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REVIEW ARTICLE

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ABSTRACT

In the treatment of depression, when pharmacotherapy, psychotherapy and the oldest brain stimulation techniques are deadlocked, the emergence of new therapies is a necessary development. The field of neuromodulation is very broad and controversial. This article provides an overview of current progress in the technological advances in neuromodulation and neurostimulation treatments for treatment-resistant depression: magnetic seizure therapy; focal electrically administered seizure therapy; low field magnetic stimulation; transcranial pulsed electromagnetic fields; transcranial direct current stimulation; epidural cortical stimulation; trigeminal nerve stimulation; transcutaneous vagus nerve stimulation; transcranial focussed ultrasound; near infra-red transcranial radiation; closed loop stimulation. The role of new interventions is expanding, probably with more efficacy. Nowadays, still under experimentation, neuromodulation will probably revolutionise the field of neuroscience. At present, major efforts are still necessary before that these therapies are likely to become widespread.

KEY POINTS

- There is a critical need for new therapies for treatment resistant depression.
- Newer therapies are expanding. In the future, these therapies, as an evidence-based adjunctive treatments, could offer a good therapeutic choice for the patients with a TRD.
- The current trend in the new neuromodulation therapies is to apply a personalised treatment.
- These news therapies can be complementary.
- That treatment approaches can provide clinically significant benefits.

ARTICLE HISTORY
Received 27 October 2018
Revised 28 January 2020
Accepted 6 February 2020

KEYWORDS
Treatments resistant depression; neuromodulation; neurostimulation; technological advances

Introduction

Treatments resistant depression (TRD) is a major clinical problem for which there are few therapeutic options. In the last two decades, numerous non-invasive and invasive neuromodulation and neurostimulation methods have been used in clinical treatment for this disease. These techniques have evolved at different levels of evidence, with different safety profiles. For each therapy, the procedures are increasingly complex and it is now clear that there is a real effort to try to better understand the possible mechanisms of action, with a multiplication of articles devoted to this subject.

Magnetic seizure therapy

Magnetic seizure therapy (MST) is a non-invasive convulsive neurostimulation therapy using a high-powered transcranial magnetic stimulation (TMS) device to produce therapeutic seizures. In a review, Kallioniemi et al. describe MST methodology, the clinical and cognitive effects of MST and how it could be individualised to each patient (Kallioniemi et al. 2019). To date, randomised controlled trials suggest that MST has similar antidepressant efficacy as electroconvulsive therapy (ECT), but without significant cognitive adverse effects (Table 1; Cretaz et al. 2015). A recent study that enrolled 37 patients with TRD compared the neurocognitive effects of MST and ECT on domains of attention, executive function, processing speed, verbal and visuospatial memory and founded no significant decline in performance within the cohort treated with MST (Fitzgerald et al. 2018). There is currently no information available as to optimal MST stimulation parameters. A neurocognitive improvement was observed in patients with TRD who completed an accelerated MST protocol (Wang et al. 2018). There are no large-scale controlled studies of relapse following maintenance MST. Actually, research in MST and the clinical application is limited to a few study centres worldwide, because a specially modified device is required. A randomised, double blind, non-inferiority clinical trial with two treatment arms has conducted in two international academic medical centres (the Centre for Addiction and Mental Health in Toronto, Canada and UT Southwestern in Dallas, Texas): CREST-MST (confirmatory efficacy and safety trial of magnetic seizure therapy for depression). The investigators are pursuing this clinical trial in an effort to compare MST, to Right Unilateral Ultrabrief Pulse Electroconvulsive Therapy (RUL-UB-ECT), in relation to suicidal thinking, cognitive side effects and depressive symptoms in 260 patients with TRD. MST treatment will be administered using the MagPro MST with a Cool TwinCoil over the frontal cortex in the midline position using 100 Hz stimulation. In the ECT arm treatment, the MECTA spectrum 5000Q machine will be used. Treatment will be administered two to three days per week. Depression symptoms will be assessed with the Hamilton depression rating scale (HDRS)−24 and suicidality with the scale for suicidal ideation. This trial is ongoing (required reporting date, 31 July 2023; ClinicalTrials.gov

Table 1. Clinical studies: magnetic seizure therapy versus electroconvulsive therapy.

