Chapter 11
Non-pharmacological Somatic Treatments for Bipolar Depression

Harold A. Sackeim

Abstract There has been an explosion of research interest in noninvasive and invasive forms of brain stimulation as treatments for bipolar depression and major depressive disorder (MDD). Electroconvulsive therapy (ECT) has the strongest evidence base. In the short term, ECT is more effective than any other intervention for MDD. MDD patients and those with bipolar disorder (BD) do not differ in response or remission rates, but BD patients respond more quickly. Magnetic Seizure Therapy (MST) and Focal Electrically Administered Seizure Therapy (FEAST) provide greater focality of stimulation than can be achieved with traditional ECT. Both techniques appear to have reduced cognitive effects, but equivalence in efficacy with traditional ECT is not established. Repetitive Transcranial Magnetic Therapy (rTMS) is an approved and widely used treatment for MDD. Efficacy appears stronger in the community than in the randomized controlled trials, perhaps due to concomitant use of pharmacotherapy. While commonly used in bipolar depression, as yet there is little information on efficacy specifically in this subgroup. Small studies have suggested that transcranial Direct Current Stimulation (tDCS) has antidepressant properties, including in bipolar depression. While promising, multisite randomized sham controlled trials are needed to test these claims. Vagus Nerve Stimulation (VNS) showed long-term antidepressant effects and good durability of benefit in treatment-resistant depression, including BD. Lack of insurance reimbursement has limited use in the USA for this indication. Initial open-label studies of Deep Brain Stimulation (DBS) at several targets were encouraging. However, two recent pivotal trials were terminated due to lack of an efficacy signal. These negative findings are leading to rethinking the role of DBS in the treatment of severe, treatment-resistant depression.

Keywords Electroconvulsive therapy (ECT) • Bipolar depression • Response rate • Magnetic seizure therapy (MST) • Focal electrically administered seizure therapy (FEAST) • Repetitive transcranial magnetic stimulation (rTMS) • Deep

H.A. Sackeim, PhD (✉)
Departments of Psychiatry and Radiology, College of Physicians and Surgeons of Columbia University, 2124 Moselem Springs Road, Fleetwood, PA 19522, USA
e-mail: has1@columbia.edu

C.A. Zarate Jr., H.K. Manji (eds.), *Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis, and Pharmacotherapy*, Milestones in Drug Therapy,
DOI 10.1007/978-3-319-31689-5_11

brain stimulation (DBS) • Vagus nerve stimulation (VNS) • Transcranial direct current stimulation (tDCS)

11.1 Introduction

The pharmacological treatment of bipolar disorder (BD) has always presented key challenges. Results from a recent national study of major depressive disorder (MDD), the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), have generally indicated that response and remission rates are disappointingly low and that large percentages of patients do not achieve substantial improvement if they have not benefited from two adequate treatment trials (Rush 2007). Furthermore, relapse is both more rapid and more likely in patients who prospectively manifest treatment resistance during sequential pharmacological trials. Similarly, the national study of bipolar depression, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), found disappointingly low rates of sustained recovery when paroxetine or bupropion were added to a mood-stabilizing agent, and these rates did not differ from the group receiving a mood-stabilizing agent and placebo (Sachs et al. 2007).

In addition to high rates of treatment resistance in bipolar depression, pharmacological management has been beset by two other major conundrums. There is considerable concern that exposure to antidepressant medications may induce or exacerbate symptoms of agitation in BD patients and, in some cases, result in a switch into a hypomanic or manic state. For example, 44 % of the first 500 patients to enter the STEP-BD study historically reported a switch to a hypomanic, manic, or mixed stated within 12 weeks of starting an antidepressant treatment (Truman et al. 2007). This was especially likely in patients with short duration of illness, exposure to multiple antidepressant trials, and a previous history of switching. An independent concern was raised during the era when tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were the mainstay of antidepressant treatment. It was suggested that these agents, while often effective in the acute treatment of bipolar depression, could accelerate the progression of illness, resulting in shorter periods of euthymia and, in some cases, inducing rapid cycling (Wehr and Goodwin 1979). These concerns about the limitations of pharmacological treatment in bipolar depression are accentuated with respect to the management of bipolar mania, where there is a high rate of morbidity and mortality and especially great need for rapid and effective treatment.

