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GUIDELINES

WFSBP Guidelines on Brain Stimulation Treatments in Psychiatry

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Introduction

Clinical psychiatrists are increasingly aware of an urgent need for new treatments for patients with severe neuropsychiatric disorders. Many patients do not respond to several courses of conventional treatments or combinations of them and are therefore called treatment resistant; or cannot tolerate them due to side effects (treatment intolerant). For more than 75 years, electroconvulsive therapy (ECT) has been the only substantially used non-pharmacological, somatic treatment of psychiatric disorders. This situation is now changing, and changing rapidly. New brain stimulation techniques are quickly emerging as highly promising novel avenues for treating psychiatric disorders in general, and major depression in particular (George et al. 1999). Research in this field is at a very important juncture, and there are signs that the first two decades of the current millennium could well be the decades of brain stimulation in psychiatry (Sackeim and George 2008). Several brain stimulation methods are approved for clinical use by the US Food and Drug Administration (FDA) and are thus available clinically (Higgins and George 2008). Other brain stimulation methods are currently under study, with the potential to cross the threshold to clinical use within the next few years.

The World Federation of Societies of Biological Psychiatry (WFSBP) has recognized the important role that brain stimulation techniques are beginning to play in on our field, possibly one day even coming close to rivalling the role of neuropyschopharmacology. The WFSBP has therefore instituted a task force on brain stimulation therapies in order to both stimulate research activity, and summarize available research data in a peer review process to provide guidance for research and treatment application of these new methods. The publication of these treatment guidelines for a wide range of psychiatric disorders is a step towards achieving these objectives.

Reflecting the rapid development in this field the WFSBP task force on Brain Stimulation will continuously update and publish these guidelines on a regular basis.

Significance of brain stimulation therapies

The human brain is enormously complex. One hundred billion neurons with 100 trillion connections sense, analyse and respond to the environment. Importantly, all of this interaction is done with a combination of electrical and chemical communication. Figure 1 shows a figure of a synapse that

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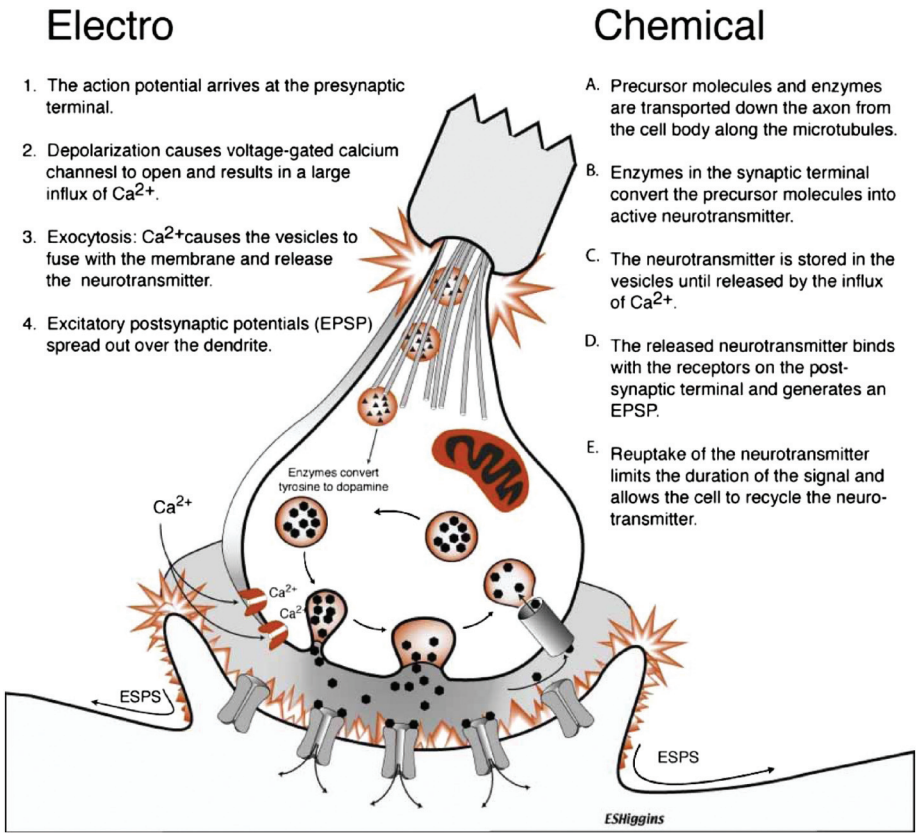

Figure 1. A cartoon of a synapse that highlighting *both* the electrical and chemical nature of one neuron communication. Reprinted with permission from Higgins ES, George MS. Brain stimulation therapies for clinicians. Washington, DC: American Psychiatric Press; 2008.

highlights *both* the electrical and chemical nature of one neuron communicating with another (Higgins and George 2007; Higgins and George 2008). That is, each bit of information is transformed into an electrical impulse that travels down an axon to a synapse, where the depolarization releases chemicals into the synaptic cleft. Essentially all of psychopharmacology can be reduced to subtly changing the probabilities of the next neuron carrying on the charge, or not. That is, the brain, in fact each neuron, constantly converts electrical information, to chemical signals, and then back again into more electrical information. The brain is an electrical organ and electricity is the currency of the brain. The brain stimulation therapies involve directly applying electrical signals to the scalp, brain or extended nervous system for the purposes of therapy.

Brain stimulation, unlike systemic pharmacology delivered orally or parenterally, focuses on electrical mechanisms of the brain, which then cause localized neurochemical changes. Applications of electrical stimulation by a variety of new and old techniques might be able to correct or positively influence underlying dysfunctions. Traditionally, brain stimulation therapies have been highly invasive and reserved for those with treatment-resistant disorders. However, there are also several new brain stimulation methods that are neither invasive or solely for the severely impaired.

The knowledge on brain stimulation therapies is likely to continue to grow substantially in the coming years. New delivery mechanisms, wider applications of existing technologies, and better understanding of the translational neurobiology of stimulation will both improve safety and efficacy of brain stimulation treatments and contribute to a better understanding of the underlying neurobiology of neuropsychiatric disorders (Schlaepfer 2003).

Major therapies

Electroconvulsive therapy (ECT)

The American Psychiatric Association (APA) has published clinical guidelines for the use of ECT (Task Force on Electroconvulsive Therapy 2001). These guidelines are currently being updated and will be published in 2010. The WFSBP has established a Task Force on Electroconvulsive Therapy, its guidelines will be report will be published in the future in addition to this report on non-seizure brain stimulation therapies. We will thus not restate those

guidelines but refer readers interested in recent summaries of the ECT process and its improvements to the ECT textbook by Abrams (2002), the German ECT handbook edited by Baghai et al. (2004), the revision of the UK handbook by Scott (2004), and the update for professionals and their patients by Fink (2009).