Author	Objective	N°	Study design	Cognitive results	Clinical outcomes
Lisanby et al. (2003)	Assert the safety and feasibility of MST for TRD	10	RCT MST × ECT	MST > ECT on multiple cognitive domains MST: elicited shorter seizures	N/A
White et al. (2006)	Evaluation of anaesthetic aspects of MST	20	RCT MST × ECT	MST resulted in lower variation on BIS and faster reorientation	ECT reduced HAM-D from 30 to 6 MST reduced HAM-D from 32 to 14 after 10 − 12 sessions
Kirov et al. (2008)	Assessment of reorientation time after HD-MST	11	RCT MST × ECT	MST faster reorientation (7 :12min) ECT (26: 35min)	N/A
Kayser et al. (2011)	Effectiveness and safety of MST compared to ECT	20	RCT MST × ECT	No cognitive loss on either group	MST: 60% response and 30% remission; ECT 40% response
Kayser et al. (2013)	Assessment of cognitive and seizure characteristics of HD-MST and ECT	7	Open-label, follow-upMST after failure to ECT	Shorter reorientation after MST; seizures similar, but shorter after MST	N/A
Hoy et al. (2013)	Effects of MST on brain glucose metabolism	10	Open-label	Glucose metabolism increased in several areas	57% of response after treatment
Fitzgerald et al. (2013)	Effectiveness and safety of MST	13	Open-label	Fast reorientation with patients reporting awakening under muscle relaxation	Five patients responded, two of which achieved remission
Polster et al. (2015)	Compare acute memory retrieval of MST and ECT	30	Open-label	Delayed recall disturbed after ECT but not after MST	N/A

MST: magnetic seizure therapy; ECT: electroconvulsive therapy; RCT: randomised clinical trials.

NCT03191058). Further research will be helpful in identifying personalised targets to maximise clinical benefit.

Focal electrically administered seizure therapy

Focal electrically administered seizure therapy (FEAST) is an experimental approach that combines unidirectional current, polarity control and asymmetric electrode arrangement (with one electrode much larger than the other). This new positioning of the electrodes and their geometry has been proposed as a means of initiating seizures in the prefrontal cortex. The aim of this technique is to induce epileptic seizures more effectively than traditional ECT, with fewer cognitive side effects. The feasibility study for depressed adults began at the Psychiatric Institute of Columbia University, New York and continued at the Medical University of South Carolina with an optimisation of the stimulation protocol. This study was the first human clinical application ($N = 17$; Nahas et al. 2013). The recovery time of the orientation was evaluated, which proved to be a good predictor of long-term memory side effects. After treatment with FEAST (median of 10 sessions), 8 of the 16 patients met the prespecified response criteria (50% reduction on the HDRS-24 scale). FEAST produces an antidepressant effect, with a clinically significant improvement, and with a relatively rapid reorientation. This first preliminary work has shown that this technique is feasible, safe and well tolerated. A study had proposed to demonstrate the benefits of using FEAST to achieve a clinically meaningful remission rate (at least 50%; Borckardt et al. 2009). FEAST was designed to increase the focality of stimulation and better match stimulus parameters with neurophysiology. Sahlem et al. reported the safety, feasibility, preliminary efficacy and cognitive effects of FEAST in a new cohort (Sahlem et al. 2016). In a recent study, 30 patients with a TRD had a treatment of three sessions of focal FEAST administered for 2 to 6 weeks. The aim of this study was to maximise the efficacy of the technique and to analyse the recovery time of the orientation, which could be used as a marker of potential long-term cognitive side effects. A two-site, open-label, non-randomised update, suggests FEAST may have a reduced time to re-orientation compared to right RUL-UB-ECT (Sahlem et al. 2019). Further work is needed to refine the technique and compare it with conventional approaches.

Low field magnetic stimulation

Low field magnetic stimulation (LFMS) is a new experimental technique. LFMS employs the unique magnetic field waveform used in echo-planar magnetic resonance spectroscopic imaging to deliver a low intensity, time-varying electric field in the brain ($E \leq 1$ V/m, 1 kHz). The device comprises a cylindrical magnetic coil, the power source, and an amplifier which generates a magnetic field which induces a rapid oscillation field at low voltage and a higher frequency than the electromagnetic fields used for TMS and ECT. This magnetic stimulation was administered using a system called synchronised TMS (sTMS, based on EEG alpha rhythm). As a mechanism of action, LFMS does not evoke neuronal action potentials, but has been shown to modulate the metabolism in broad regions of human cerebral cortex (Volkow et al. 2010). The construction and testing of a portable electromagnetic device enabled a double-blind, randomised, placebo-controlled study. The authors studied the effects of LFMS in a large group of patients with bipolar disorders ($n = 41$) and TRD ($n = 22$). Subjects received treatment for 20 min. The change in mood was then immediately evaluated, using the visual analogue scale (VAS) and the HDRS-17. In patients treated with LFMS, an improvement (10% of baseline) was observed in mood relative to controls. There was also a large penetration of the field emitted by the LFMS through the cerebral cortex (Rohan et al. 2014). LFMS shown in preliminary studies to have immediate mood elevating effects. Its tolerance is good, but its efficacy remains controversial (Leuchter et al. 2015). For example, in a 4-day double-

