Nonpharmacological, somatic treatments of depression: electroconvulsive therapy and novel brain stimulation modalities

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For more than 50 years, electroconvulsive therapy (ECT) has been the only nonpharmacological, somatic treatment of psychiatric disorders in widespread clinical use. Other modalities, such as insulin coma therapy, were used for varying periods, but no longer have any place in clinical psychiatry. This situation is now changing. Brain stimulation techniques are rapidly becoming a highly promising novel avenue for treatment of psychiatric disorders in general, and major depression in particular. 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. Several different approaches are under study. Some have the potential to cross the threshold to clinical use,

Until recently, a review of nonpharmacological, somatic treatments of psychiatric disorders would have included only electroconvulsive therapy (ECT). This situation is now changing very substantially. Although ECT remains the only modality in widespread clinical use, several new techniques are under investigation. Their principal indication in the psychiatric context is the treatment of major depression, but other applications are also being studied. All the novel treatments involve brain stimulation, which is achieved by different technological methods. The treatment closest to the threshold of clinical acceptability is transcranial magnetic stimulation (TMS). Although TMS is safe and relatively easy to administer, its efficacy has still to be definitively established. Other modalities, at various stages of research development, include magnetic seizure therapy (MST), deep brain stimulation (DBS), and vagus nerve stimulation (VNS). We briefly review the development and technical aspects of these treatments, their potential role in the treatment of major depression, adverse effects, and putative mechanism of action. As the only one of these treatment modalities that is in widespread clinical use, more extended consideration is given to ECT. Although more than half a century has elapsed since ECT was first introduced, it remains the most effective treatment for major depression, with efficacy in patients refractory to antidepressant drugs and an acceptable safety profile. Although they hold considerable promise, the novel brain stimulation techniques reviewed here will be need to be further developed before they achieve clinical acceptability.

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Selected abbreviations and acronyms

DBS *deep brain stimulation*
ECT *electroconvulsive therapy*
MST *magnetic seizure therapy*
TMS *transcranial magnetic stimulation*
VNS *vagus nerve stimulation*

while others are still at a very limited stage of application in the research context only.

In this review, we will consider several novel brain stimulation techniques for the treatment of depression: transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST), deep brain stimulation (DBS), and vagus nerve stimulation (VNS). A comprehensive evaluation of each modality is not possible in this context. We will provide an overview of key aspects of each treatment such as its development, technique, application in major depression, adverse effects, and putative mechanism(s) of action. The novel brain stimulation modalities will be discussed on the background of a wider consideration of ECT, which is used extensively and has been the focus of intensive basic and clinical research for several decades.

Electroconvulsive therapy

Development of ECT

The production of epileptiform convulsions as a treatment for psychiatric illness was introduced in 1934 by the Hungarian psychiatrist, Laszlo Meduna.[1] The first treatments were drug-induced convulsions.[2] A few years later, electrical seizure induction was introduced by Cerletti and Bini in Rome.[3,4] The introduction of antidepressant drugs during the 1950s and 1960s reduced the use of ECT as a first-line therapy for depression. Nevertheless, ECT is still the treatment of choice in pharmacotherapy-resistant cases. Although ECT is considered effective and safe, it continues to be regarded with suspicion by much of the public and the medical profession. Hollywood films such as *The Snakepit* (1948) and *One Flew Over the Cuckoo's Nest* (1975) set an antipsychiatric and anti-ECT tone that has never completely abated.[5] Unmodified ECT was indeed associated with serious complications such as extremity fractures and compressive spinal fractures. However, for more than 50 years ECT has been administered under general anesthesia with neuromuscular relaxants, and this has eliminated these serious complications.[6] Interestingly, the fear of permanent brain damage caused by ECT was recently placed in a different perspective by reports that ECT might actually increase new neuron growth (neurogenesis) in the hippocampus.[7]

In order to minimize short- and longer-term memory deficits associated with ECT, major research efforts have been invested in trying to limit the stimulus path and to adapt the stimulus intensity to the seizure threshold of the individual patient.[8] There are two main modalities of ECT, differentiated by electrode placement: bilateral and unilateral ECT. In bilateral ECT the electrical stimulus traverses both cerebral hemispheres, while in unilateral ECT only the nondominant cerebral hemisphere is stimulated. In both cases, effective treatment requires that a generalized seizure be elicited. Although unilateral ECT results in fewer cognitive adverse effects, its efficacy relative to bilateral ECT was a source of controversy for many years.[9] Recently, Sackeim and colleagues found that high-dosage unilateral ECT (electrical dosage 500% above seizure threshold) and moderately suprathreshold bilateral ECT (electrical dosage 150% above seizure threshold,) are equivalent in response rate.[10] Importantly, high-dose unilateral ECT is not associated with increased cognitive adverse effects. These findings underscore an important basic concept in ECT: although the seizure may seem to be an all-or-none event, not every generalized seizure has antidepressant properties. Stimulus intensity relative to threshold is a major factor in the efficacy of the therapy.[11,12]

Technique of ECT administration

Pretreatment evaluation includes complete medical history, physical, neurological, and preanesthesia examinations, and relevant laboratory tests. Patients' concurrent medications should be noted, since they might affect the seizure threshold or interact with other medications used during ECT *(Table I)*. Pretreatment preparations include 6- to 12-hour fasting, removal of dentures or other foreign objects from the patient's mouth, insertion of a bite block into the mouth, and preoxygenation (100% O_2 at a rate of 5 L/min).

Anesthetic agents should induce rapid unconsciousness and recovery and minimally affect hemodynamic parameters or seizure threshold.[18] The most commonly used anesthetic is methohexital (0.75 to 1.0 mg/kg), due to its rapid onset, short duration of action, minimal anticonvulsive effect, and rapid recovery.[19] Other anesthetics

include thiopental, propofol, and etomidate. A muscle relaxant agent is administered 1 to 2 minutes after the anesthetic agent. Muscle relaxation eliminates injuries resulting from motor activity during the treatment, and is of particular importance in patients who are at high risk for fractures or disk herniation. Succinylcholine, a short-acting depolarizing agent (0.5 to 1.0 mg/kg), is used in most patients. Before the muscle relaxant is administered, a blood pressure cuff is inflated above the systolic blood pressure at one ankle, to allow observation of the motor seizure. A peripherally acting anticholinergic such as glycopyrrolate may used to increase heart rate before treatment, especially if the patient is bradycardic.