Vagus nerve stimulation (VNS)

Definition. Vagus nerve stimulation (VNS) therapy involves intermittent repeated stimulation of the left vagus nerve with a small electrical pulse from an implanted neurostimulator to a bipolar lead wrapped around the nerve in the neck (George et al. 2000, 2007; Kosel and Schlaepfer 2003). Although some have speculated that one might be able to stimulate the vagus nerve non-invasively through the skin, there is insufficient evidence to support this in clinical work at the moment (Huston et al. 2007). The stimulating wire wrapped around the nerve is directional, and this unidirectional feature likely helps minimize efferent side effects from stimulating vagal efferent (descending) fibers. However, it is likely that at least some patients have had the leads reversed, without noticeable harm (Koo et al. 2001).

The vagus nerve is actually a large nerve bundle, composed of different sized nerves (both unmyelinated and myelinated). The vagus nerve is thus a complex structure and the current form of VNS is imprecise with respect to activating discrete nerves within the bundle. Microsurgical techniques might theoretically allow for more focal VNS.

Evidence. On the basis of two RCTs, VNS was initially approved for use in treatment-resistant epilepsy and is widely used in this condition as an adjunctive treatment with medications (Uthman et al. 1993; Ben-Menachem et al. 1994; George et al. 1994; The Vagus Nerve Stimulation Study Group 1995).

No class I evidence on the efficacy of VNS in major depression has been demonstrated yet. An initial pilot open-label study in 59 patients with treatment-resistant depression demonstrated good results – a 30% response rate at 10 weeks (Rush et al. 2000). In these studies, VNS was added adjunctively to the treatment in patients remaining on antidepressant medications. Even more encouraging were the extended results in this treatment-resistant cohort who had all failed several antidepressant medication trials and over half had failed to respond or did not tolerate ECT. Patients continued to improve after the acute phase of the trial, although they were allowed to change medications. Patients were actually responding better at 1 year than they were at 3 months (Marangell et al. 2002; Nahas et al. 2005). This is unusual in the treatment of depression.

A recent open-label trial from Europe largely confirmed and extended the open-label US results, with a similar rate and time-course of response. In this study in 74 treatment-resistant unipolar depressed patients, VNS therapy was effective in reducing the severity of depression and efficacy increased over time (Schlaepfer et al. 2008b). Efficacy ratings were in the same range as those previously reported from the US study using a similar protocol. However, at 12 months reduction of symptom severity was significantly higher in the European sample than seen in the US trial. This might be explained by a small but significant difference in the baseline HAMD-24 score and the lower number of treatments in the current episode in the European study.

A pivotal multi-centred, randomized, double-blinded trial of VNS was not successful in demonstrating an acute adjunctive effect (10 weeks) of VNS for treatment-resistant depression. In this trial, active VNS failed to statistically separate from sham treatment in 235 outpatients (Rush et al. 2005). The response rates for acute treatment of treatment-resistant depression were 15% for active treatment and 10% for sham treatment.

A parallel but nonrandomized group was also studied and compared to those patients who received VNS in the pivotal trial above. Thus one group received the addition of VNS and the other received "treatment as usual" (TAU). The TAU group consisted of patients that were not a concurrent control group in the study and the VNS patients were receiving open-label VNS treatment over the period that was compared with the TAU group. Patients were followed for 12 months during which time both groups received similar treatment (medications and ECT) except for the VNS difference. At the end point the response rates were significantly different: 27% for the VNS group and 13% for the treatment as usual group (George et al. 2005). The FDA considered all these studies when evaluating VNS for depression. Notably, despite the relatively modest response rate at the defined study endpoint, the enduring long-term benefits in this particularly difficult to treat patient population was a likely critical factor in the ultimate approval. They were most impressed with the long-term enduring benefits for this difficult to treat population. In 2005, the FDA approved VNS for patients with chronic or recurrent depression, either unipolar or bipolar, with a history of failing to respond to at least four antidepressant trials. Interestingly, as with VNS for epilepsy, results of two large (60 and 76 patients) uncontrolled trials suggest long-term antidepressant efficacy developing rather slowly over the course of months and continuing

for up to 3 years in some cases (Sackeim et al. 2007). Novel effects of VNS have been seen in several animal models and may provide explanations for these slower but more durable clinical effects (Valdes-Cruz et al. 2008; Biggio et al. 2009; Manta et al. 2009).

Adverse effects. The adverse events associated with VNS are best separated into those associated with the complications of the surgery and those resulting from the side effects of stimulation. Although there are some safety data from the industry sponsored clinical trials in treatment-resistant depression (Rush et al. 2000; Schlaepfer et al. 2008b), much of the VNS safety literature has been generated from its clinical use in epilepsy.

Surgical complications. The risks associated with VNS surgery are minimal. Wound infections are infrequent (less than 3%) and managed with antibiotics. Pain at the surgical site commonly resolves within 2 weeks. Rarely left vocal cord paresis persists after surgery (<1 in 1000), but usually resolves slowly over the ensuing weeks. Temporary asystole during the initial testing of the device is a rare but serious surgical complication. In approximately one out of 1000 cases asystole has been reported in the operating room during initial lead testing. It may be a result of aberrant electrical stimulation resulting from poor haemostatic control. That is, blood in the surgical field causes arcing of the current and the cardiac branch gets depolarized. Fortunately, no deaths have been reported as normal cardiac rhythm has always been restored. Postoperatively these patients have been able to safely use VNS. More importantly, no cardiac events have been reported when the device is turned on for the first time after surgery.

Physical side effects from stimulation. After the initial testing of the device in the operating room, the patient is typically allowed to heal for 2 weeks before the stimulator is again turned on. Typically the generator is set to deliver intermittent trains of stimulation, lasting several seconds, followed by an off time between 30 s and several minutes. Side effects are typically restricted to the seconds when the stimulation is actually occurring and are mild. Side effects classified as moderate diminish typically over time. The most common side effects in the acute study period were voice alteration (63%), cough (26%), pain (20%) and dyspnea (10%). After 1 year of stimulation the most common side effects were voice alteration (55%) and dyspnoea (10%). These device-related side effects correlate with stimulation intensity and can be minimized with reductions in the stimulation parameters.

Parasympathetic response? One would speculate that VNS might increase the impulses going down the vagus nerve to the internal organs and induce a parasympathetic response. However, this has not been an issue. Vital signs have remained stable. Cardiac slowing has not been a problem. This may be due to the placement of the leads above the branches from the vagus nerve descending to the heart.