blind study of LMFS in TRD ($n = 84$), there were no differences between LFMS-treated patients and those treated with sham (with the exception of a slight, non-significantly greater improvement than sham in the VAS sad mood on LFMS-treated patients (Fava et al. 2018). In a double-blind randomised controlled trial, 30 participants with TRD were randomised to three 20-min active or sham LFMS treatments with 48 h between treatments. The response was assessed immediately following LFMS treatment using the HDRS-6, the positive and negative affect scale and the VAS. In this study, two of three primary outcome variables of mood symptoms showed greater improvement after three treatments in the active LFMS group than in sham LFMS. This is the first study to demonstrate mood-enhancing effects of LFMS in unipolar TRD (Dubin et al. 2019).

Transcranial pulsed electromagnetic field

Transcranial pulsed electromagnetic field (T-PEMF) is an experimental approach that uses a generator to provide electrical pulses to a set of coils, which produce low pulsed electromagnetic fields. The stimulation intensity is lower than that generated by a TMS and is insufficient to depolarise the cortical neurons. A series of treatment sessions is usually administered over several consecutive days for several weeks. The mechanisms by which electromagnetic fields can produce an antidepressant effect are far from understood. It probably produces an increase in cortical excitability, the angiogenesis and alters intracellular signalling in healthy controls. The connectivity between different cortical regions is disrupted in depression, and an antidepressant treatment should be targeted at restoring the communication between neuronal networks. T-PEMF has an antidepressant effect, possibly involving a restoration of the disrupted brain connectivity in TRD (Van Belkum et al. 2016). The antidepressant effects of T-PEMF stimulation have been investigated in both preclinical and clinical studies. A double-blind randomised controlled trial showed efficacy of T-PEMF in TRD, using a head device with coils and continuous trains of alternating currents. After stimulating 50 patients with TRD for 5 weeks in a row, HDRS-17 scores improved significantly in the treatment group as opposed to placebo (Martiny et al. 2010). In a dose-remission study, it was found that augmentation with T-PEMF stimulation (50 Hz; 0.4 V/m) in 65 patients with TRD for 8 weeks reduced HDRS-17 scores. A twice daily dose of T-PEMF was superior to once daily (Straaso et al. 2014). This technique appears to be well tolerated. Although the numbers of studies are still limited, the antidepressant effects of T-PEMF is promising.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is an experimental, non-invasive brain stimulation technique that delivers a continuous low-amplitude electrical current to a specified cortical region. Conventionally, tDCS involves two electrodes placed on the scalp. Typical electrode sizes range between 4 and 35 cm^2. The size of the electrodes and their montage are highly relevant for the efficacy of the stimulation. There is no cohesive summary evaluating the optimal stimulus parameters, frequency or duration of tDCS for the treatment of TRD. The stimulation is focussed on the left dorsolateral prefrontal cortex (DLPFC) and modulates the neuronal excitability (Meron et al. 2015). This stimulation may result in changes in membrane resting potentials and modify synaptic transmission in the DLPFC, which reduction of depression (Palm et al. 2016). Repeated use of tDCS may lead to neuroplasticity effects, mediated via *N*-methyl-D-aspartate receptor-dependent mechanisms. TDCS may also induce long-term cortical plastic change via metabolic pathways, for example, increasing BDNF release (Fritsch et al. 2010). The after-effects of tDCS have been linked to non-synaptic mechanisms involving neurogenesis (Ardolino et al. 2005). The magnitude and direction of the induced aftereffects are highly dependent on the duration, intensity of the stimulation, electrode size and montage. The duration of the aftereffects also depend on the functional state of the brain. A high individual variability was observed and the reason for this high variability is far from being understood. The stimulation of a single brain area may thus influence and/or be influenced by other regions and networks. Because of this complexity, the type of stimulation that was originally seen as 'excitatory' (anodal tDCS) might not always increase 'cortical excitability' and vice versa. A better description of the tDCS effect in the future might be that it modifies the 'excitability-inhibitory balance' in the stimulated and related cortical areas (Singh et al. 2019). Several randomised controlled clinical trials (RCT) evaluated the effects of tDCS on the severity of depressive symptoms. Most of the clinical trials have concentrated on enhancing the neural activity in the left DLPFC with anodal stimulation and/or reducing the neural activity in the right DLPFC with cathodal stimulation (Welch et al. 2019). Computer modelling and neuroimaging tDCS studies suggest that, in fact, the stimulation also largely affects deeper brain structures, such as amygdala and hippocampus (Bikson et al. 2012). In the SELECT-TDCS trial (Sertraline vs. Electrical Current Therapy; Valiengo et al. 2013; Brunoni, Moffa, et al. 2016; Brunoni, Tortella, et al. 2016) and [ELECT-TDCS] (Escitalopram vs. Electrical Current Therapy for Treating Depression Clinical Study; Brunoni et al. 2017), the combination of anodal tDCS with administration of antidepressant medication was superior to each treatment applied alone and to placebo, suggesting an additive interaction of tDCS and antidepressant medication. Also, cognitive behavioural therapy combined with active bifrontal tDCS increased the efficacy of the stimulation (Bajbouj et al. 2018). The efficacy of tDCS may be delayed: a pilot study enrolled 18 patients with TRD. Twelve sessions of tDCS were administered. Participants of 33.3% were therapeutically responsive to tDCS. Montgomery-Åsberg Depression Rating Scale scores of responders were significantly lower than those of non-responders at the 6th and 8th week. Regarding change of cognitive performance, improved accuracy of paired association and social cognition was observed at the 8th week (Li et al. 2019). The antidepressant effect of anodal tDCS on the left DLPFC was investigated in many randomised-controlled trials as well as in several case reports and open-labelled studies (Lefaucheur et al. 2017). Unfortunately, no solid conclusions can be made based on these data. Larger controlled studies with optimised montages and sufficient periods of observation are warranted. Further research is needed to establish the efficacy of tDCS as monotherapy or combination therapy for acute treatment of TRD.