ECT is administered using two electrodes, located bilaterally or unilaterally, as illustrated in *Figure 1*. The electrical stimulus is a brief pulse waveform (bidirectional rectangular pulse). The intensity of the ECT stimulus is assessed in terms of the total delivered charge. This total charge (Q, measured using units of millicoulombs) can be defined as:

$$Q = (I/1000) * PW * 2F * D$$

where I is current (milliamperes), PW is pulse width (milliseconds), F is frequency (hertz, cycle per second) and D is duration (seconds). The standard pulse width used in ECT is 1 millisecond or greater. Recently, it has been found that an ultrabrief stimulus, using 0.3 millisecond pulse width, requires less energy to produce a generalized seizure. This may be related to the fact that neuronal depolarization is 0.3 to 1.0 milliseconds, and long pulse width may result in excess stimulation after neurons have fired and are in a refractory or relative refractory phase. Although the amnesia and cognitive side effects following ECT are reduced with ultrabrief stimulation, data regarding its efficacy relative to the traditional stimulus are still insufficient.

The electrical path of the ECT stimulus includes the ECT output device, stimulus electrodes, scalp, skull, cerebrospinal fluid, and brain tissue. The most variable impediment is the patient impedance (mostly scalp and skull), measured in ohms. Energy is another unit that assesses the intensity of the total electrical stimulus. It is dependent on the impedance during stimulation, and can be calculated as

$$U = (Q/1000) * (I/1000) * R$$

where Q is charge (millicoulombs), I is current (milliamperes), and R is resistance (ohms).

Seizure threshold, defined as the minimal stimulus intensity necessary to produce a seizure, differs up to 40-fold among patients *(Figure 2)*. For example, seizure threshold is higher in men than in women and is higher in older than younger adults. Seizure threshold is also altered by mechanical factors that impede the path of the stimulus

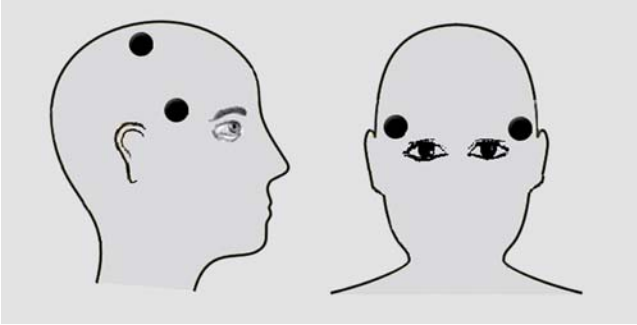

Figure 1. Electrode placement in ECT. In bilateral ECT, bifrontotemporal electrode placement is used: the electrodes are placed 5 cm above the midpoint of the distance between the auditory meatus and the external canthus. In unilateral ECT, the d'Elia positioning is used: one electrode is placed at the standard frontotemporal position, and the other electrode is placed near the vertex (3 cm down from the midpoint of a line joining the two auditory meati and the sagittal midline of the skull). ECT, electroconvulsive therapy.

Drug	Concomitant administration with ECT
Lithium[13]	Discontinue before ECT. Lithium decreases the intracellular production of acetylcholine, may prolong the action of succinylcholine, and may prolong seizure duration
Tricyclic antidepressant, monoamine oxidase inhibitors selective serotonin reuptake inhibitors[14,15]	Safe
Bupropion[16]	Controversial. Bupropion may cause prolonged seizure
Benzodiazepines	Safe, but have an anticonvulsive activity, and might raise the seizure threshold
Antipsychotics[17]	Safe
Clozapine[18]	Controversial, might induce late seizures

Table I. Drug coadministration with electroconvulsive therapy.

and increase resistance. Seizure threshold may change in the same patient during the ECT course, and tends to increase, as shown in *Figure 3*.

Optimal stimulus intensity during ECT is important because excessive electrical stimulation increases cognitive deficits. On the other hand, insufficient electrical stimulation, barely above the seizure threshold, reduces efficacy. In a study that compared bilateral and right unilateral ECT at different stimulus intensities, Sackeim and colleagues concluded that the optimal electrical dosage is 2.5 times the seizure threshold for bilateral ECT and 4 to 6 times the seizure threshold for unilateral ECT.[10] For ultrabrief stimulation (pulse width 0.3 millisecond), the electrical dosage might be higher.

Determining the stimulus energy requires a method to estimate the patient's seizure threshold in the first treatment session. Empirical titration involves administration of subconvulsive intensities in the first treatment and finding the stimulus energy that produces a seizure. In subsequent sessions, a fixed stimulus above the seizure threshold is administered. In every treatment session, up to three trials of stimulus may be conducted. Using empirical titration permits accurate determination of the seizure threshold. Another method to estimate seizure threshold, the preselected dosage method, involves use of known predictors of seizure threshold such as electrode placement, age, and gender. Based on these criteria, a suprathreshold dose is preselected and given at the first and subsequent treatments, unless severe cognitive side effects occur. This approach eliminates the need for subconvulsive stimulations in establishing seizure threshold, but is less accurate than the titration method.

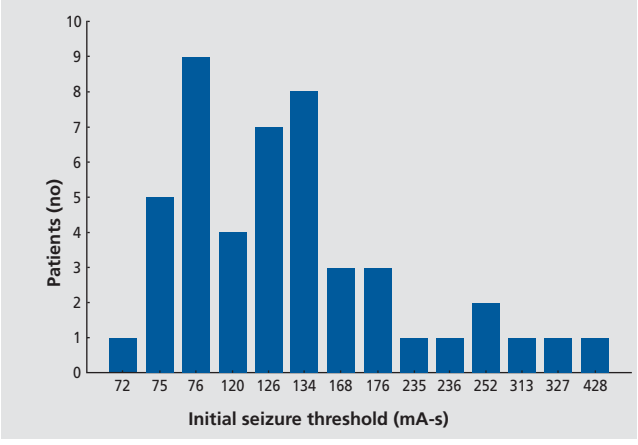

Figure 2. Initial seizure threshold in milliampere seconds (millicoulombs) as determined by a titration technique at the first treatment of a bilateral ECT course.[20] ECT, electroconvulsive therapy.

The motor seizure consists of two phases. The tonic phase lasts 10 to 20 seconds and involves contraction of the jaw and facial muscles, plantar extension, and high-frequency sharp EEG activity. The second phase, the clonic phase, involves rhythmic contractions and bursts of polyspike EEG activity which persist for a few seconds after the clonic movements stop. A seizure is effective if it lasts at least 20 to 25 seconds. Prolonged seizures can be terminated with intravenous benzodiazepines.