Psychiatric side effects. As with any effective treatment for depression, unintended activation is a worrisome side effect. Hypomania and frank mania have been reported (1–3%) (Frick et al. 2005). Usually these symptoms developed in patients with a prior diagnosis of bipolar disorder. Reducing the intensity of the stimulation or adding a mood-stabilizing agent has been used empirically to manage such symptoms. Likewise, cognitive impairment has not been documented and actually many patients report improved cognitive function (Sackeim et al. 2001).

VNS and MRI. The presence of the wire in the neck can cause heating with some medical interventions like diathermy, which is contraindicated in patients with VNS. Also, although MRI scanning of the head and neck can be done (Bohning et al. 2001; Chae et al. 2003; Cantello et al. 2007; Nahas et al. 2007), it should be done only with MRI coils that minimize heating in the neck (Cyberonics Inc. August 2006).

VNS and suicidality. Treatment-associated emergence of suicidal ideation is a concern with antidepressant medications but has not been reported as a direct side effect of VNS; this has not been studied in a large enough population to determine if this is also a problem with VNS.

Cognitive side effects. Cognitive impairment has not been an issue and actually many patients report improved cognitive function. The lack of cognitive impairments is one advantage in using VNS in children with epilepsy.

VNS and ECT. Preliminary evidence suggests that vagus nerve stimulation may be safely administered during a course of ECT, although future trials are needed to assess the safety of combined ECT and vagus nerve stimulation (Husain et al. 2002; Sharma et al. 2008).

VNS for other neuropsychiatric conditions. Open-label series have found some evidence of beneficial effects in anxiety disorders (Greenberg et al. 2008). A trial of VNS, placed in the abdomen below the

diaphragm, was not successful in treating obesity (Roslin and Kurian 2001) even though animal and other preclinical data suggested appetite suppressing properties. One double-blind study found an acute effect of VNS on food craving (Bodenlos et al. 2007).

Recommendation of the WFSBP Task Force for the Long-Term Management of Patients with Treatment-Resistant Depression. Psychiatrists should be aware of the clinical data suggesting long-term clinical response in some treatment-resistant patients. When deciding whether to recommend VNS for a patient, they should be aware of the safety issues, as well as the cost and the likelihood of response and the time course of response. VNS is not an acute treatment for depression and it is possible that peak benefit may not be evident until 10–12 months after initiating therapy. It therefore takes months for an effect to emerge, when it does. There is no Class I evidence for efficacy in acute or chronic depression, even though the FDA approved VNS in 2005 as an adjunctive treatment for adult patients with treatment-resistant depression (either bipolar or unipolar). Despite the clear lack of Class I evidence, based on the substantial safety literature and experience with epilepsy, and positive depression studies to date (which were uncontrolled but studied larger patient numbers), we recommend that psychiatrists consider using VNS along with other options in highly treatment-resistant patients with a chronic course who have tried and failed more than three other antidepressants. Prior response to ECT seems to be a predictor of response to VNS (Sackeim et al. 2007; Schlaepfer et al. 2008b). There is insufficient evidence to recommend VNS for other neuropsychiatric disorders, except epilepsy where it is an established and recommended treatment option.

Repetitive transcranial magnetic stimulation (rTMS)

Definition. Repetitive transcranial magnetic stimulation (rTMS) refers to the administration of series of pulsed magnetic stimuli to the brain for the purpose of altering brain function. rTMS delivers magnetic pulses to the cortex using a stimulating coil, which is applied directly to the head. The equipment necessary to deliver rTMS consists of two parts: one, a stimulator, which generates brief pulses of strong electrical currents whose frequency and intensity can be varied; and, two, a stimulation coil connected to the stimulator. The magnetic field generated at the coil passes unimpeded through scalp and skull and induces an electrical current in the underlying tissue, which in turn depolarizes neurons (George et al. 2003; Schlaepfer and Kosel 2004a). The main advantage of this method of stimulation is its non-invasiveness and the possibility to stimulate relatively small brain volumes. With recent technology, single, paired or repetitive magnetic pulses can be generated and delivered.

Types of coils. The majority of the research and clinical work with TMS has used either round or figure-of-eight coils, which are able to directly stimulate only the outermost layers of cortex (Nahas et al. 2001). Recently one group has created a new form of TMS coil that penetrates deeper into the brain (Roth et al. 2002, 2005; Levkovitz et al. 2007). There have been only a few studies with this deeper coil and the recommendations and discussions below largely apply to use of the round or figure-of-eight superficial coils.

Use as a research tool. Because it is non-invasive and allows one to stimulate the brain in an awake alert human, TMS is emerging as an important research tool. When the TMS device produces a pulse over the motor cortex, descending fibres are activated and volleys of electrical impulses descend through connected fibres into the spinal cord and out to the peripheral nerve where it can ultimately cause a muscle to twitch. The minimum amount of energy needed to produce contraction of the thumb (abductor pollicis brevis) is called the motor threshold (MT) (Fitzgerald et al. 2006; Fox et al. 2006; Sacco et al. 2009). Because this is so easy to generate, and varies widely across individuals, the MT is used as a measure of general cortical excitability and most TMS studies (both research and clinical) report the TMS intensity as a function of individual MT (and not as an absolute physical value) (Di Lazzaro et al. 2008). Although this convention has helped in making TMS safer, it is severely insufficient, in that it is referenced only to each machine, and thus is not a universal number. Future work is focusing on more universal, constant, measures of the magnetic field delivered.

TMS in general results in more activation of the CNS tissue, and a wider area of activation with a stronger, more intense pulse. The circumstance with frequency is more complex. In general frequencies of less than 1 per second ($\leq$ 1 Hz) are inhibitory (Hoffman and Cavus 2002). This may be because low frequency TMS more selectively stimulates the inhibitory GABA neurons, or this frequency is long-term depression (LTD)-like, although it is important to note that sometimes even low frequency TMS increases hippocampal reactivity to afferent stimulation and facilitates long-term potentiation (LTP) but not LTD effects (Levkovitz et al. 1999).

Conversely, higher frequency stimulation is behaviorally excitatory (Ziemann et al. 2008). However, high frequency TMS over some brain regions can temporarily block or knockout the function of that part of the brain (Pascual-Leone et al. 1991; Epstein et al. 1996).