Non-pharmacological somatic treatments have a long history in the care of patients with BD. Indeed, electroconvulsive therapy (ECT) is the biological intervention with the longest history of continuous use in psychiatry, and it remains the most effective acute treatment available for either MDD or BD (American Psychiatric Association 2001). This is a powerful statement that indicates that ECT is one of the few treatments with therapeutic properties in the acute treatment of either bipolar depression or mania and, even more remarkably, most likely the most

effective acute treatment available for either condition. The essential limitations of ECT—adverse cognitive effects and high rates of relapse—are discussed below (Sackeim et al. 2001a, b; Prudic et al. 2004). New developments in this field created forms of ECT that dramatically reduce the frequency and severity of adverse cognitive effects. These include critical alterations in the administration of ECT, such as the use of ultrabrief electrical stimuli (Tor et al. 2015; Sackeim et al. 2008), and the development of new forms of convulsive therapy, particularly Magnetic Seizure Therapy (MST) (Sackeim 1994) and Focal Electrically Administered Seizure Therapy (FEAST) (Sackeim 2004).

ECT has developed to the point that the total exposure of the brain to an electrical stimulus over a complete course of treatment may be less than 1/10th of a second. The electrical stimulus that is applied is less than 1 amp at the scalp surface and markedly below that in neuronal tissue. Thus, a modest and remarkably transient electrical stimulus results in the most profound acute antidepressant and antimanic effects seen in BD. Since the intensity of the electrical stimulus is known not to result in neuronal injury, and since this stimulus is "ephemeral," having no "metabolites," residue, or other long-term physical existence in the brain, the therapeutic properties of ECT must result from the brain's response to being stimulated in this fashion. In essence, ECT is a paradigm for how endogenous neural processes can produce profound antidepressant and antimanic effects if triggered in an appropriate fashion.

This observation provides the essential rationale for a host of other brain stimulation technologies that do not rely on seizure induction as part of their therapeutic mechanism of action. ECT is a model where an intense single train of stimulation produces an ictal event that, in turn, results in a large set of neurochemical, neurophysiological, and neuroanatomic alterations, some of which are targeted at seizure suppression, some of which are intrinsic to the electrical stimulation (independent of whether a seizure occurs), and others that may be seizure induced but are not critical in seizure termination. In other words, it has become apparent in recent years that electrical stimulation of the brain, independent of whether seizures are produced, results in neurochemical release; the specifics of the magnitude and type of neurotransmitter and peptides involved depend on the intensity and patterns of stimulation. Beyond neurochemical alterations, electrical stimulation of the brain can enhance or block signal transmission and, perhaps in some cases, improve signal-to-noise ratios compromised by damage in distal regions. Consequently, the field of brain stimulation, currently in its early development, opens the possibility for focal control of neurochemical alterations, second messenger processes, and modulation of brain communication systems in ways that have never been achieved with pharmacological interventions. This chapter reviews both what is known about current brain stimulation technologies in the treatment of bipolar depression, as well as highlighting the potential for new developments.

11.1.1 Electroconvulsive Therapy

Meduna, acting under the view common at the time that there was an intrinsic antagonism between epilepsy and schizophrenia, introduced convulsive therapy. While others had tried blood transfusion across these illnesses, Meduna tested the bold concept that exogenously induced seizures might reduce symptoms of this disorder. Using camphor in oil as the induction method, he reported that a remarkable number of patients with a diagnosis of schizophrenia showed marked symptomatic improvement with this method (Meduna 1935). This assertion proved controversial, since the predominant view at the time in biological psychiatry was that the major forms of mental illness were due to congenital or degenerative conditions and could not be ameliorated, even palliatively, by any intervention. As a result of taking this position, Meduna lost his academic position. His method of chemical seizure induction was quickly replaced by the use of Metrazol, a gamma aminobutyric acid (GABA) antagonist, that more reliably resulted in seizures, and convulsive therapy was widely adopted worldwide.