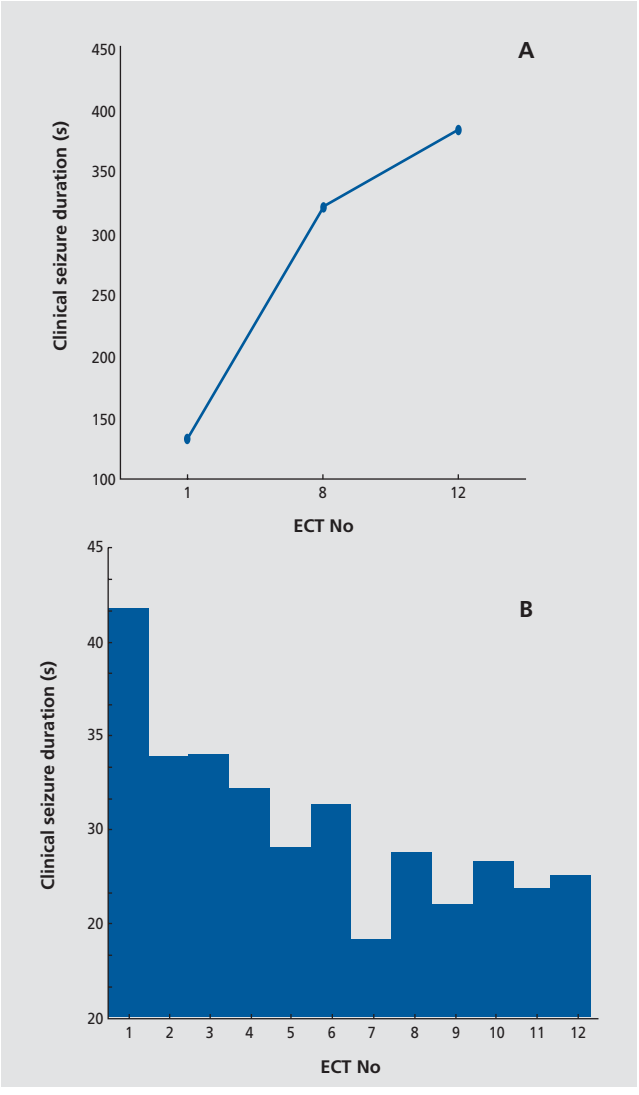

Figure 3. Increase in seizure threshold measured by titration at treatments 1, 8, and 12 (A) and decrease in seizure duration measured clinically in a cuffed limb (B) in patients treated with bilateral ECT.[20] ECT, electroconvulsive therapy

In the United States, ECT is usually administered three times weekly. In other parts of the world, twice-weekly administration is more common. Twice-weekly administration has been shown experimentally to be an optimum schedule for bilateral ECT, considering maximal antidepressant effect and minimal cognitive impairment.[21,22] If clinical indications require a more rapid antidepressant effect, three times weekly administration might be used.[21,22] The number of treatments during an ECT course is usually 8 to 12; the treatment is terminated when a plateau of improvement is reached, usually when the patient does not continue to improve after two consecutive treatments.

ECT in the treatment of major depression

It is well established that ECT is an effective treatment for major depression, superior to placebo, simulated ECT (anesthesia only), and antidepressant medication.[23-26] Of patients with major depression who receive ECT as a first-line treatment, 80% to 90% show significant improvement. Currently, most patients with major depression treated with ECT have failed two or more courses of antidepressant medication. ECT is effective in over half of these patients.[10,27] ECT is indicated in patients intolerant of antidepressant medication and those with medical illnesses that contraindicate the use of antidepressants. ECT may be considered as a first-line treatment in severe depression or depression with specific features, such as psychosis,[28,29] catatonia,[30] melancholia (mainly food refusal leading to nutritional deficit),[31] or suicidality.[32-34] ECT is also effective and safe in the elderly, among whom depressions tend to be persistent, and the patients suffer from other systemic disorders and consume many medications.[35] During pregnancy, ECT is usually only considered if the fetus is at risk from the unstable psychiatric condition of the mother.[36] ECT may also be considered for patients who have previously shown a positive response to ECT or patients who prefer this treatment.

Although it is difficult to predict response to ECT, there are factors associated with poorer response to ECT such as refractoriness to antidepressant medication, chronicity of the depression, and personality disorders.[37,38] Relapse rate during the 6 months following ECT exceeds 50%,[39,40] with the bulk of the relapses occurring within 1 month of termination of the treatment course. Continuation therapy markedly reduces the relapse rate.[41] Following ECT, continuation therapy might include pharmacotherapy,[42] maintenance ECT,[43] or a combination of maintenance ECT and an antidepressant agent. In a recent multicenter randomized study, the combination of lithium and nortriptyline was shown to reduce the relapse rate by 50%.[44]

Adverse effects

The most important adverse effect of ECT is memory impairment. Concern about memory loss is intensified for the patient and family by the transient confusion that occurs after each seizure. High-dose unilateral ECT produces less severe and persistent cognitive adverse effects than bilateral ECT.[10] In the postictal period, bilateral ECT causes more prolonged disorientation and more severe retrograde amnesia than unilateral ECT. One week and 2 months after the course, bilateral ECT is associated with greater anterograde and retrograde memory deficits. During the first 2 months after ECT, bilateral ECT is associated with greater retrograde amnesia than unilateral ECT. Most patients return to their cognitive baselines 6 months after ECT, although a few patients complain of permanent memory loss.

Other side effects of ECT include headache, nausea, vomiting, myalgia, back pain, or damage to teeth if appropriate precautions are not taken.

Patients with increased intracranial pressure (due to an intracranial mass or obstruction of cerebrospinal fluid flow) are at risk for brain edema or herniation after ECT. Most clinicians regard increased intracranial pressure as an absolute contraindication to ECT. In these patients, pretreatment with steroid, diuretic, or antihypertensive agents can reduce the risk. Several coexisting disease processes warrant special attention due to their potential for complications in the context of ECT. The cardiovascular risk of ECT is a product of the stress of ECT itself, the severity and stability of coronary artery disease, and hemodynamic changes after the ECT (parasympathetic and then sympathetic response).[45] Identifying and controlling risk factors such as hypertension, arrhythmias (especially tachycardia), angina, congestive heart failure, and diabetes mellitus can minimize the risk of post-ECT ischemia.[18] Controlling hypertension is especially important since during ECT, systemic blood pressure increases acutely.

The estimated mortality rate with ECT is between two and ten per 100 000, about 0.002% per treatment, and 0.01% for each patient.[46,47] This mortality rate is equivalent to the mortality rate with general anesthesia (1:50,000).[48]

Mechanism of action

The mechanism of action of ECT has intrigued psychiatrists and neuroscientists since the treatment was first introduced. Laszlo Meduna,[1] the inventor of convulsive therapy, suggested that chemically induced seizures were effective in the treatment of schizophrenia by "changing the chemical composition of the brain." The first comprehensive book on ECT mechanisms was published in 1974.[49] A second book on the topic appeared a decade later.[50] Several dedicated review papers and book chapters have been published since. In the course of ECT an electrical current traverses brain tissue and a grand mal seizure ensues; it is inevitable that events such as these will have major physiological consequences. As noted by Seymour Kety,[51] ECT ".. involves massive discharge over wide areas of the brain, activation of the peripheral autonomic nervous system, release of the secretion of many endocrine glands.." and as a result ".. the difficulty lies not in demonstrating such changes but in differentiating.. which of the changes may be related to the important antidepressive and amnestic effects and which are quite irrelevant to these."