Space does not permit a thorough overview of TMS research uses in this document on treatment guidelines, other than to highlight the active areas. TMS can be used as a measure of cortical excitability, and has been used to investigate medication effects, emotional states, plasticity in learning and stroke recovery, sleep (Massimini et al. 2007; Tononi and Koch 2008), and in a host of disease states. TMS can be combined with brain imaging to directly stimulate circuits and image the resultant changes. When precisely applied over critical brain regions, TMS can help causally determine whether a brain region is involved in a behaviour, and how information flows through the brain during a task. There is much excitement, but little hard evidence, that TMS might be used to actually augment task performance, memory formation, or recovery from injury.

We strongly support the statement from the International Society on Transcranial Stimulation (ISTS) regarding the research uses of TMS (Belmaker et al. 2003), and that even when being used for research in healthy adults, TMS is a medical procedure that should only be used under the supervision of a licensed medical doctor (see below).

Evidence. Largely because of its non-invasiveness, TMS has been investigated in almost all neuropsychiatric conditions. Until only recently, there has not been a TMS industry to promote or perform this work and thus much of the clinical work has been single site and non-industry funded, with relatively small sample sizes.

Depression. Depression has been the most widely studied condition with TMS (George et al. 2003; Schlaepfer and Kosel 2004b; Kosel and Schlaepfer 2005; Schlaepfer and Kosel 2005). Two initial studies from Europe and one from Israel used TMS over the vertex as a potential antidepressant (Hoflich et al. 1993; Grisaru et al. 1994; Kolbinger et al. 1995). In the US George, Wassermann and Post performed initial safety studies in healthy controls, an open study, and then a double blind controlled trial of repeated left prefrontal TMS for 2 weeks (George et al. 1995, 1996, 1997). These initial studies were hampered by concerns about safety and dose and were thus limited to treatment durations of 2 weeks or less and a relatively small TMS dose (intensity relative to motor threshold, number of pulses in a day, total number of pulses). Gradually, with more safety data, doses have increased and the time of treatment lengthened. A small study established a positive dose–effect correlation in a relatively older patient population (Mosimann et al. 2002) and general efficacy has been demonstrated in these patients as well (Mosimann et al. 2004). Currently there have been more than 25 randomized controlled trials (RCTs) of TMS in depression, and at least six different meta-analyses of these studies. Not surprisingly, depending on which trials are selected, and the meta-analysis method chosen, the meta-analyses have drawn different conclusions. Most meta-analyses have found an overall positive effect (Holtzheimer et al. 2001; Burt et al. 2002; Kozel and George 2002; Herrmann and Ebmeier 2006), and one other, using the very stringent COCHRANE criteria focusing on clinical significance of effects not (Martin et al. 2002). For example, one recent meta-analysis of repetitive TMS for depression examined 25 published sham-controlled studies (Mitchell and Loo 2006). The authors concluded that left prefrontal TMS provided statistical superiority over sham treatment for patients with depression. However, they concluded that the clinical benefits are marginal in the majority of reports and there is still considerable uncertainty concerning the optimal stimulation parameters. Those clinical features that appear to be associated with greater response include younger age, lack of refractoriness to antidepressants and no psychotic features (Holtzheimer et al. 2004; Avery et al. 2008).

Most of the initial studies were single site studies with small sample sizes (Holtzheimer et al. 2004). More recently the field has evolved and large multisite trials have been completed. A large trial in Germany of TMS as an adjunct failed to find a positive effect of TMS over sham (Herwig et al. 2007). This study was unique in several respects. TMS was added simultaneously with a variety of medications in patients with only modestly treatment-resistant depression. Additionally the researchers used a novel active sham technique over the temporal lobe, which may have biological activity. Nevertheless this was a large multisite trial where active prefrontal TMS did not differ from sham.

In the US, a TMS manufacturer, Neuronetics, Malevern, PA, conducted a large (12 sites, most in US but also Canada and Australia) study of daily left prefrontal rTMS for 4–6 weeks (with weekends off) (120% MT, 10 Hz, 4 on, 26 off, 3000 stimuli per day). Three hundred unipolar treatment-resistant patients were antidepressant medication free and were rated with two rating scales (HRSD, MADRS). Before conducting the experiment, the company chose the Montgomery–Åsberg Depression Rating Scale (MADRS) as

the primary outcome measure (and did not tell investigators in the field) while using the Hamilton Rating Scale (HRSD) as the entry criteria. At 6 weeks the MADRS for the active treatment group was not statistically different from the control group: $P = 0.058$. However, the decrease in HRSD, a secondary outcome measure, was indeed statistically superior for those in the active treatment group. In retrospect, it was determined that six subjects had very low entry MADRS scores and would not have been included in the study, had this been the entry screen measure. If these subjects are excluded, then there is a statistically significant effect of active TMS over sham. An initial FDA hearing on the data did not allow the exclusion of these subjects. The published manuscript, however, did (O'Reardon et al. 2005). A *post hoc* analysis of the data found a strong effect of treatment resistance on outcome, with those patients who had failed >3 trials, having no real response (Avery et al. 2008). In contrast, those with only one failed treatment trial had an overwhelming effect ($P < 0.001$). In light of good safety data, and this *post hoc* subgroup analysis showing a large effect in some patients, the FDA approved TMS for depression in October 2008 with a labelling that is consistent with the trial in terms of targeting TMS to those with only modest treatment resistance.

Although the majority of trials of rTMS in depression have used high frequency stimulation targeted at the left dorsolateral prefrontal cortex, at this stage it remains quite uncertain whether this is the optimal therapeutic strategy. A number of small trials have indicated that low frequency rTMS applied to the right DLPFC has similar efficacy and low frequency stimulation appears to be better tolerated and have a lesser risk of seizure induction. Studies have also suggested that a number of other strategies, such as sequential bilateral rTMS and priming rTMS, may have similar if not greater efficacy although few head to head trials have been published to date. The role of more novel approaches such as theta burst stimulation and "deep TMS" are not yet clear.

One recent development in terms of TMS positioning has highlighted that better understanding of the TMS methods used will likely boost clinical antidepressant efficacy. The early NIMH studies used a rough measurement technique known as the 5-cm rule to place the TMS coil roughly over the prefrontal cortex (George et al. 1995, 1996, 1997). Because the location of the motor strip varies between individuals, and skull size (hat size) also varies, this simple rule results in a large variation of actual location on scalp. It became obvious that this was an insufficient technique, but was nevertheless used in most trials, including the one for FDA approval (Herwig et al. 2001). One study suggested that the 5-cm rule resulted in 30% of patients being treated over supplementary motor area (SMA) rather than prefrontal cortex (Herwig et al. 2001).