Epidural cortical stimulation

Chronic epidural cortical stimulation (EpCS) of the motor or sensory areas has been used over the past 10 years to treat intractable pain syndromes, enhance recovery from stroke and for Parkinson's disease. EpCS generally offers a wide range of stimulation configurations that can ultimately affect the size of the induced electrical field, its directionality and the specificity in activated neuronal elements by varying pulse width, intensity and frequency parameters. An industry-sponsored multicenter trial

Table 2. Trigeminal nerve stimulation studies for treatments-resistant depression.

Authors	Study design	N°
Schrader et al. (2011)	Open	5
Cooka et al. (2013)	Open-label	11
Shiozawa et al. (2014)	Open	11
Shiozawa et al. (2015)	RCT	40
Gorgulho et al. (2019)	RCT	20
Gorgulho et al. (2019)	RCT	20
Generoso et al. (2019)	RCT	24

RCT: randomised clinical trial; TNS: trigeminal nerve stimulation.

stimulation of the left DLPF cortex was modestly successful (Dougherty et al. 2008). The anterior and midlateral prefrontal cortices play complementary roles in integrating emotional and cognitive experiences and in modulating subcortical regions. Both regions offer a distinct opportunity for targeted antidepressant treatments. This therapy (bilateral EpCS) in this area is a promising new technology for TRD (Nahas et al. 2010). To examine the long-term safety and efficacy of EpCS of the frontopolar cortex (FPC) and DLPFC for treatment of TRD, five patients with severe TRD were recruited in an open-label study. Participants were implanted with bilateral EpCS and received constant, chronic stimulation throughout the 5 years with Medtronic IPGs. Efficacy of EpCS was assessed with the HRSD-24. All five patients tolerated therapy at 5 years, 3/5 continued to be in remission (60%). These results suggest that chronic bilateral EpCS over the FPC and DLPFC is a promising and potentially durable new technology for treating TRD, both acutely and over 5 years (Williams et al. 2016).

Trigeminal nerve stimulation

Trigeminal nerve stimulation (TNS) is an experimental procedure for TRD. Direct cardiac risk does not exist because, unlike the vagus nerve, it does not contain autonomic fibres. It is assumed that the procedure affects the afferent fibres of the trigeminal nerve, which project on structures of the central nervous system that may be involved in depression, such as locus coeruleus and the nucleus of tractus solitarius. An external pulse generator delivers electrical current through bilateral skin electrodes. They are placed on the forehead to stimulate supraorbital and supratrochlear nerves of the V1 branch of the trigeminal nerve. In an open-label study (Table 2), 11 adults with unipolar depression successfully treated with at least two antidepressant drugs had nocturnal stimulation on the V1 branch for 8 weeks. Of the 11 patients, four were in remission. All subjects completed the study. Only one patient had a minor adverse event (skin rash in the electrode contact areas, but this patient used the device for more than 12 h in a row overnight; Cooka et al. 2013). In all randomised and observational studies, the procedure was well tolerated. Only a few transient and light paresthesias have been described, which occurred during the first few seconds of stimulation (Shiozawa et al. 2015). The TREND study is a single-centre, double-blind, randomised, controlled, phase II clinical trial. Twenty unipolar TRD patients will receive V1 TNS as adjuvant to medical therapy and randomised to active vs sham stimulation throughout a 24-week period. An additional 24-week open-label phase will follow. Data concerning efficacy, placebo response, relapse and side effects related to surgery or electrical stimulation will be recorded. The main outcome measure is improvement in depression scores using HDRS-17, Beck Depression Inventory Self-Report (BDI-SR), 30-item Inventory for Depressive Symptomatology-Self-Report (IDS-SR-30) and UKU scales under continuous TNS as adjuvant to antidepressants This study protocol is designed to define efficacy of this novel adjuvant therapy for TRD (Gorgulho et al. 2019). A randomised, double blind and sham-controlled phase II clinical trial will study the effect of a 10-day transcutaneous TNS protocol for depression amelioration (Generoso et al. 2019).

