression, the rationale being that one could modulate neuronal circuitry implicated in mood and its regulation (Marangell *et al*. 2007). One such neuromodulation approach has been vagus nerve stimulation (VNS). VNS is used to reduce seizure frequency in partial epilepsy and the observation that this seemed to improve mood in some patients under uncontrolled conditions led to its proposed use for depression.

It involves using a cardiac pacemaker-sized generator [manufactured by Cyberonics Inc., Houston, TX, USA (www.vnstherapy.com)] that is surgically implanted in the chest wall and connected to wires wrapped around the left vagus nerve. About 80% of vagus fibres are afferent and thus provide direct access to the nucleus tractus solitarius and indirectly other related deep brain structures. The VNS device costs about $15000 and the surgery takes less than an hour to complete. A hand-held telemetric device is then used to programme intermittent, but ongoing, stimulation of the vagus nerve, e.g. for 30 s every 5 min continuing daily until the stimulator is switched off. Its mechanism of action is unknown but VNS has been reported to alter metabolism of various limbic structures and levels of central neurotransmitters, providing some theoretical basis for a potential antidepressant effect (Marangell *et al*. 2007).

Only one randomized sham-controlled trial of VNS for treatment-resistant depression ($n=235$) has been performed and this found no significant difference between real or sham VNS after 10 weeks of active treatment (Rush *et al*. 2005*a*). However, uncontrolled follow-up studies of 202 participants in this trial reported that after 1 year of VNS the rate for response ($\geqslant$50% reduction in baseline HRSD-24 score) was 27·2% and that after a second year of VNS about three quarters of the latter group continued to be responders (Rush *et al*. 2005*b*; Sackeim *et al*. 2007). After 1 year of VNS the rate for remission (HRSD-24 $\leqslant$9) was 15·8%. These findings raised the possibility that long-term treatment with VNS may be beneficial to a proportion of this highly resistant group. Based mainly on some of these reports, and somewhat controversially, the Food and Drug Administration (FDA) in the USA approved the Cyberonics VNS device for patients who had not responded to at least four standard treatments for depression (Lurie & Stine, 2006; Shuchman, 2007).

Despite this FDA approval, private health insurers in the USA have been reluctant to provide routine cover for VNS for depression. In May 2007 the Centers for Medicare and Medicaid Services, national providers of health insurance in the USA, decided not to cover VNS on the grounds that 'there is sufficient

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evidence to conclude that vagus nerve stimulation is not reasonable and necessary for treatment of resistant depression' (Centers for Medicare & Medicaid Services, 2007).

In this issue, Thomas Schlaepfer and colleagues present the findings of a multi-centre open study ($n=74$) of 1 year of VNS in treatment-resistant depression (Schlaepfer *et al*. 2008). This is a partly industry-funded European replication of an open study previously carried out in the USA (Rush *et al*. 2000; Nahas *et al*. 2005). They also took the opportunity to compare the European results with the earlier USA study. The results of the two studies are broadly similar with remission rates gradually increasing over the 1 year to 33% for the European group compared to 27% for the USA group who had a greater degree of treatment resistance. As the authors acknowledge, interpretation of the study is limited by it being uncontrolled but the study does confirm that VNS is reasonably well tolerated and safe. Another, possibly reassuring, conclusion to be made is that European and American patients seem to respond quite similarly to prolonged VNS treatment. However, whether this is a therapeutic or a placebo response remains unknown. So to paraphrase the popular Las Vegas slogan, as far as VNS being a clinically useful treatment for depression is concerned, the current evidence-base suggests that what happens in the vagus stays in the vagus.

Other neuromodulation techniques

What about other brain stimulation techniques for depression such as TMS or DBS? Recent randomized controlled trials of TMS for depression have been disappointing, finding no significant differences between real and sham rTMS on the primary outcome measures the trials were originally designed to test (Herwig *et al*. 2007; O'Reardon *et al*. 2007; Mogg *et al*. 2007). It is also becoming evident that blinding is difficult to maintain in TMS trials and this may enhance placebo effects (Mogg *et al*. 2007). TMS for depression has been reviewed by both the National Institute for Clinical Excellence in the United Kingdom (www.nice.org.uk) and the FDA in the USA (FDA Neurological Devices Panel, 2007). Preliminary reports were unsupportive regarding routine use of TMS for depression and final recommendations are imminent.

DBS requires surgical implantation of electrodes into deep brain structures and is established for intractable symptoms in Parkinson's disease and essential tremor (Ressler & Mayberg, 2007). Only a few open trials of DBS in a handful of patients have been reported for depression employing stimulation of a variety of sites including subgenual cingulate region Cg25, inferior thalamic peduncle, ventral caudate nucleus, internal globus pallidus and nucleus accumbens. While early reports appear promising, these studies have all the limitations described above and below of being unrandomized, uncontrolled and unblinded. As with VNS, potentially optimal treatment parameters (e.g. stimulation frequency, site, dose, duration, etc.) are not known for either TMS or DBS, which is a major limitation to future trial design.

The problem of control treatments and blinding

Another major difficulty for clinical trials using brain stimulation techniques is use of an appropriate sham/control treatment. In the few trials of rTMS where success of blinding has been formally measured, up to two thirds of patients correctly identify treatment (Mogg *et al*. 2007). Blinding was not measured in the largest TMS trial to date ($n=301$) but 35·8% of patients receiving real TMS complained of application-site pain compared to only 3·8% of the sham-treated group (O'Reardon *et al*. 2007). Maintenance of blinding was not reported in the single VNS randomized controlled trial (Rush *et al*. 2005*a*). However, voice alteration was a common adverse event reported by 68% of the VNS group compared to 38% of the sham group while increase in cough occurred in 29% of the real group compared to only 9% of the sham group. Similar findings are reported by Schlaepfer and colleagues in this issue. It is therefore unlikely that blinding was successful.