An Australian group has performed a randomized controlled trial and a more anterior and lateral location did indeed produce superior antidepressant response (Fitzgerald et al. 2009). These findings suggest that the TMS effect is not non-specific, and that the location of the coil clearly matters, even within broad boundaries of a specific lobe. It is not clear whether individualized location will be needed or used, or whether general algorithms will suffice for most patients. There are several other large multisite trials currently underway to test these findings for potential replication.

There have been only a few case series of using TMS intermittently for *maintenance or prevention of depression* (Dannon et al. 2002; Grunhaus et al. 2003; Li et al. 2004; O'Reardon et al. 2005), and no long-term placebo controlled trials of maintenance TMS.

Other neuropsychiatric conditions. Because TMS can reversibly alter cortical function, it is being actively researched in many conditions: negative symptoms in schizophrenia, or hallucinations, anxiety, PTSD, OCD, tinnitus and migraine. *Auditory hallucinations* are part of the positive symptoms of schizophrenia. These types of hallucinations are believed to result from aberrant activation of the language perception area at the junction of the left temporal and parietal cortices (Higgins and George 2007). Low frequency TMS has been used to potentially inhibit this area in patients with schizophrenia and provide relief from auditory hallucinations. A recent meta-analysis examined the efficacy of low frequency TMS as a treatment of resistant auditory hallucinations in schizophrenia (Aleman et al. 2007). Ten sham-controlled studies have incorporated 212 patients. Their review concluded that TMS was effective in reducing auditory hallucinations. Unfortunately, TMS had no effect on other positive symptoms or the cognitive deficits of schizophrenia. Larger studies are needed to definitely establish the efficacy, tolerability and utility of TMS for schizophrenia. There have been several RCTs of using intermittent daily prefrontal TMS to treat negative symptoms in patients with schizophrenia. A recent comprehensive review concluded that there is also preliminary but limited evidence that rTMS could have a role in reducing the negative symptoms of schizophrenia and perhaps in augmenting cognitive function (Fitzgerald and Daskalakis 2008).

Tinnitus is a common, often disabling disorder, for which there is no adequate treatment. As many as 8% of adults over 50 years old suffer from tinnitus

which can often be quite distressing. Recent functional imaging studies have identified increased activity in the auditory cortex in patients with tinnitus. Low frequency TMS offers a possible mechanism to inhibit the overactive auditory cortex that may be producing tinnitus. Several small controlled trials from one research group in Germany have produced impressive results. (Langguth et al. 2008) Larger, multicenter studies are needed to see if these positive effects can be replicated.

Numerous small controlled studies have evaluated the utility of TMS in patients with *pain*. Multiple sites have been tested including prefrontal cortex, motor cortex and parietal cortex (Lefaucher et al. 2001; Lefaucheur 2004; Lefaucheur et al. 2001; Pridmore and Oberoi 2000; Rollnik et al. 2003; Andre-Obadia et al. 2006). In general TMS provides effective pain relief in these different locations in diverse pain conditions. Unfortunately, the effect of TMS on pain only lasts for a short duration. Consequently, the utility of TMS as a practical treatment for chronic pain conditions has yet to be established.

Recent studies suggest TMS may have some utility in managing *acute pain*. In two different studies of patients recovering from gastric by-pass surgery, 20 min of real or sham TMS was administered to the prefrontal cortex of every patient. Then their use of self-administered morphine was followed over the next 48 h. Those receiving real TMS used 40% less morphine in the next 24 h, with the majority of the reduction occurring in the first 8 h after TMS (Borckardt et al. 2006, 2008). The handheld device, mentioned above, is being studied as a treatment for migraine headaches. Preliminary results have been encouraging. Larger studies are underway.

Theoretically low frequency TMS could be used to treat cortical *epilepsy*. Early studies showed that TMS could reduce EEG epileptiform abnormalities. Initial case studies were positive. A controlled study of daily TMS by Theodore et al. over the cortical site of seizures for 1 week found a statistically significant reduction in seizures (Theodore et al. 2002). However, the authors concluded that TMS treatment was not clinically significant. More recently, another controlled trial concluded that "active" rTMS was no better than placebo for seizure reduction (Cantello et al. 2007). Thus the idea of using inhibitory doses of TMS to calm cortical targets is intriguing. However, the controlled trials to date have not been as successful.

Adverse events. In general TMS is regarded as safe and without enduring side effects. There have been no reported lasting neurologicAL, cognitive or ardiovascular sequelae as a result of TMS. However, TMS can alter brain function (such as improving mood), so clinicians and researchers must remain vigilant about the possible development of long-term problems.

Seizures. Inducing a seizure is the primary safety concern with TMS. A summary document from a recent international safety meeting on TMS now reports 12 cases of seizures induced with TMS (Wassermann 1997). They estimate these 12 cases occurred with a sample size of several thousand. This puts the risk at less than one half of one percent. Most of these patients were healthy volunteers without a history of epilepsy. Fortunately, there are no reports that the individuals affected experienced recurrence. Also, all of the seizures occurred during TMS administration when the patient was sitting down and near an investigator. Also, all of the seizures were self-limited without needing medications or other interventions. Of the reported cases the majority were receiving TMS to the motor cortex – the most epileptogenic region of the cortex. Additionally, most (but not all) were receiving trains of stimulation outside of suggested limits. These cases suggest that TMS induced seizures will remain a small but significant adverse event even in patients without a history of seizures and even when TMS is used within suggested guidelines.

Hearing impairment. One patient reported a temporary hearing loss after TMS. In light of this an extensive study of auditory threshold was conducted before and after 4 weeks of TMS in over 300 patients. No changes were found (Janicak et al. 2008). However, patients and TMS operators should wear earplugs when receiving TMS.

Headache. Headaches are the most common complaint after TMS, typically relieved by non-narcotic analgesics such as aspirin. The incidence of headache did not differ between active and sham in the largest clinical trials to date (Janicak et al. 2008).

Cognitive impairment. Repeated analysis of cognitive functioning of TMS patients has not found any enduring negative effects from the procedure (Little et al. 2000; Schulze-Rauschenbach et al. 2005; Janicak et al. 2008). After a session, patients are able to drive home and return to work.

Recommendations of the WFSBP Task Force regarding TMS. For the acute management of patients with moderately treatment-resistant depression. There is sufficient class I evidence of acute efficacy for TMS in depression in medication-free unipolar depressed patients. The large body of evidence from single site small sample trials suggests that it may also be useful clinically in moderately treatment-resistant patients,

either alone or used adjunctively with medications. We thus recommend that psychiatrists consider using TMS in non-psychotic adults with major depression. Typically patients will have tried and failed at least one attempt at medication therapy, although this is not required. There are only limited data about using it in a maintenance fashion after acute response.