Table 3. Comparison of new somatic therapies for treatments-resistant depression.

Somatic therapy	Form of stimulation	Convulsive	Surgical	Anaesthesia	Deep	Focal
ECT	Electric	+	−	+	+	−
FEAST		+	−	−	+	+
CES		−	−	−	−	−*
tDCS		−	−	−	−*	−*
VNS		−	+	+	+**	−**
tVNS		−	−	−	+**	−
TNS		−	−	−	+***	−
DBS		−	+	+	+	+
EpCS		−	+	+	−	+
MST	Magnetic	+	−	+	−	+
rTMS		−	−	−	−*	+
DTMS		−	−	−	+*	+
T-PEMF		−	−	−	−	−
LFMS		−	−	−	+	−
tFUS	Ultrasonic	−	−	−	+	+
NIR	Light	−	+	+	−	+

*Depending on the type of coil or electrode; **Limited to vagal efferences; ***Limited to Trigeminal Effects.

ECT: electroconvulsive therapy; FEAST: focal electrically administered seizure therapy; CES: cranial electrical stimulation; tDCS: transcranial direct current stimulation; VNS: vagus nerve stimulation; tVNS: transcutaneous vagus nerve stimulation; TNS: trigeminal nerve stimulation; DBS: deep brain stimulation; EpCS: epidural cortical stimulation; MST: magnetic seizure therapy; rTMS: repetitive transcranial magnetic stimulation; DTMS: deep transcranial magnetic stimulation; T-PEMF: transcranial pulsed electromagnetic fields; LFMS: low field magnetic stimulation; tFUS: transcranial focussed ultrasound; NIR: near infra-red transcranial radiation.

Transcutaneous vagus nerve stimulation

Transcutaneous vagus nerve stimulation (tVNS) it is a relatively new, non-invasive VNS method based on the rationale that there is afferent/efferent vagus nerve distribution on the surface of the ear (Carreno and Frazer 2016). tVNS involves an intra-auricular electrode (NEMOS, Cerbomed, Erlangen, Germany), a portable stimulator and digital user interface that controls signal amplitude (gammaCore, electroCore LLC, Basking Ridge, NJ, USA).This new neuromodulation system is non-invasively, making it an attractive therapy option compared to VNS. According to CERBOMED, the intensity, pulse duration and frequency of tVNS stimulation were optimised to induce signals in the myelinated thick Aβ fibres. This system has direct bonds with the nucleus of tractus solitarius. The justification for the use of tVNS is the fact that anatomical studies have shown that the ear is the only place on the surface of the human body where the afferent distribution of the vagus nerve is found. Thus, direct stimulation of afferent nerve fibres on the ear should produce a similar effect to the classic VNS in reducing depressive symptoms without the burden of surgery. One systematic search strategy revealed three studies applying tVNS for the TRD (Cimpianu et al. 2017; Table 3). Hein et al. reported the outcomes of two randomised double-blind trials in one publication investigating the efficacy of tVNS. In the first study, 22 patients were enrolled and 1:1 randomised to active or sham tVNS. tVNS was administered bilaterally, using a microstimulator. Stimulation parameters were chosen by the investigator. The stimulation lasted 15 min once a day for the duration of 2 weeks, on 5 days each week. In the second study, 15 patients were enrolled: out of them 7 received active tVNS and 8 sham tVNS. The stimulation lasted also 15 min but twice a day, 5 days a week, for 2 weeks.