It has been argued that highly treatment-resistant patients, as involved in the above studies, are less likely to experience placebo effects. However, as can be seen from Fig. 1 in Schlaepfer *et al*.'s paper, patients' depression ratings began to fall during the 2 weeks post-surgery and *before* the VNS device was turned on (Schlaepfer *et al*. 2008). Thus this patient group are not immune to placebo effects and this must be accounted for. As voice alteration and cough are so common with VNS, implanting a stimulator and having no stimulation at all is not going to be a suitable control. Clearly a sham VNS condition would need to control for very common side-effects and so most likely will require some degree of stimulation. However, as therapeutic stimulation parameters are unknown, one possibility is that such a potential sham condition could itself be therapeutic!

The mother of all therapeutic neuromodulation techniques is of course electroconvulsive therapy (ECT). Although not focused in its administration, ECT continues to be the most powerful treatment available for severe depression (Eranti *et al*. 2007). There is therefore great merit in pursuing brain stimulation as a therapeutic approach for depression with a

view to refining technique, increasing effectiveness and reducing side-effects. Having other demonstrably effective therapeutic neuromodulation techniques would be of great clinical benefit. However, until reasonable control conditions are established, and success of blinding is routinely measured, it will be difficult to interpret trial results. These are challenges to be faced rather than ignored. In the meantime, and until proven otherwise, vagus rules will continue to apply.

Declaration of Interest

None.

References

Centers for Medicare & Medicaid Services (2007). Decision memo for vagus nerve stimulation for treatment of resistant depression (TRD) (CAG-00313R). (http://www.cms.hhs.gov/MCD/viewdecisionmemo.asp?id=195) Accessed 13 November 2007.

Eranti S, Mogg A, Pluck G, Landau S, Purvis R, Brown RG, Howard R, Knapp M, Philpot M, Rabe-Hesketh S, Romeo R, Rothwell J, Edwards D, McLoughlin DM (2007). A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *American Journal of Psychiatry* **164**, 73–81.

FDA Neurological Devices Panel (2007). Executive Summary of premarket notification (510(k)) submission, K061053, submitted by Neuronetics, Inc., to request marketing clearance for the NeuroStar™ TMS System for the proposed indications for the treatment of Major Depresssive Disorder (http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_01-FDAExecutiveSummary.pdf). Accessed 13 November 2007.

Herwig U, Fallgatter AJ, Hoppner J, Eschweiler GW, Kron M, Hajak G, Padberg F, Naderi-Heiden A, Abler B, Eichhammer P, Grossheinrich N, Hay B, Kammer T, Langguth B, Laske C, Plewnia C, Richter MM, Schulz M, Unterecker C, Zinke A, Spitzer M, Schonfeldt-Lecuona C (2007). Antidepressant effects of augmentative transcanial magnetic stimulation. *British Journal of Psychiatry* **191**, 441–448.

Lurie P, Stine N (2006). Responding to three articles regarding vagus nerve stimulation (VNS) for depression. *Biological Psychiatry* **60**, 1382–1383.

Marangell LB, Martinez M, Jurdi RA, Zboyan H (2007). Neurostimulation therapies in depression: a review of new modalities. *Acta Psychiatrica Scandinavica* **116**, 174–181.

Mogg A, Pluck G, Eranti SV, Landau S, Purvis R, Brown RG, Curtis V, Howard R, Philpot M, McLoughlin DM (2007). A randomized, controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. *Psychological Medicine*. Published online: 15 October 2007. doi:10.1017/S0033291707001663.

Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, Martinez JM, George MS (2005). Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *Journal of Clinical Psychiatry* **66**, 1097–1104.

O'Reardon JP, Solvason BH, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, Demitrack MA, George MS, Sackeim HA (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression:a multisite randomized controlled trial. *Biological Psychiatry* **62**, 1208–1216.

Ressler KJ, Mayberg HS (2007). Targeting abnormal neural circuits in mood and anxiety disorders: from the lab to the clinic. *Nature Neuroscience* **10**, 1116–1124.

Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, Nahas Z, Haines S, Simpson RK, Goodman R (2000). Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study. *Biological Psychiatry* **47**, 276–286.

Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ, Rapaport MH, Zajecka J, Nierenberg AA, Husain MM, Ginsberg D, Cooke RG (2005*a*). Vagus nerve stimulation for treatment-resistant depression: A randomized, controlled acute phase trial. *Biological Psychiatry* **58**, 347–354.

Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, Lavori P, Howland R, Kling MA, Rittberg B, Carpenter L, Ninan P, Moreno F, Schwartz T, Conway C, Burke M, Barry JJ (2005*b*). Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biological Psychiatry* **58**, 355–363.

Sackeim HA, Brannan SK, Rush AJ, George MS, Marangell LB, Allen J (2007). Durability of antidepressant response to vagus nerve stimulation (VNS™). *International Journal of Neuropsychopharmacology* **10**, 817–826.

Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M, O'Keane V, Corcoran C, Adolfsson R, Trimble M, Rau H, Hoff H-J, Padberg F, Müller-Siecheneder F, Audenaert K, Van den Abbeele D, Matthews K, Christmas D, Stanga Z, Hasdemir M (2008). Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychological Medicine*. Published online: 4 January 2008. doi:10.1017/S0033291707001924.

Shuchman M (2007). Approving the vagus-nerve stimulator for depression. *New England Journal of Medicine* **356**, 1604–1607.