As rTMS efficacy data is continuing to emerge, the choice of stimulation parameters including frequency, laterality, intensity and duration of treatment will need to be determined by a psychiatrist familiar with the relevant and recent rTMS literature.

Recommendations of the WFSBP Task Force regarding who should administer TMS. The WFSBP Task Force endorses the International Society of Transcranial Stimulation (ISTS) Guidelines concerning TMS administration (Belmaker et al. 2003). Published in 2002 before FDA approval of TMS for depression, they state:

> Repetitive transcranial magnetic stimulation (rTMS), defined as the administration of a series of magnetic stimuli to the brain for the purpose of altering brain function, is an experimental medical intervention. rTMS is currently used to probe various aspects of brain function in the context of research studies approved by local ethics committees. rTMS is also under investigation as a potential treatment for various neurological and psychiatric disorders. In light of the growing interest in using rTMS in a variety of experimental risks and potential benefits in patients, the informed consent process, setting of rTMS stimulation parameters, and monitoring of subjects during and after rTMS.
>
> Those who administer rTMS should be trained as "first responders" in order to render appropriate care in the event of seizure. rTMS should be performed in a medical setting with appropriate emergency facilities to manage seizures and their consequences. Patients and research subjects should be continuously monitored during the administration of rTMS for signs of epileptic activity or other adverse effects by a trained individual, according to criteria established in the clinical or experimental protocol. This monitoring may include electrophysiological recording and/or visual inspection. During the informed consent process, patients and study participants should be informed of the risk of seizure and its possible medical and social consequences. The dosage of rTMS should generally be limited by published safety guidelines (e.g., Wassermann, Clin Neurophysiol, 1998;108:1 or any subsequent updates). If there is a compelling scientific or clinical reason to exceed such guidelines, the rationale for doing so should be considered carefully, documented and the patients or study participants should be informed that they may be at higher risk for seizure. The long-term risks of rTMS are not known. However, the limited data available at this time (2002) from repeated application of high intensity, time-varying magnetic fields to humans, as in magnetic resonance imaging, do no suggest that they are significant.
>
> The use of rTMS should comply with regulations put forward by local regulatory bodies, medical professional organizations, and medical licensing boards.
>
> We recommend immediate responsibility and supervision by a **licensed physician** (our bolding) because of the possibility of adverse events necessitating medical intervention. For research uses, clearly the exact circumstances of implementation have to be consistent with the risk of the study protocol, which is determined by patient or subject population being researched and the stimulation parameters chosen (patient or subject population, parameters).

Magnetic seizure therapy (MST)

Definition. MST is a method, which uses rTMS, as described above, but at much higher doses and at convulsive parameters in order to purposefully induce therapeutic seizures under general anesthesia in the same setting as that used for ECT (Kosel et al. 2003; Lisanby et al. 2001a, 2003b; White et al. 2006; Kirov et al. 2008; Cycowicz et al. 2008; Spellman et al. 2008; Cycowicz et al. 2009; Rowny et al. 2009).

Evidence. The initial hope for MST was that it might have several advantages over ECT (Sackeim [1994). Early testing in non-human animals largely confirmed these ideas and found that magnetically induced seizures compared to ECT seizures were more spatially precise, less susceptible to surface tissue impedance and had greater control of intracerebral spatial distribution and spread to deep brain structures (Lisanby et al. 2003c). In 2000, the new method to induce therapeutic seizures was first used in a proof of concept study in Switzerland, this demonstrated the feasibility of reproducibly inducing seizures in humans (Lisanby et al. 2001b). Effects of MST on cognitive functioning have been examined in humans and non-human primates (Kosel et al. 2003; Lisanby et al. 2003a; Moscrip et al. 2006). Moderate-dose MST, administered at 2.5 times the seizure threshold, resulted in fewer cognitive adverse

effects than ECS, also provided at 2.5 times seizure threshold. Patients take significantly less time to complete cognitive tasks and showed greater accuracy after moderate-dose MST than ECS in animals or ECT in humans. In addition to studying the cognitive safety profile seen with MST, some studies have examined its clinical efficacy compared to ECT. Mainly for ethical reasons, there has not been a study of MST compared to sham MST. There have been two parallel comparison trials of MST and ECT, each with 10 MST patients and 10 with conventional ECT (White et al. 2006; Kayser et al. 2009). Both studies established antidepressant efficacy of MST and even failed to find a difference between ECT and MST, although the small sample sizes would have only been able to detect large differences and do not afford the statistical power to establish equivalency. Given the clearly established (both in these and other studies) better side effect profile of MST the demonstrated antidepressant efficacy is important.

Side effects. MST appears to have a side effect and risk profile similar to ECT, but with a significantly more favourable cognitive profile than ECT, with a drastically shorter time to full recovery after seizure (Lisanby et al. 2003b; Kirov et al. 2008; Kayser et al. 2009).

Recommendation of the WFSBP Task Force regarding MST. The equipment for MST is still in a prototype stage and is not commercially available (Magstim, Magventure). However, MST for the acute treatment of major depression appears to be a potentially useful variant of ECT, especially in terms of reduced cognitive side effects. In addition, all studies so far demonstrate a dramatically shorter time to full orientation after MST-induced seizures compared to ones induced by ECT. Because there are only two small sample studies to date with relatively uniform and restricted entry criteria, it is not known whether all the rules concerning ECT and depression apply equally to MST. For example, it has not been studied in psychotic depression, a condition where ECT is our best treatment. At this time there is insufficient evidence to recommend MST for general clinical use in treating any neuropsychiatric disorder, although the small studies to date are promising.

Deep brain stimulation (DBS)

Definition. Recent advances in stereotaxic neurosurgical methods have provided a novel and promising technique for alleviating symptoms in psychiatric patients with well characterized psychiatric disorders that are resistant to available interventions. Deep brain stimulation (DBS) has emerged as a generally recognized technology, having been developed initially to treat patients with Parkinson's disease. DBS involves the MRI and electrophysiologically guided stereotaxic placement of unilateral or bilateral electrodes in target brain regions connected to a permanently implanted neurostimulator, which electrically stimulates that brain region (Schlaepfer and Lieb 2005; Schlaepfer and Bewernick 2008). In these guidelines the term deep brain stimulation refers to methods where electrodes are implanted deep in the brain under the dura. We separately review the electrical stimulation techniques where electrical grids are placed beneath the skull but on top of the dura (extradurally) over the superficial cortex (see below).