The stimulation parameters were fixed to a frequency of 1.5 Hz and intensity 130 A. In both studies and in the pooled analysis, active stimulation was associated with a significant improvement on a BDI-SR measure compared to controls but not on the HDRS. Effect sizes were not reported. Treatment was well tolerated (Hein et al. 2013). tVNS can modulate the default mode network (DMN) functional connectivity (FC) in mild or moderate major depressive disorder patients. In a study, 49 patients were recruited and received tVNS or sham tVNS treatments. Thirty-four patients completed the study and were included in data analysis. After 1 month of tVNS treatment, the HAMD-24 score reduced significantly in the tVNS group as compared to the stVNS group. After tVNS, DMN FC showed significant changes in brain regions involved in emotional modulation. Some FC changes are also associated with depression severity changes (Fang et al. 2016). Rong et al. enrolled in a non-randomised study 160 patients that received either active tVNS for 12 weeks ($N = 91$) or 4 weeks of sham, followed by 8 weeks of active transcutaneous stimulation ($N = 69$). Active tVNS was superior to sham tVNS after 4 weeks of treatment (primary endpoint: improvement of the 24-item HDRS) and this efficacy was maintained until week 12 (Rong et al. 2016). A publication from the same group reported in 49 patients a significant HDRS improvement after 4 weeks of active tVNS compared to sham stimulation and showed that active tVNS modulates amygdala and lateral prefrontal network resting-state FC (Liu et al. 2016). The safe and low-cost characteristics of tVNS have the potential to significantly expand the clinical application of tVNS (Roberts et al. 2016).

Transcranial focussed ultrasound

Transcranial focussed ultrasound (tFUS) is emerging as a neuromodulation approach that combines noninvasiveness with focus that can be relatively sharp even in regions deep in the brain. Ultrasound effects depend on intensity, frequency and other factors, including tissue properties. High intensity ultrasound can cause heating and cavitation, which can damage or destroy tissue. A mid-range intensity can cause a slight beneficial warm-up (diathermy), but also soft tissue injuries. It has been postulated that the brief application of low-intensity, non-thermal ultrasound could improve naturally occurring vibrations in the brain proteins involved in the support mechanisms of conscious mental states (Bistritsky et al. 2011). It can reversibly stimulate and modulate intact brain circuits through non-thermal mechanisms of action (Wang, Vila-Rodriguez, et al. 2019; Wang, Zhang, et al. 2019). The tFUS could therefore modulate the functioning of the brain. It can excite or inhibit cellular activity, depending on specific stimulation parameters. Because of these properties, it has been suggested that tFUS may be an alternative strategy for the treatment of TRD (Tsai 2015). Device-related parameter needs optimisation before launching systematic investigation of tFUS applications in humans. Hence, the frequencies of both unfocused tFUS (1 to 15 MHZ) and focussed tFUS (<1 MHZ) could be suitable for neuromodulation. Both yielded an after-effect on enhancing the cortical motor excitability in human subjects, indicating the frequency alone may not be a significant parameter to change the properties of brain modulatory effect associating with tFUS (Gibson et al. 2018). To evaluate a possible modulation of mental states by tFUS, in a pilot study were investigated the effects produced by subthermal application of FUS (on the frontal scalp) in patients with chronic pain as well as in volunteers, using GE LOGIC ultrasound imaging. Subjective evaluations of pain and mood were examined. The results of this study showed a significant improvement in affects at 10 and 40 min after tFUS compared with placebo (Hameroff et al. 2013). However, research on tFUS is still in its early stages, especially in human studies and further research on the frequency and duration of tFUS stimulation is needed to test the effectiveness of this intervention in depressive disorders (Wang, Vila-Rodriguez, et al. 2019; Wang, Zhang, et al. 2019).