An important implication of Kety's highly relevant observation is that research into the mechanism of action of ECT should take into account clinical aspects of the treatment that have a potentially important impact in the research context. The first consideration is that long-standing changes induced by repeated administrations of electroconvulsive shock (ECS) are much more likely to be relevant to the therapeutic mechanism of ECT than transient effects of a single ECS. The therapeutic spectrum of ECT is another highly relevant consideration. In addition to its antidepressant properties, ECT has antimanic, antipsychotic, anticatatonic, antiepileptic, and anticonvulsant effects, and is used clinically for all these indications. It is highly implausible that a single mechanism of action will explain all these varied, and in some cases opposite, clinical effects. In considering the antidepressant mechanism of ECT, it is also important to note that ECT is substantially more effective than antidepressants; more than 50% of patients who have not responded to at least two adequate trials of antidepressant medication will respond to ECT. Furthermore, ECT is effective in patients with psychotic depression whereas antidepressant drugs are not, unless administered in conjunction with an antipsychotic. All these observations provide some explanation of why a definitive understanding of the mechanism of action of ECT has proved so elusive in spite of the enormous efforts that have been invested.

A comprehensive analysis of the various theories of ECT action in depression and the evidence that has been gathered in support of them is beyond the scope of this paper. The overall focus of recent work may be summarized under a few general headings. Recent intriguing findings regarding the effect of ECT on synaptic plasticity and neurogenesis will be considered more extensively.

One important research direction has been the effect of ECT on neurotransmitters, receptors, and postreceptor signaling mechanisms in the brain, particularly those that are implicated in the mechanism of action of antidepressant drugs. The emphasis has been primarily on serotonergic, noradrenergic, and dopaminergic systems with some consideration of γ-aminobutyric acid (GABA)-ergic and more recently glutamatergic mechanisms.[52-55] Electrophysiological studies suggest that an important effect of ECS on brain serotonergic systems in rodent brain is sensitization of postsynaptic serotonin $(5\text{-HT})_{1A}$ receptors and a consequent increase in serotonergic transmission.[56] This may be reflected in patients in increased responsiveness to serotonergically mediated neuroendocrine challenges.[57] There is great variability, however, in the overall effect of ECS on serotonin receptors as well as regional differences.[54,58] In the noradrenergic system, the density of postsynaptic β-adrenergic receptors is reduced by ECS, while autoreceptors that modulate noradrenaline release are inhibited.[52,53] The net effect may be an increase in postsynaptic signal transduction.[55,58] Dopaminergic function is increased postsynaptically, a finding that is consistent with the antiparkinsonian effects of ECT but difficult to reconcile with its antipsychotic action.[59]

A second major research direction may be termed neurophysiological. It encompasses the extensive work that has been done to evaluate the effects of ECT on brain electrical activity and cerebral blood flow (CBF) and metabolism. There is considerable evidence that depressed patients have reduced CBF and metabolism compared with normal subjects, although in some brain areas it may be increased.[60,61] Some studies suggest that reduced CBF in depression is reversed by ECT, but others report a further reduction.[62,63] Reduced brain function as a consequence of ECT is consistent with the hypothesis that recruitment of endogenous inhibitory processes to terminate the seizure is important in the therapeutic action of ECT.[59]

A third research direction takes as its starting point the substantial endocrine effects of ECT and suggests that these effects are implicated in the therapeutic mechanism of the treatment.[64] Plasma prolactin levels are acutely increased by ECT.[65,66] This is a consistent finding, but it has been difficult to explain how it might be related to the therapeutic action of ECT. Another focus has been on the effect of ECT on thyrotropin-releasing hormone (TRH) and TRH-receptor function.[67]

More recently there has been a great deal of emphasis on the effect of ECS on synaptic plasticity and neurogenesis. Adult neurogenesis, the lifelong addition of new neurons, was first documented in rat hippocampus.[68] It is now well established that neurogenesis occurs in several different species, including humans.[69] The newly generated cells mature into functional neurons.[70] Neurogenesis is regulated by many factors. Upregulation of neurogenesis occurs in response to enriched environment,[71] exercise,[72,73] and learning. Downregulation of neurogenesis occurs in response to aging[74,75] and stress (psychological or environmental).[76] It is well established that the volume of hippocampus is decreased in patients suffering from depression.[71,72] Repeated stress causes atrophy of dendrites in the CA3 region, and both acute and chronic stress suppresses neurogenesis of rat dentate gyrus granule neurons. The hippocampus is an especially plastic and vulnerable region, and a target of stress hormones (gonadal, thyroid, and adrenal hormones). This cell loss might explain the reduction in hippocampal volume observed in depression. Decreased neurogenesis might also explain some of the symptoms of depression, such as cognitive abnormalities and loss of inhibitory control of the hypothalamic-pituitary-adrenal (HPA) axis. Recently, it has been demonstrated that chronic administration of several classes of antidepressant treatment, such as serotonin or norepinephrine selective reuptake inhibitors, monoamine oxidase inhibitors, lithium, and ECS upregulates neurogenesis in adult rodent hippocampus.[79-84] ECS influences some molecular markers of neuronal plasticity; for example, ECS decreases the level of phosphorylated heavy and light neurofilament subunit (NF-H and NF-L), that may be part of the cytoskeletal remodeling.[85] ECS also influences several trophic factors that are related to neurogenesis, for example, brain-derived neurotrophic factor (BDNF), which increases the synaptic strength, survival, and growth of adult neurons. ECS prolongs the expression of BDNF and its receptor, trkB, and blocks the downregulation of BDNF mRNA in the hippocampus in response to restraint stress.[86] ECS has been demonstrated to change gene transcription in rat hippocampus, including genes that are related to neurogenesis, such as BDNF-MAP kinase-cAMP-cAMP response element-binding protein pathway and other immediate-early genes.[87]

Transcranial magnetic stimulation

Development of TMS

From the late 19th century many attempts were made to induce neural activity by magnetic stimulation until Barker and colleagues showed 20 years ago that magnetic stimulation of the human motor cortex produces depolarization of cortical areas.[88] Transcranial magnetic stimulation has been found to be a noninvasive, easily tolerated method of probing cortical brain function. During the last decade, many studies have indicated that TMS has antidepressant properties,[89,90] but its clinical effect is not yet clear.