Evidence. Parkinson's disease and other primary movement disorders. The first modern use of DBS involved treatment for Parkinson's disease tremor (Limousin et al. 1995; Limousin et al. 1998). This success and subsequent FDA approval has been followed by application of comparable methods to the treatment of essential tremor, dystonia and epilepsy (Halpern et al. 2007; Tisch et al. 2007). DBS for these various disorders involves placing the electrodes at one of several different target locations: the subthalamic nucleus (STN), globus pallidus (interna) (GPi) for PD, and modulating defined or putative neural circuits using continuous stimulation and stimulus parameters unique to each condition.

Obsessive–compulsive disorder. The neuropsychiatric use of DBS began with work for treatment-resistant OCD patients in Belgium with the electrodes implanted bilaterally in the anterior limb of the internal capsule (Nuttin et al. [1999,2003; Greenberg et al. 2008). This DBS placement was based on the hypothesis that neuromodulation mediated by high frequency DBS would mimic ablation of the same target, a rare but tested procedure for the treatment of intractable OCD patients. Based on a open case series of patients in the US and Europe demonstrating safety of ventral anterior capsule DBS and improvement in OCD symptoms, a humanitarian device exemption (HDE) was granted to Medtronic (Minneapolis, MN) in February 2009 to use DBS "in conjunction with medications for the treatment of chronic, treatment-resistant adult OCD patients to aid in the management of the symptoms". An HDE is granted when a treatment is deemed safe but does not require a randomized placebo controlled clinical trial, as efficacy is not claimed. Patients can

seek treatment under an HDE from a facility with IRB approval to perform the procedure.

Depression. The development of DBS for depression has taken a different strategy to that used for OCD, capitalizing not only on clues from past ablative targets but also on findings from basic and imaging neuroscience studies. A first strategy built on the observation that OCD patients undergoing DBS to the anterior limb of the capsula interna (ALIC) showed mood improvement independent of OCD symptoms changes. As ventral capsulotomy had also been previously used to treat intractable depression, this target was tested using DBS in this patient population. Lead by researchers at Brown University, 15 treatment-resistant patients were implanted in an open-label fashion with the DBS electrodes as an adjunctive treatment. Researchers reported a 40% response rate at 6 months (Malone et al. 2009).

In a second strategy, researchers at the University of Toronto targeted the subcallosal white matter tracts immediately adjacent to the subcallosal cingulate gyrus (Brodmann Area cg25), bilaterally, with the intent to modulate a putative depression circuit critical to antidepressant response identified using other interventions (109. In an open-label study of 20 treatment-resistant unipolar depressed patients, Brodmann Area cg25 a 60% response rate was seen at 6 months that was sustained at 1 year (Lozano et al. 2008; McNeely et al. 2008).

Following yet a third line of reasoning postulating the critical role of the nucleus accumbens in the anhedonia characteristic of major depression (Schlaepfer et al. 2008a), investigators at the University of Bonn, Germany, assessed effects of bilateral high frequency stimulation to the nucleus accumbens (NAcc) directly. Acute anti-anhedonic and short-term antidepressant effects have been demonstrated (Schlaepfer et al. 2008a) with long follow-up showing response in 50% of the patients (Bewernick et al. [2009).

While these first reports are encouraging, randomized placebo-controlled studies will be needed to determine actual clinical efficacy. Such industry sponsored trials for both the ALIC and the Cg25WM targets are in progress. Also necessary will be direct comparisons of differential symptom response, side-effect profiles and optimal stimulation parameters between these stimulation sites. As with Parkinson's disease, where stimulation several distinct targets within the motor circuit proved effective, they showed different side-effect profiles and differential effects on core PD symptoms. Future research studies might in fact be designed to determine if DBS target selection might be optimized for individual depressed patients.

Other indications. There are case reports and ongoing studies of DBS in the treatment of Gilles de la Tourette syndrome, substance abuse, obesity and schizophrenia. With these and future potential indications, it is expected that hypothesis driven brain targets will be tested in context of known or putative neural circuits relevant to the pathogenesis of the disorder or known mechanisms mediating available standard treatments.

Adverse events. For DBS for all indications, side effects are seen related to the operation itself (e.g., bleeding, seizures, stroke, electrode breakage, local infections at the implantation site or generator location) or to the stimulation (e.g., autonomic dysfunction, motor slowing/abnormal movements, increase of mood, anxiety, agitation, hypomania) (Synofzyk and Schlaepfer 2008). Fortunately, the safety of the stereotactic operation technique has been improved in the last years with the help of improved structural neuroimaging. Nonetheless, rates of hemorrhage with DBS surgery are between 0.2 and 5% (Greenberg et al. 2003; Malone and Pandya 2006; Lozano et al. 2008; Bewernick et al. 2009; Malone et al. 2009).

Recommendation of the WFSBP Task Force regarding DBS. Continued research in deep brain stimulation (DBS) for neuropsychiatric disorders is supported, first, by evidence of beneficial affective outcomes and decreased obsession symptoms in patients undergoing DBS for the treatment of movement disorders and, second, by data from a small number of early case reports of successful outcomes in some research participants with these disorders undergoing DBS as a treatment for severe, treatment-resistant neuropsychiatric disorders.

DBS, although it is less invasive than ablative surgery as it is reversible and does not intentionally damage brain tissue, it is nevertheless an invasive procedure and should be performed by a team pairing a psychiatrist with experience with treatment-resistant patients and an experienced stereotaxic neurosurgeon. Referring clinicians further need to be cognizant that these procedures are experimental and should be performed only within controlled research or industry sponsored trials with institutional and preferably external ethical oversight. Recognizing that these patients may represent a more vulnerable population (i.e. intractable chronic illness unresponsive to available treatments) multiple international initiatives are carefully examining strategies to define appropriate ethical standard appropriate to this unique new potential treatment strategy. As this paper is being updated we will reference those publications as they are being published.

Other brain stimulation methods

Here we summarize brain stimulation treatments proposed for neuropsychiatric disorders which are either in an early stage of development or where there is insufficient data to judge efficacy and safety.

Extradural cortical stimulation (ePCS)

Another form of invasive electrical stimulation involves implanting a grid of electrodes underneath the skull but outside the dura. This form of "cortical stimulation" has been used for many years over motor cortex to control pain. Nahas and colleagues reported a small case series has been performed over the prefrontal cortex in depressed patients, using intermittent stimulation (Hajcak et al. 2008). Additionally a small case series was reported of constant high frequency cortical stimulation over the prefrontal cortex in depressed patients (Dougherty and Thase 2008). Northstar Neuroscience, a medical device company, has been given conditional FDA approval to run a second study of its brain-stimulation device against depression in which 24 patients will be enrolled. Preliminary results are expected to be available in the second half of 2009.