In 1938, Cerletti and Bini in Rome demonstrated that electrical stimulation was a preferred method. It had the advantages of ensuring only one seizure occurred, whereas recirculation was always possible with chemical induction and, more critically, seizure induction was instantaneous following the electrical stimulus. This advantage was critical since chemical methods often involved a substantial delay, frequently resulting in full panic attacks prior to seizure onset, and subsequent refusal of treatment. The electrical stimulus itself was poorly conceived and basically varied only as a function of the amplitude of the sine wave voltage waveform output by the standard electrical grid with crude control over the duration of exposure. There was little consideration about whether this type of electrical signal was optimal for stimulating neural tissue. Subsequent developments during the 1950s introduced the use of muscle relaxants (first curare and then succinylcholine) to block convulsive motor manifestations. This innovation markedly reduced the rate of vertebral fractures, but required the introduction of general anesthesia. Whereas the application of the electrical stimulus invariably resulted in loss of consciousness, the pre-application of a muscle paralyzing agent, and the subsequent inability to breathe without assistance, necessitated the use of general anesthesia for psychological reasons.

Soon after the introduction of ECT, it was recognized that the intervention had greater success in the treatment of mood disorders than schizophrenia, at least in the short term. Of course, diagnosis at the time had questionable reliability, but the general consensus has been that mood disorders were under-recognized and schizophrenia over-diagnosed in the USA. Thus, the observation that mood disorders responded at remarkably high rates to ECT, and more so than in patients with schizophrenia, if anything, likely underestimated the true difference. Early on, Kalinowsky and others would claim that approximately 80–90 % of patients with depressive illness would achieve remission after receiving approximately six to 12 treatments with ECT (Kalinowsky and Hoch 1946).

This estimate, extending across MDD and BD depressive conditions, has not been realized in recent years. Regardless of treatment methods, remission rates with ECT are somewhat more modest (Prudic et al. 2004; Sackeim et al. 1993, 2000, 2009; Kellner et al. 2006). This shift is likely due to the fact that when ECT was introduced, there were few, if any, competitive treatments, and ECT was commonly used at the outset. Today, resistance to pharmacological treatments is the leading indication for the use of ECT. Several, but not all, studies have found that degree of medication resistance is predictive of ECT outcome and that, in general, patients who have not benefited from adequate psychopharmacology and/or who have long durations of their current episode of depression have somewhat inferior outcomes (Prudic et al. 1990; Sackeim et al. 2000; Heijnen et al. 2010). Thus, remission rates on the order of 60–70 % may be a more realistic estimate, especially if remission is defined as maintaining nearly complete symptomatic improvement for at least one week following ECT.

This extent of expected clinical improvement with ECT exceeds that of any other known antidepressant treatment (American Psychiatric Association 2001). Typically, in ECT research, the bar is set higher for what is defined as response or remission than in standard pharmacological trials, and yet the response and remission rates are higher, despite the concentration on patients with treatment resistance. For example, in the STAR*D study, remission rates among MDD patients who had not achieved adequate benefit after two pharmacological treatments were on the order of 10 % (Rush 2007). Such patients would be expected to remit at substantially higher rates if treated with ECT.

Part of the evidence base supporting the efficacy of ECT in MDD derives from randomized trials comparing ECT to antidepressant pharmacotherapy (Janicak et al. 1985; Folkerts et al. 1997). While such trials were not double-blind and had other limitations, ECT was consistently superior in efficacy. The first such trial was recently conducted in bipolar depression (Schoeyen et al. 2015). Schoeyen and colleagues randomized 73 patients with BD-I or BD-II depression to right unilateral ECT or algorithmic pharmacological treatment. Outcome was assessed by blinded raters after six weeks. All patients had failed two or more trials of antidepressants or mood stabilizers. The ECT group had greater symptomatic improvement and superior response rate (ECT = 74 % vs. pharmacotherapy = 35 %). However, there was no difference in remission rate, suggesting that ECT may have been terminated prior to full benefit.

There is no evidence that the distinction between MDD and bipolar depression has bearing on likelihood of achieving response or remission with ECT. Retrospective and prospective comparisons have generally indicated that both forms of depression respond or remit at approximately the same rate. However, there are two caveats to this generalization. First, patients with bipolar depression require fewer treatments to achieve response or remission than patients with MDD. This was first reported in samples treated in randomized protocols at the New York State Psychiatric Institute (NYSPI), with the observation that, on average, patients with bipolar depression required approximately 1.5 fewer treatments than MDD patients to meet the same outcome criteria (Daly et al. 2001). This observation was later

replicated in a large naturalistic study of patients treated in community settings (Sackeim and Prudic 2005) and in Europe (Sienaert et al. 2009).