Transcranial near-infra-red radiation

Brain photobiomodulation (PBM) therapy using near infra-red transcranial radiation (NIR) light is an innovative treatment for TRD. Light has fundamental physical properties, which are relevant for its clinical use. The NIR has a number of biological effects, but it is essential to understand the physical interactions that exist between tissue and light. The penetration of NIR into the human brain (3 cm) is subjected to attenuation by multiple tissues and multiple interfaces that absorb and reflect NIR to varying degrees. Improved neurogenesis, neuroprotective effects and bioenergetic changes in red light have been documented in in vivo models. Red/NIR light is able to stimulate complex IV of the mitochondrial respiratory chain, increase ATP synthesis, activation of transcription factors and gene expression (Hennessy and Hamblin 2017). Brain PBM therapy enhances the metabolic capacity of neurons and stimulates anti-inflammatory, anti-apoptotic and antioxidant responses, as well as neurogenesis and synaptogenesis (Salehpour et al. 2018). In a double-blind randomised study in healthy volunteers, exposure to coherent NIR significantly improved overall affect, sustained attention and visual memory (Barrett and Gonzalez-Lima 2013). Schiffer et al. exposed 10 patients with TRD to a single NIR treatment, light emitting diode source placed at two locations on the forehead for 4 min each. It was found that, after 2 weeks, the HDRS score for the group had decreased by about 10 points and 60% had achieved remission, although by the 4-week mark symptoms had begun to reappear (Schiffer et al. 2009). Additionally, Cassano et al. (2015), in a proof of concept, prospective, double blind, randomised study versus sham, studied the effects of multiple NIR treatments (6 sessions) administered over 3 weeks. At completion of the study, two out of four patients had achieved remission, and the mean HDRS-17 score had decreased from the baseline of 19.8 ± 4.4 to 13 ± 5.35 after treatment. Patients tolerated the treatment well without any serious adverse events. A study by Disner et al. revealed that NIR therapy delivered to the right forehead was more effective for alleviation of depression symptoms than NIR therapy to the left forehead (Disner et al. 2016). This technique may become an innovative treatment for TRD, but clinical evidence is still needed. The results of some studies (but on a small population) confirm the preliminary data on NIR. To date, studies on antidepressant effects of NIR therapy have had relatively short follow-up periods.

Closed loop stimulation (CLS)

The closed loop concept should overcome many of the challenges that arise from open-loop treatments. A recent study began in July 2019. This is a single-centre 3-stage feasibility study of personalised closed-loop stimulation for TRD. The study will test whether personalised responsive neurostimulation can safely and effectively treat depression. The device used in this study is called the NeuroPace Responsive Neurostimulation System. It is currently FDA approved to treat patients with epilepsy. A primary analysis will be done in 2030 (ClinicalTrials.gov NCT04004169).

Discussion

The development of effective and sustainable treatment modalities for TRD has been a global aim for decades. The current therapeutics of TRD are far from satisfactory due to the high rate of non-response to treatments, high rates of relapse and frequent intolerable side effects. This non-systematic literature review provides an overview of current progress in the technological advances in neuromodulation and neurostimulation treatments for TRD. There are several psychiatric neuromodulation and neurostimulations techniques that allow modifying the cerebral activity and many new innovative forms of electrical, magnetic brain stimulation, including the use of low intensity ultrasound or light (Table 3).

MST and FEAST versus ECT

If the preliminary findings across multiple clinical studies are confirmed in large RCT currently underway, MST may provide a new safe and efficacious non-invasive neuromodulation antidepressant therapeutic option. The optimal stimulation parameters for MST are still being investigated and how best to individualise the dose, remains an open question. If the efficacy of FEAST and MST could be optimised, these techniques would eventually be possible to replace the traditional ECT.

LFMS versus TMS

LFMS is a promising, well-tolerated treatment for TRD with a potentially rapid onset of action. In addition to optimising the dosing protocol and testing the durability of mood improvements, we need to better characterise the subgroup of patients who respond to LFMS. Using functional neuroimaging to understand the circuit abnormalities that are predictive of treatment response has shown great promise for TMS (Drysdale et al. 2017). Mapping these abnormalities in LFMS responders could eventually help match the treatment to depressed patients most likely to benefit and will guide advancements in LFMS coil design to optimise treatment (Wang et al. 2018). LFMS may have safety advantages over TMS that could broaden its clinical applicability, it is likely to be better tolerated than TMS, carry a lower seizure risk, and thus could potentially be administered in an unsupervised setting.

tDCS

tDCS is a promising therapeutic strategy that offers the opportunity for non-invasive modulation of cortical excitability and plasticity in psychiatric disorders. Studies evaluating the efficacy of tDCS in acute and maintenance treatment of TRD have demonstrated mixed results, but tDCS can be a good option for TRD, with potential advantages, is inexpensive and easily administered, with a relative benign profile of side effects. The majority of meta-analyses have found that tDCS is superior to sham stimulation with an effect size comparable to that of repetitive TMS and antidepressant medication in primary care (Brunoni, Moffa, et al. 2016; Brunoni, Tortella, et al. 2016). The tDCS is recommended as a third-line treatment for TRD and it has Level 2 Evidence for acute efficacy. However, further research is needed to establish the role of tDCS. Many questions still remain unanswered, regarding the optimal stimulation parameters, the effect of tasks given during tDCS sessions and the possible influence of add-on medications (Bennabi and Haffen 2018).

EpCS

EpCS is a unique therapeutic approach. It is more direct than TMS or VNS and potentially safer than DBS. This technique, which is less invasive compared to DBS, most likely merits further study (Williams et al. 2018; Williams et al. 2019).