Technique of TMS

In TMS, a magnetic field is generated by an electric current, and this magnetic field induces an electric current within the brain. The patient is awake, and sessions last 20 to 60 min. The treatment lasts a few weeks, since multiple sessions are indicated. An alternating electric current passes through a metal coil that is placed on the patient's scalp.[91] The electric current induces an alternating magnetic field, perpendicular in orientation to the current flow. The magnetic field passes through the scalp and skull without impedance and causes depolarization of cortical brain cells. The electrical current is parallel and opposite in direction to the electrical current in the coil. The stimulated brain area depends on two major factors: the coil design[92] and the coil orientation.[93] The magnetic field depolarizes cells to a depth of 2 cm below the scalp, near the gray-white junction of the nervous tissue.[94] Single-pulse TMS is generated by a single magnetic pulse, while repetitive TMS (rTMS) is generated by magnetic pulses given in a regular frequency. The stimulation frequency might be fast (more than 1 Hz) or slow (1 Hz and less). The two frequencies of stimulation have opposite effects on brain excitability and metabolism. Fast rTMS and slow rTMS have been associated with increased and decreased cortical excitability and regional blood flow,

respectively.[95,96] Slow frequency stimulation has a lower risk of inducing seizures.[97] The intensity of the magnetic pulse is measured relative to the motor threshold, which is the lowest intensity of stimulation that produces specific muscle contraction in at least 5 of 10 trials.[98]
Most studies uses fast rTMS over the left hemisphere and slow rTMS over the right hemisphere. Using fast rTMS over the left dorsolateral prefrontal cortex is based on the finding that functional activity in this area is low in patients suffering from major depression[99] and assumes that fast rTMS will enhance activity in this brain area. Use of slow rTMS over the right dorsolateral prefrontal cortex is aimed at reducing overactivity in this brain area and thus resolving a suspected hemispheric imbalance.[100]

TMS in the treatment of major depression

Administering rTMS to healthy individuals has not been shown to induce significant mood changes,[101] although left prefrontal rTMS is associated with transient decreased happiness and right prefrontal rTMS with transient decreased sadness.[102,103] Compared with sham administration, slow and fast rTMS have been shown to have some antidepressant properties.[104-109] However, analyzing these studies is difficult due to the different techniques used such as different frequencies, coil design, and positions.
A systematic review by Burt et al evaluated the antidepressant effect of TMS.[110] A meta-analysis of open and uncontrolled studies showed an antidepressant effect, but the clinical significance of this effect was uncertain, since most patients did not meet standard criteria for clinical response or remission. A meta-analysis of controlled studies showed that rTMS has superior antidepressant properties compared with sham administration *(Figure 4)*. However, similarly to the uncontrolled studies, the therapeutic effect was of doubtful clinical significance due to modest average effect and small average difference in improvement between active and sham conditions. A subsequent systematic review and meta-analysis included 14 trials.[111] Pooled analysis using the Hamilton Rating Scale for Depression showed an effect in favor of rTMS compared with sham after 2 weeks of treatment, but this was not significant at follow-up 2 weeks after the intervention period. The conclusion of this analysis was that "current trials are of low quality and provide insufficient evidence to support the use of rTMS in the treatment of depression." This conclusion is shared by two other reviews[112,113] but not by another meta-analysis of randomized sham-controlled trials of left prefrontal rTMS that found an "acute antidepressant treatment with statistically significant effect sizes and measurable clinical improvement."[114] It is clear that further controlled studies using standardized methodology are needed in order to establish the place of rTMS in the treatment of major depression.
A few studies have compared the antidepressant effect of rTMS and ECT.[115-118] These suggest that the antidepressant effect of rTMS is similar or slightly inferior to the antidepressant effect of ECT; however, in these studies the average improvement with ECT was unusually low. Comparing psychotic and nonpsychotic patients, it has been reported that rTMS and ECT have a similar

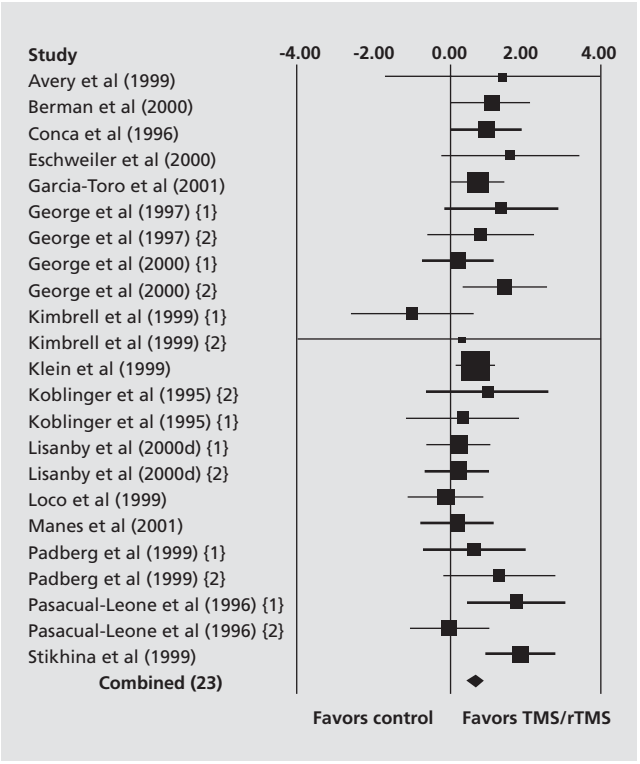

Figure 4. Meta-analysis of controlled trials of TMS. Figure shows effect size (d) and 95% confidence intervals for randomized, controlled studies of TMS and rTMS in the treatment of depression. The size of the boxes is proportional to the sample size. The overall combined effect size is indicated by a diamond. See Burt et al[104] for a review of the individual studies included in the meta-analysis.
Reproduced from reference 104: Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol*. 2002;5:73-103. Copyright © Cambridge University Press, 2002.

antidepressant effect in nonpsychotic major depressive disorder,[116,117] but ECT has been found to be superior for psychotic major depressive disorder.[117]

Older age, treatment refractoriness, and psychotic depression have been found to be negative predictors of depression improvement with TMS.[115,119] Pretreatment cerebral metabolism has been found to correlate with antidepressant response to TMS[120]; for example, hypometabolism in the temporal lobes, cerebellum, anterior and occipital cingulate regions has been associated with improvement with fast rTMS while hypermetabolism had been associated with improvement with slow rTMS.[121]

Some preliminary data suggest that TMS might be used as a maintenance treatment for patients with depression.[122] TMS has recently been shown to accelerate the antidepressant effect of amitriptyline[123]; previously it had not been shown that concomitant use of antidepressant medication influences the therapeutic effect of TMS.[110]

Course duration of more than 10 days had been found to be associated with a better antidepressant effect,[124] and treatment for at least 4 weeks is considered to have clinically meaningful benefits.[125] More intense magnetic pulses (100% to 110% of motor threshold) have been shown to be more effective that less intense pulses (80% to 90% of motor threshold), and more pulses per day (1200 to 1600 pulses per day) has been shown to be more effective than fewer pulses per day (800 to 1000 pulses per day).[124] High-frequency rTMS has not been shown to be superior to low-frequency rTMS.[126,127] Low-frequency rTMS is considered safer, and its use is recommended.[110]

Adverse effects

TMS is considered a safe procedure, without clinically significant changes in cognitive parameters,[128] hearing, or hormone levels.[129] The major risk of TMS is seizure induction, associated primarily with high-frequency rTMS. Since the introduction of standards of safety for the administration of TMS,[105] no TMS-induced seizure has been reported. Other adverse effects include headaches, scalp facial muscle twitching, and mild tinnitus, which usually respond to analgesics.