This observation reflects a large effect since the bulk of clinical gains with ECT are usually obtained within the first six treatments. Bipolar depressed patients appear to achieve this benefit more rapidly. The only factor known to have substantial impact on the speed of response with ECT is the extent to which electrical dosage exceeds seizure threshold, with higher dosage leading to more rapid improvement (Sackeim et al. 1993). However, multiple studies have failed to find a difference in initial seizure threshold in MDD and bipolar depression, and in the studies at NYSPI, dosage was always adjusted to a specific level relative to seizure threshold for all patients in a treatment condition. BD patients improved more rapidly regardless of whether they received right unilateral or bilateral ECT or of the particular dosage that was applied. This would suggest that the neurophysiological response to exogenous seizure induction differs in MDD and bipolar depression. For example, it has long been speculated that it is the endogenous anticonvulsant response of the brain in terminating the seizure that is critical to achieving antidepressant effects (Sackeim et al. 1983), while others have noted that ECT results in remarkably rapid onset of neuroplastic changes, including neurogenesis (Perera et al. 2007). Thus, a variety of avenues need exploration to account for the more rapid onset of benefit in bipolar depression.

The second area in which the efficacy of ECT for bipolar depression may be altered pertains to the subset of patients with psychotic or delusional depression. It has often been stated that psychotic features are overrepresented in patients with bipolar depression relative to MDD, although this is not firmly established. Regardless, most studies that have compared the efficacy of ECT in patients with and without psychotic features have found higher rates of response and remission in psychotic depression (American Psychiatric Association 2001). Until the advent of atypical antipsychotic medications, only a very small minority of patients with psychotic depression had received an adequate combined pharmacological trial prior to ECT, since the dosage of antipsychotic medication considered adequate was often intolerable, especially in the elderly, and especially when combined with the available antidepressant medications (Mulsant et al. 1997). Relatively low rates of established medication resistance continue to characterize patients with psychotic features, since ECT is also often considered due to clinical urgency, history of response, and patient preference.

Two principal issues distinguish the management of the patient with bipolar depression during ECT. The first pertains to concomitant pharmacological agents and the second to the emergence of hypomania or mania. In general, in the USA, it had long been recommended that all patients be withdrawn from psychotropic agents during ECT, with the exception of antipsychotics in patients with psychotic features (American Psychiatric Association 2001). There was little evidence that concomitant antidepressant medications enhanced clinical outcome and some concern that concomitant anxiolytics, especially benzodiazepines and perhaps anticonvulsants, interfered with the therapeutic process.

Recently, a large, multisite study randomized MDD patients and those with bipolar depression to concomitant treatment with placebo, nortriptyline, or venlafaxine during the course of ECT (Sackeim et al. 2009). There was significant enhancement of the therapeutic benefit in patients treated with nortriptyline or venlafaxine relative to placebo and some evidence that concurrent nortriptyline reduced the cognitive side effects of ECT. Over 20 % of the 316 participants in this study had bipolar depression, and there was no evidence that these effects differed with polarity. Thus, this recent evidence is leading to revision of the longstanding view that antidepressants should be stopped during the administration of ECT. For instance, in the intent-to-treat sample, the remission rates following ECT among MDD patients for those treated with nortriptyline or placebo were 61.2 % and 43.7 %, respectively. The comparable remission rates for bipolar depressed patients were 72.0 % and 59.3 %. This reflects a substantial enhancement of outcomes.

Research with schizophrenia has supported the safety and clinical utility of combining antipsychotic medications and ECT, with evidence for synergistic clinical effects (Sackeim 2003). However, there has long been concern that agents with anticonvulsant properties, especially benzodiazepines, may interfere with the seizure process and diminish efficacy. The evidence for diminished efficacy is entirely circumstantial, stemming mainly from naturalistic, retrospective studies. It is possible that the most agitated patients are the most likely to receive the highest doses of these agents, and these observations are confounded. Nonetheless, it is prudent to limit both benzodiazepine and anticonvulsant use during the ECT course. Since ECT has profound anticonvulsant properties, often leading to a decrease in anticonvulsant dosage in epilepsy patients, and since improvement is usually marked and rapid in psychic anxiety, these dosage limitations are usually well tolerated. Another problematic issue is exposure to lithium during the ECT course. It is well established that a minority of individuals will develop a severe organic brain syndrome when the two are combined, which diminishes rapidly once the lithium is stopped. For this reason, most expert groups recommend discontinuation of lithium during an acute ECT course or, at minimum, withholding doses the evening before a treatment (American Psychiatric Association 2001).