The use of cranial nerve stimulation in TRD is still limited to a few research protocols. TNS and tVNS are techniques that, despite their recent development, have satisfactory outcomes.

tVNS versus VNS

Electrical stimulation of the auricular vagus nerve is an emerging technology in the field of bioelectronic medicine with applications in therapy (Kong et al. 2018; Kaniusas et al. 2019). tVNS, as a non-invasive intervention, has beneficial effects on TRD based on clinical observations. A systematic review and meta-analysis preliminarily demonstrated that tVNS stimulation is an effective method for treating major depressive disorder (Wu et al. 2018). tVNS is safe and well tolerated at the doses tested in research studies to date (Redgrave et al. 2018). Compared to traditional VNS, tVNS has the advantage of being low cost, safe and non-invasive. Additional controlled studies are needed to overcome the difficulties of standardising and disseminating the technique. Long-term clinical outcomes will be invaluable in clinical practice.

tFUS

tFUS an abundance of evidence has recently accumulated showing that tFUS is a promising brain stimulation tool (Darrow 2019). tFUS is useful for non-invasively modulating brain circuit activity (Fini and Tyler 2017). Compared to magnetic or electric non-invasive brain stimulation, tFUS has a higher spatial resolution and can reach deep structures. The initial safety profiles seem promising. The high spatial resolution of tFUS and the possibility of stimulating cortical and deep brain regions suggest many potential applications, such as cortical and subcortical mapping, the study of FC, the modulation of neurotransmission (Di Biase et al. 2019). Further research is needed to clarify tFUS efficacy and underlying mechanisms (Mooney et al. 2018) and to optimise stimulation parameters and targeting accuracy.

PBM therapy using NIR

Light is an innovative treatment. Its therapeutic role in depression has gained increasing interest, but clinical evidence for its efficacy is limited. In the transcranial NIR approach, delivering a sufficient dose to achieve optimal stimulation is challenging due to exponential attenuation of light penetration in tissue. Alternative approaches such as intracranial and intranasal light (Zomorrodi et al. 2019) delivery methods have been suggested to overcome this limitation. The systemic metabolic and hemodynamic profile of repeated t-PBM appeared benign (Cassano et al. 2019).

CLS versus alternative open-loop treatments

CLS It is currently FDA approved to treat patients with epilepsy. In current clinical practice, alternative open-loop treatments, such as VNS, TMS and DBS, provide more focal treatment for patients who have TRD compared to pharmaceuticals or ECT. In addition, implanted devices require stimulation adjustments, which can sometimes induce variable undesirable side effects as well as significant patient discomfort. The use of a closed-loop device, which focally stimulates specific populations of dysfunctional neurons, is

expected to lead to improved therapeutic efficacy, with a profile of lesser side effects (Ward and Irazoqui 2010).

The growing use of repetitive transcranial magnetic stimulation (rTMS) has increased the visibility and acceptability of nonsurgical brain stimulation approaches to TRD. In a systematic review and network meta-analysis of non-surgical brain stimulation for depression (18 distinct treatment protocols or sham therapy, 113 clinical trials, 6750 patients), 10 of 18 treatment strategies showed efficacy. This exhaustive analysis founded that there is evidence for the consideration these techniques as alternatives or add-on treatments for patients with TRD (Mutz et al. 2019).

Conclusions

We have seen that technological advances and new knowledge about the dysfunction of the brain circuits have led to the development of various neuromodulation techniques. All these techniques attempt to change the brain's neuronal activity in a more or less focal way. Actually, the field of neuromodulation is very broad and controversial. For numerous practical and technical reasons, there have been many failures at demonstrating that treatment approaches can provide clinically significant benefits. The role of new somatic interventions is expanding, probably with more efficiency. Many of these therapies are still in their early stages of exploration. Once the all new neuromodulation techniques can be applied, the therapeutic arsenal for depression patients will be increasingly richer. This news therapies can be complementary, especially when this was done with multiple methods. For MST, tDCS, VNS, as there is not yet sufficient evidence to recommend them in the first line, but as add-on strategies, they probably should be considered (Müller et al. 2018). Specific guidelines from different countries have been published. In fact, novel treatments need to be regularly updated and integrated into the therapeutic arsenal of the psychiatrist. The current trend, and in particular the new neuromodulation therapies, is to apply a personalised treatment. At present, major efforts are still needed before these types of therapies are likely to become widespread. The data from these new approaches to brain stimulation are still too preliminary for meaningful conclusions about their safety and efficacy. It is therefore normal to be very interested in research in this field. In the future, this modern therapeutic concept is likely to become increasingly accessible in everyday practice. Additional research is needed to delineate the advantages of these treatments.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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