Recommendation. This line of work is clinically indicated for chronic pain. The depression research is still investigational and not ready for clinical use.

Transcranial direct current stimulation (tDCS)

A German neurophysiology research group has led a recent resurrection of this technology, and there is now very active investigation of tDCS (Nitsche and Paulus 2009). Clearly, tDCS has effects on the brain – it can boost cortical excitability (Boros et al. 2008) and improve memory (Boggio et al. 2009) in healthy people. Whether these effects can be used therapeutically remains to be determined.

tDCS involves passing a weak (usually $\leq$1 mA) direct DC current through the brain between two electrodes. The current enters the brain from the anode, travels through the tissue and exits out the cathode. Some researchers refer to this as either cathodal tDCS or anodal tDCS depending on which electrode is placed over the region that is being modified. The administration of tDCS is relatively easy. Many researchers simply use damp sponges as the electrodes. These can be placed anywhere on the scalp and are held in place with an elastic headband.

Side effects of tDCS depend on the placement of the electrode, whether it is anodal or cathodal, the intensity of the stimulation, and the length of time the patient is treated. In the older prefrontal treatment literature, skin burns could occur, and some patients felt uncomfortable or even had dizziness. Modern treatments are minimally troublesome at worst.

Evidence. As with all of the new stimulation techniques, there have been groups trying out the technology in many neuropsychiatric disorders. Single site small sample studies have suggested some positive effects of tDCS in pain, migraine, fibromyalgia, depression and epilepsy. None of the studies were large or multisite, and the sample sizes have been small. Further work is needed to see if these early promising studies replicate.

Recommendations tDCS is not ready for clinical use at this time

Cranial electrotherapy stimulation (CES, alpha-stim). Cranial electrotherapy stimulation (CES) is another form of electrical current applied to the peripheral skin in order to influence the brain. CES is sometimes called Electrosleep, or Cranial Electrosleep as it can make a user sleepy or "spacey" during the stimulation.

One device is commercially marketed in the United States as "Alpha-Stim" and has received much publicity recently. The devices are "FDA approved" for anxiety, insomnia, or depression because they were grandfathered in when the medical device act was passed in 1979. CES, like ECT that was also grandfathered in, has not been examined the way VNS, TMS or the antidepressant medications have. Unlike ECT, CES has not been subjected to any large multicenter randomized blinded studies.

CES involves applying a pulsed, low-amplitude electrical current to the head using electrodes clipped to the earlobes. The current comes from a battery source that looks like a TENS device, but has a high frequency cycling design. Thus, using the nomenclature adopted for this guideline document, CES is a specific type of transcutaneous alternating current as the pulse is bidirectional. The user can increase the intensity from 10 up to 500 millionths of an ampere, but the frequency is set at 0.5 Hz. Since CES generates an alternating bidirectional current, it does not matter which ear is the anode or cathode. The standard session lasts 20 min/day but can go as long as 60 min if needed.

Adverse events. Many patients will experience mild dizziness, vertigo, and sometimes anxiety or nausea when they start the device. These effects are dose dependent and generally treatment is applied at a setting that is tolerable. In some CES studies patients have noted headache, skin irritation (e.g., burns) and lightheadedness or vertigo during or following treatment. Activation is described as a potential side

effect in the brochure, but frank mania or hypomania are not mentioned.

Evidence of clinical effects. It is difficult to provide a measured assessment of the clinical studies of the CES device, as there are numerous small studies in nontraditional journals for a poorly characterized variety of psychiatric and neurological conditions. In general the device seems to promote "stress reduction". As such, the best use of the device may be for anxiety, depression and insomnia. However, there are reports of CES benefiting fibromyalgia, headaches, tremor, ADHD, cognitive dysfunction as well as substance abuse withdrawal. Although many studies on CES have been published in the last 30 years, most have used relatively small samples in which only a dozen or so patients received the active treatment. In addition, the frequency and duration of CES treatment has not been established for different conditions. While short-term CES (e.g., one to five treatments of 23–30 min each) may help with acute anxiety, some researchers argue that chronic conditions may require longer periods of treatment (Jarzembski 1985) and that effective therapy for patients with clinical depression or anxiety disorders may only result from daily CES for 2–4 weeks. The lack of negative studies reported in the literature is troublesome. A single meta-analysis of studies with CES was published over a decade ago (Klawansky et al. 1995). They reviewed randomized controlled trials of CES for anxiety, brain dysfunction, headache, and insomnia. A total of eight trials on anxiety were combined and analysed using effect sizes to compare outcome measures. Overall, CES was significantly more effective than sham treatment (effect size = 0.62) although placebo effects may have been a factor since many patients who received sham therapy also improved (30%) (Klawansky et al. 1995).

Recommendation. The CES studies are small and of poor quality but the device is inexpensive and it appears relatively safe. It is hard to know whether the treatment is truly effective or not. Rigorous academic studies are needed and we do not recommend its clinical use.

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Statement of Interest

Dr Schlaepfer received limited support for an investigator-initiated study on DBS for treatment-resistant major depression from Medtronic. Inc., a manufacturer of DBS devices from 2005 to 2007. He was the lead investigator of the European D03 VNS study of Cyberonics Inc., limited study support was received until 2005.

Dr George has no equity ownership in any device or pharmaceutical company and his total industry-related compensation per year is less than 10% of his university salary. His institution, MUSC has filed eight patents or invention disclosures in his name regarding brain imaging and stimulation. He is the study chair of a large NIMH sponsored trial of TMS in depression (called OPT-TMS) and is on the executive committee of a large veterans administration (VA) trial of TMS in Depression (CSP#556). He thus has received no compensation from any TMS manufacturer for the last 4 years, but is an unpaid consultant to Neuronetics, Brainsway, and Neostim, as well as PureTech Ventures. MUSC is a site in a multisite Brainsway sponsored trial. Neuronetics has donated equipment for an investigator initiated VA trial of TMS in acute suicide. Dr George has been a paid consultant or received research grants from Cyberonics (VNS) and Neuropace (DBS), but not in the past year. Medtronic donated equipment for an investigator-initiated trial of epidural cortical stimulation conducted at MUSC (PI, Dr Nahas). Within the past 3 years he has received industry support for two TMS studies investigating the effects of medications on brain excitability (Jazz pharmaceuticals, Glaxo Smith Kline). He is the editor in chief of an Elsevier sponsored journal, Brain Stimulation. He is currently funded by NIMH, NIDA, VA and DOD.

Dr Mayberg is a consultatnt to St. Jude Medical, a DBS device manufacturer. In addition, she licenses intellectual property to St. Jude Medical.

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