Major limitations in the use of ECT are its side effects, rates of relapse, and patient acceptability. There is always the concern that treatment of the patient in a mixed state or in bipolar depression will provoke a hypomanic or manic reaction. This certainly does happen with ECT. However, careful examination of the outcomes of hundreds of patients prospectively followed at NYSPI showed that such reactions occurred at remarkably small rates. It is not clear why this is so, but may reflect the antimanic properties of the treatment and/or its marked anticonvulsant effects. There is little consensus on how to manage emergent mania during ECT. Many practitioners will continue the treatment if symptoms are mild. Many would terminate the ongoing course of ECT, institute a new pharmacological regimen, and observe the patient if severe manic symptoms emerged.

Only in recent years have the adverse long-term effects of ECT on memory been documented. Both randomized and naturalistic studies have shown that methods of ECT administration substantially differ in their impact on the degree of retrograde

amnesia observed six months following the treatment (Sackeim et al. 2007b, 2008; Sackeim 2014). Indeed, recent work has shown that the objective findings covary with patients' subjective reports of deficits (Berman et al. 2008; Brakemeier et al. 2011). It is established that ECT techniques alter the likelihood of long-term negative effects. For instance, the introduction of ultrabrief pulse stimulation, when coupled with right unilateral electrode placement, substantially reduces cognitive effects at all time points (Sackeim et al. 2008). There is also evidence that, at baseline, older patients with bipolar depression have greater cognitive impairment, especially memory deficits, than similarly aged MDD patients, presumably as a consequence of a history of more frequent episodes (Burt et al. 2000). However, there is no evidence that BD patients are more at risk than MDD patients with respect to ECT's cognitive effects.

ECT is one of the only psychiatric treatments that is typically discontinued once found effective. Relapse is common following ECT-induced remission, and modern prospective studies document that approximately 50 % of remitted patients relapse despite aggressive continuation therapy with pharmacological agents or ECT, with medication resistance a strong predictor (Kellner et al. 2006; Sackeim et al. 1990, 2001a; Jelovac et al. 2013). However, STAR*D and other recent studies have reported similarly high rates of relapse despite continuation of the same pharmacological regimen that produced response or remission, with medication resistance again predicting more rapid and frequent relapse (Rush 2007). Durability of benefit appears to be a significant and general problem in the management of depression. Although sample sizes have generally been small, there is no evidence that relapse risk following ECT differs in MDD and bipolar depression.

11.1.2 Magnetic Seizure Therapy

It has been established that the current paths of the ECT stimulus and the dosing within those paths have profound effects on the efficacy and side effects of the treatment (Sackeim et al. 1987, 1993, 2000). Yet, with traditional ECT, the high impedance of the skull and other anatomic reasons limit the capacity to restrict current paths. A treatment method that offered superior control over anatomic distribution of current and greater precision in intracerebral dosing (current densities) would provide a major advance. Sackeim proposed that use of a time-varying train of magnetic pulses might achieve these goals, terming the intervention MST (Sackeim 1994). Compared to traditional ECT, the transparency of the scalp and skull to the magnetic field allows for greater anatomic precision, and the fact that dosage is primarily determined by distance from the coil limits deep stimulation and allows for greater dosing precision (Deng et al. 2015).

The future of this modality is uncertain. Preliminary studies have generally shown a relatively low level of cognitive side effects but uncertain efficacy (Lisanby et al. 2001, 2003). The major limitation in MST development, making its future uncertain, is largely engineering issues. It has been difficult to develop

MST systems sufficiently powerful to elicit seizures from regions in frontal cortex using coils that maximize focality of stimulation. This limitation is especially problematic since the extent that dosage is substantially above seizure threshold can be a critical determinant of efficacy. MST is also largely limited to seizure initiation in superficial cortex.

11.1.3 Focal Electrically Applied Seizure Therapy (FEAST)

FEAST is another new intervention that also offers the possibility of greater anatomic precision in site of seizure initiation. Sackeim reasoned that by using unidirectional current flow, which would establish a consistent anode and cathode, as well as altering the geometry and positioning of electrodes, one could achieve greater precision in the anatomic distribution of currents paths (Sackeim 2004). The basic principles underlying FEAST have been validated in research with nonhuman primates (Cycowicz et al. 2008) and in small open clinical investigations (Nahas et al. 2013). Relative to ECT, FEAST appears to have fewer cognitive side effects, but equivalence in efficacy is not yet established.