Mechanism of action

TMS causes functional changes in the brain. Performing magnetic resonance imaging (MRI) scans before and after rTMS in depressed patients did not reveal any structural difference, and volumetric analysis of the prefrontal lobe showed no changes.[130] However, many studies have demonstrated that TMS changes cortical excitability[131] and that higher intensity TMS causes greater activation than lower intensity TMS.[132] These changes in cortical excitability occur at the primary site of excitation (neuronal activation in sites under the coil) as well as in distant brain areas.[133]

Clinical improvement in depression using rTMS has been associated with changes in cerebral blood flow in the prefrontal and paralimbic areas.[134] SPECT scans that were obtained from patients with major depression resistant to medication before and after 10 days of rTMS, demonstrated that treatment responders had significantly less pretreatment blood flow in the left amygdala compared with nonresponders, and only the responders demonstrated two patterns of change in regional blood flow with treatment: a reduction in orbitofrontal blood flow and/or a reduction in anterior cingulate blood flow.[135]

Using animal models, rTMS-induced changes in neurotransmitters have been found. Some of these changes are similar to the effect of other antidepressant therapy (such as ECS).[136-138] For example, a single rTMS session was associated with increased hippocampal dopamine and serotonin.[136] Chronic rTMS was associated with upregulation of β-adrenergic and serotonin receptors in the frontal cortex, with downregulation of β-adrenergic receptors in the striatum[137] and with subsensitivity of presynaptic serotonergic autoreceptors, an effect that is shared with antidepressant drugs.[132]

rTMS has been shown to have some metabolic and neuroendocrine effects. Using proton magnetic resonance spectroscopy following high-frequency rTMS in healthy volunteers, it was demonstrated that rTMS affects cortical glutamate/glutamine levels, both close to the stimulation site (left dorsolateral prefrontal cortex) and in remote brain regions (right dorsolateral prefrontal cortex, left cingulate cortex). These data indicate that rTMS may act via stimulation of glutamatergic prefrontal neurons.[139] rTMS has been shown to increase thyroid-stimulating hormone (TSH) in healthy individuals[140] and in patients with major depression.[141] In patients with depression who remitted after rTMS, reversal of dexamethasone suppression test (DST) abnormality was demonstrated.[142]

rTMS has recently been associated with neuroplasticity and neurogenesis. For example, rTMS can modulate astroglial gene expression; following rTMS, an increased

level of glial fibrillary acidic protein (GFAP) messenger ribonucleic acid (mRNA) was found in the hippocampal dentate gyrus.[143] rTMS can also increase immediate early gene expression, such as c-fos and c-jun.[144,145]
It had been suggested that a change in local blood-brain barrier settings, allowing passage of peripheral substances directly into brain parenchyma, may be the mechanism of TMS. However, it has recently been demonstrated that TMS does not result in leakage of the blood-brain barrier in patients with depression.[146]

Magnetic seizure therapy

Magnetic seizure therapy (MST) is a novel brain stimulation method that uses transcranial magnetic stimulation at convulsive parameters in order to induce therapeutic seizures under general anesthesia, in the same setting used for ECT.[147] After its introduction in 2000, a few case reports described successful treatment of patients suffering from major depression using MST[110,148] but it is not yet established that MST has antidepressant efficacy. In a recent study by Lisanby et al,[110] 10 patients with major depression received two treatments with MST followed by two treatments with ECT, in randomized order. MST seizures were found to have shorter duration, lower ictal EEG amplitude, and less postictal suppression than ECT seizures.[149] MST might cause fewer cognitive side effects than ECT, by inducing more focused seizures and sparing cortical regions associated with memory loss. In a nonhuman primate model (Rhesus macaque monkeys), MST was shown to result in a more favorable acute cognitive side-effect profile than ECT with regard to long-term memory of a constant target, short-term memory of a variable target, and recall of previously learned three-item lists.[150,151] Preliminary clinical data are seen as suggesting that MST has antidepressant properties and fewer cognitive side effects than ECT.[152] For example, patients recover orientation more quickly and have fewer attention difficulties or less retrograde amnesia after MST compared with ECT.[153]

Deep brain stimulation

Development of DBS

Deep brain stimulation (DBS) was introduced in the late 1980s by Benabid and colleagues, for the treatment of movement disorders.[153] Their original assumption was that chronic high-frequency stimulation of the brain areas might be similar to surgical ablation of these areas.[154] For example, thalamic stimulation for the treatment of intractable tremor was found to have clinical benefits similar to those achieved by surgical thalamotomy[155] and stimulation of the subthalamic nucleus or globus pallidus internus for the treatment of Parkinson's disease could replace the traditional pallidotomy.[156] Over the last decade, DBS has become a popular treatment for movement disorders such as Parkinson's disease and essential tremor.[157] During the last few years, DBS has been suggested as a treatment for psychiatric disorders, such as depression[158] and obsessive-compulsive disorder.[159]

Technical aspects

The surgical procedure for the implantation of DBS electrodes is based on stereotactic techniques that include imaging modalities, physiological mapping, and surgical navigation computers.[160] A stereotactic frame is fixed to the patient's head, and preoperative magnetic resonance images are obtained. Under local anesthesia, a burr hole is drilled, the underlying dura mater is opened, and microelectrodes are inserted using MRI guidance. The electrode location is confirmed by postoperative MRI. Right and left quadripolar electrodes are implanted. The electrodes remain externalized for a week for clinical testing, and then are connected to a pulse generator that is implanted in the infraclavicular region. The frequency, intensity, and pulse width of the stimulation are programmable, within safety limits. The physician sets the stimulus parameters, and the patient might also alter a few parameters by him- or herself. Stimulation can be programmed to continuous or intermittent firing, or to on and off cycles during fixed time intervals. DBS is reversible, and the stimulation parameters can be changed according to patient's symptoms or disease progression.

DBS in the treatment of major depression

To date, a few case reports suggest that DBS might be a useful treatment for refractory depression. Recently, Mayberg and colleagues[158] found that DBS of the white matter tracts adjacent to the subgenual cingulate gyrus was associated with improvement in depressive symptoms in 6 patients with refractory depression. By 1 and 6

months, two and four patients met criteria for clinical response, respectively. Remission was achieved by three patients after 6 months.[158] Deep brain stimulation of the ventral caudate nucleus improved anxiety, depressive, and compulsive symptoms in one patient who suffered from resistant obsessive-compulsive disorder and resistant major depression.[159] Deep-brain stimulation of the inferior thalamic peduncle improved depressive symptoms in one patient suffering from recurrent unipolar depression and borderline personality disorder.[161]

Adverse effects

Major side effects of DBS are seizure (1% to 3%), hemorrhage (1% to 5%), infection (2% to 25%, usually superficial infections but rarely cerebritis or brain abscess) and hardware-related complications (about 25%) that include fracture of leads, disconnection, lead movement, and malfunction.[162,163] Stimulation-induced adverse effects such as parasthesia, muscle contraction, dysarthria, or diplopia are usually reversible with changes in stimulation parameters.[164]

Mechanism of action

Investigating the mechanism of deep brain stimulation reveals a basic paradox: the clinical effect of deep brain stimulation, which is usually regarded as a method of activating neurons, is similar to the traditional ablation of specific brain areas.[165] Studies aimed at resolving this paradox have led to the development of four major theories regarding the mechanism of action of DBS. The first theory suggests that irregular activity in neurons converging with other neurons can result in a loss of information transfer and thus cause clinical pathology. The therapeutic effect of DBS may be due to its driving neurons at regular frequencies, and thus modulating the pathological network activity and increasing neuronal activity in the output nuclei.[166] Many studies using functional imaging demonstrate increased cortical activity during DBS treatment. For example, activation of the thalamus and basal ganglia was demonstrated by fMRI studies[167] and activation of motor cortex and supplementary motor area was demonstrated by PET studies.[168,169] The second theory suggests that excitation of axon terminals near the stimulation electrode releases inhibitory factors that cause synaptic inhibition of the neuron.[170] The third theory suggests that high-frequency tetanus produces a blockade of the spontaneous activities of neurons as a result of a strong depression of intrinsic voltage-gated currents,[171] and thus DBS causes a depolarization blockade. Theories of synaptic inhibition and depolarization blockade are both supported by the decreased recordings of somatic activity in the stimulated nuclei. The fourth theory suggests that the stimulation causes synaptic depression by transmitter depletion.[172,173]
Although depression is probably a disorder of multiple brain areas, neuronal pathways, neurotransmitters, and genomic systems, DBS requires stimulation of a single brain area. Many studies indicate that the limbic-cortical pathways and specifically the subgenual cingulate (Cg25) are involved in acute sadness and in the antidepressant effect of medications, electroconvulsive therapy, and transcranial magnetic stimulation.[174-176] Therefore, this area was first tested by Mayberg and colleagues for the efficacy of DBS as a treatment for major depression. By using pretreatment and post-treatment PET scans, it was demonstrated that the cerebral blood flow abnormalities related to depression, such as decreased blood flow in the prefrontal area and increased blood flow in the subgenual cingulate (Cg25), were normalized after DBS in the treatment-responsive patients.[158]

Vagus nerve stimulation

Development of VNS

The vagus nerve, the longest of the cranial nerves, is a mixed nerve, with 80% of the fibers carrying afferent information (to the brain) and 20% of the fibers carrying efferent information (from the brain). Afferent sensory fibers within the vagus nerve terminate in the nucleus tractus solitarius (NTS), which innervates many brain regions that are related to psychiatric disorders (for example, locus ceruleus, amygdala, and hypothalamus). The potential of vagal nerve stimulation to influence central nervous system function was demonstrated long before its use as a therapeutic intervention was considered.[177,178] During the 1980s, Zabara showed that VNS has an anticonvulsant action in dogs[179] and during the 1990s VNS became a treatment modality for epilepsy in humans.[180,181] In 2000, VNS was found to be associated with mood improvements in patients with epilepsy.[182,183] VNS has also been demonstrated to affect specific brain areas including the limbic system[184] and to alter concentration of monoamines within the central nervous system

(such as serotonin, norepinephrine, GABA, and glutamate).[185,186] These clinical and laboratory findings, together with the efficacy of anticonvulsant medications as a treatment for depressive episodes, has led to the hypothesis that VNS might be an effective treatment for major depression.[187]

Technique of VNS

VNS is performed in humans by stimulation of the left cervical vagus nerve using a subcutaneous generator that sends an electrical signal to the nerve.[188] The generator is implanted into the left chest wall. Bipolar electrodes are wrapped around the left vagus in the neck through a special incision, and tunneled under the skin toward the chest.[189] The stimulation parameters that can be adjusted by the physician include current intensity, pulse width, frequency, and duration of the on and off periods. The generator is designed to shut off in the presence of a magnetic field, and the patient is given a magnet that can turn off the stimulation when held over the generator.

VNS in the treatment of major depression

VNS was recently demonstrated to have an antidepressant effect in a rat model, significantly better than sham treatment, and similar to other antidepressant treatments (desipramine or ECS).[190] During the past 5 years, Sackeim, Rush, and colleagues have published results of open and randomized controlled studies of VNS in the treatment of major depression. A preliminary open study of VNS in 60 patients with treatment-resistant nonpsychotic major depressive episode revealed a response rate of 30% to 38% by 10 weeks of treatment.[191] A 2-year follow-up of this open study found a response rate of 40% to 44% after 1 year and 42% after 2 years, and a remission rate of 27% after 1 year and 22% after 2 years.[192,193] A randomized controlled study of VNS in over 200 patients with treatment-resistant, nonpsychotic, major depressive episode showed that acute treatment (10 weeks) yielded a response rate of 15% that was similar to the response rate with sham treatment (10%).[194] After the acute treatment, all patients (VNS and sham groups) received long-term treatment with VNS for another 12 months. This was associated with a response rate of 27% and a remission rate of 16%.[195] The response rate in the group of patients who were receiving VNS plus medication or ECT for a year (27%) was significantly better than the response rate of a similar but nonrandomized group of patients with treatment-resistant depression who were receiving only medication or ECT for a year (response rate was only 13%).[196]

Adverse effects

The most common side effects of VNS are voice alteration or hoarseness (55%), coughing (17%), shortness of breath (15%), headache (22%), neck pain (17%), dysphagia (20%), and pain (15%). Although most side effects usually resolve within a few weeks, voice alteration and dyspnea might persist for long periods. Reduction in current intensity decreases the severity of these symptoms.[191]

Mechanism of action

VNS most probably alters synaptic activities at vagal afferent terminations, stimulates deep brain areas, and thus modulates antidepressant neuronal circuits in multiple limbic system structures. Brain imaging studies reveal some of these suspected brain changes. PET measurements of cerebral blood flow in 10 patients with epilepsy before and during acute VNS treatment (both low- and high-stimulation VNS) demonstrated increased blood flow in the rostral, dorsal-central medulla, the right postcentral gyrus, bilaterally in the hypothalami, thalami, and insular cortices, and in the cerebellar hemispheres inferiorly. Decreased blood flow was demonstrated bilaterally in hippocampus, amygdala, and posterior cingulate gyri.[184] Similar changes in cerebral blood flow were also demonstrated during prolonged VNS treatment.[197] Some of these findings share features with changes of regional cerebral blood flow previously associated with the administration of antidepressant drugs (such as selective serotonin reuptake inhibitors).[198] fMRI studies confirmed that VNS induces changes in the orbitofrontal and parieto-occipital cortex bilaterally, left temporal cortex, hypothalamus, and left amygdala[199] and suggested that VNS at different frequencies has frequency or dose-dependent modulatory effects on brain activities.[200]
In addition, VNS is associated with neurobiological changes that are related to the pathogenesis of depression:

- VNS has been found to alter concentrations of neurotransmitters that are probably involved in the mechanism of depression. VNS was associated with increased

GABA, 5-hydroxyindoleacetic acid and homovanillic acid levels and decreased aspartate and glutamate levels.[186,201]

- VNS was associated with neuroimmunological changes such as a marked peripheral increase in pro- and anti-inflammatory circulating cytokines, such as IL-6, TNF-α, and TGF-β.[202]
- A preliminary study suggests that VNS treatment changes the hypothalamic-pituitary-adrenal (HPA) axis stress system. In patients with chronic depression, corticotrophin-releasing hormone (CRH) challenge causes increased adrenocorticotrophic hormone (ACTH) levels. VNS treatment of depressed patients reversed this abnormally increased ACTH response to CRH challenge.[203]
- VNS treatment was associated with improvement in abnormal sleep architecture in patients with depression.[204]

Conclusions

Several novel nonpharmacological, somatic treatments for major depression have been reviewed. All are based on the principle of brain stimulation. Other than ECT, TMS is the only one of these treatments that is relatively widely used. The clinical efficacy of TMS is not conclusively established, and its precise therapeutic niche still needs to be defined. TMS does not appear to be a viable alternative to ECT for treatment-refractory, depressed patients. There is very great interest in the potential of MST. If magnetically induced seizures are effective clinically but induce fewer cognitive adverse effects than ECT, this would be a very great advantage. Early studies suggest that this may be so, but the field is still at a very early stage of development and further research is needed. The last two modalities discussed, DBS and VNS, are both characterized by high cost and the potential for troublesome adverse effects. Both entail surgical procedures. Their indication, if efficacy is established and technical issues are resolved, would be for highly resistant patients where the complexity of the treatment and its expense are warranted. Some trials of VNS have been conducted. Their results suggest equivocal efficacy in the short term, but longer-term effects might be more promising. The clinical application of DBS is still at very early stage.

In practical terms ECT remains the only widely available, nonpharmacological, somatic treatment of depression that is effective, safe, and relatively inexpensive. This is likely to remain the situation in the short term. In the longer term, other approaches to brain stimulation may become clinically viable and eventually replace ECT. Such a projection must be made with due caution. The epitaph of ECT has been written repeatedly over the past 50 years. Nevertheless, it remains one of the longest-standing, continuously used treatments in medicine. Research efforts over the next decade in the field of brain stimulation will be crucial in establishing how long ECT will continue to occupy this unique position. ❑

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Tratamientos somáticos no farmacológicos de la depresión: terapia electroconvulsiva y nuevas modalidades de estimulación cerebral

Hasta hace muy poco tiempo una revisión de los tratamientos somáticos, no farmacológicos de los trastornos psiquiátricos habría incluido sólo la terapia electrocovulsiva (TEC). Esta situación está cambiando significativamente en la actualidad. Aunque la TEC permanece como la única modalidad de amplio uso clínico, existen nuevas técnicas que están en investigación. La principal indicación en el ámbito psiquiátrico es el tratamiento de la depresión mayor, pero también se están estudiando otras aplicaciones. Todos los nuevos tratamientos incorporan la estimulación cerebral, la que se obtiene a través de diferentes métodos tecnológicos. El tratamiento más cercano al límite de la aceptación clínica es la estimulación magnética transcraneal (EMT). Aunque la EMT es segura y relativamente fácil de administrar, su eficacia aun no ha sido definitivamente establecida. Otras modalidades, en diversas etapas de investigación, incluyen la terapia magnética convulsiva (TMC), la estimulación cerebral profunda (ECP) y la estimulación del nervio vago (ENV). Se revisa brevemente el desarrollo y los aspectos técnicos de estos tratamientos, su potencial papel en el tratamiento de la depresión, los efectos adversos y los mecanismos de acción. Se revisa en mayor extensión la TEC por ser la única de estas modalidades terapéuticas que se utiliza ampliamente en clínica. Aunque ha transcurrido más de medio siglo desde que la TEC fue introducida por primera vez, ésta continúa siendo el tratamiento más efectivo para la depresión mayor, con eficacia en pacientes refractarios a los fármacos antidepresivos y con un aceptable perfil de seguridad. Aunque las nuevas técnicas de estimulación cerebral revisadas acá parecen promisorias, requerirán de un mayor desarrollo a futuro antes de que alcancen aceptación clínica.

Traitements somatiques, non pharmacologiques de la dépression : électrochoc et nouvelles modalités de stimulation cérébrale

Il y a peu de temps encore, une analyse des traitements somatiques non pharmacologiques des troubles psychiatriques n'aurait compris que l'électrochoc. Cette situation est en train de changer notablement. Bien que l'électrochoc reste la seule modalité en pratique clinique courante, plusieurs nouvelles techniques sont en expérimentation. Leur indication principale dans le contexte psychiatrique est le traitement de la dépression majeure, mais d'autres applications sont en cours d'étude. Tous les nouveaux traitements font intervenir la stimulation cérébrale, réalisée par différentes techniques. Le traitement le plus proche du seuil d'acceptabilité clinique est la stimulation magnétique transcrânienne (SMT). Bien que la SMT soit sûre et relativement facile à administrer, son efficacité doit encore être définitivement établie. D'autres modalités, à différents stades de recherche, comprennent le traitement d'attaque magnétique (TAM), la stimulation cérébrale profonde (SCP) et la stimulation du nerf vagal (SNV). Nous analysons brièvement le développement et les aspects techniques de ces traitements, leur rôle potentiel dans le traitement de la dépression majeure, leurs effets indésirables et leur mécanisme d'action reconnu. Une attention plus importante est portée à l'électrochoc, car c'est le seul de ces traitements qui est utilisé en pratique clinique courante. Bien que l'introduction de l'électrochoc remonte à plus d'un demi siècle, il reste le traitement le plus efficace de la dépression majeure, efficace chez les patients résistants aux antidépresseurs et doté d'un profil de sécurité acceptable. Bien que très prometteuses, les nouvelles techniques de stimulation cérébrale analysées ici devront faire l'objet d'un développement ultérieur avant d'obtenir une acceptabilité clinique.

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