11.1.4 Repetitive Transcranial Magnetic Stimulation (rTMS)

One can induce current in neural tissue by exposing the tissue to a time-varying magnetic field. With a magnetic coil placed on the surface of the head, anatomic resolution and distribution are determined mainly by coil geometry, and detectable current densities can generally reach 2 cm deep. There are a large number of open and blinded studies that raised the possibility that repetitive stimulation at high frequency ($>$5 Hz) over the left dorsolateral prefrontal cortex (DLPFC) has antidepressant effects, and a smaller set of studies suggested that slow stimulation ($\leq$1 Hz) over the right DLPFC has similar effects. Several meta-analyses have concluded that randomized sham-controlled trials have shown consistent antidepressant effects (Burt et al. 2002). A large industry-sponsored multisite trial reported generally positive findings (O'Reardon et al. 2007), and superior antidepressant effects with left DLPFC high frequency relative to an active sham condition were also observed in the NIH-supported multisite trial (George et al. 2010). These findings led to FDA approval of rTMS specifically for treatment-resistant MDD.

There is considerable skepticism in the field regarding the clinical utility of rTMS in the treatment of depression. While it was incontrovertible that active rTMS exerted greater antidepressant properties than sham interventions, it was uncertain whether the magnitude of benefit was clinically significant given the relatively low remission rates (Sackeim 2000). However, a recent multisite open study of patients receiving rTMS in the community reports an impressively high

rate of short-term remission (Carpenter et al. 2012). It is speculated that rTMS coupled with antidepressant pharmacology may be particularly potent. Surprisingly, follow-up of this same sample suggested strong durability of benefit when combined with rapid reintroduction of rTMS with emergent symptoms (Dunner et al. 2014). Thus, rTMS has become frequently used. Although originally approved only for MDD, use in bipolar depression is common. Some practitioners claim that rTMS can at times fundamentally alter the course of BD. However, as yet there is no evidence that patients with bipolar depression differ in response to rTMS from patients with MDD.

11.1.5 Transcranial Direct Current Stimulation (tDCS) and Related Technologies

There has been an explosion in recent years in research using a variety of methods to stimulate the brain with low intensity noninvasive current. The most studied technique, transcranial Direct Current Stimulation (tDCS), involves passage of a low amperage (e.g., 1 mA) direct current between anode and cathode electrodes placed on the scalp. It is believed that exposure to the direct current alters the firing rate of neuronal populations due to a change in neuronal membrane electrical potential. A variety of other techniques involve alterations in the electrical signal, such as use of alternating current or pulsed current.

Scores of studies have reported enhancement or decrement in human cognitive abilities after exposure to tDCS, although there is dispute regarding the reliability of these effects (Horvath et al. 2015). A small literature has examined potential antidepressant effects of these techniques, with most work concentrating on tDCS. While meta-analysis indicates that tDCS has antidepressant effects greater than sham, the findings derived from small samples were heterogeneous (Shiozawa et al. 2014). More rigorous, large-scale studies are needed to determine whether tDCS (or related techniques) deserve a clinical role. There is initial evidence of efficacy in bipolar depression (Brunoni et al. 2011), and a randomized controlled trial in bipolar depression is underway (Pereira Junior Bde et al. 2015).

11.1.6 Vagus Nerve Stimulation (VNS)

VNS is a treatment approved by the FDA and labeled specifically for treatment-resistant depression, both MDD and BD. Eighty percent of the fibers in the vagus nerve are afferent to brain, and basic research has shown that repetitive electrical stimulation of the vagus nerve can have widespread effects on brain physiology and neurochemistry. It became established that VNS had anticonvulsant properties and was approved for the treatment of epilepsy in 1997. An initial pilot study in

60 patients suggested that VNS had clinically significant long-term effects in patients with marked medication resistance (Sackeim et al. 2001b). A subsequent randomized, sham-controlled, multisite study failed to detect a difference between active and sham VNS after a 10-week treatment period (Rush et al. 2005). However, as in the pilot study, a substantial number of patients were improved after a year. Of special note, it also seems that VNS has remarkable durability of benefit (Sackeim et al. 2007a). A surprisingly large percentage of patients who showed clinical benefit after starting VNS maintained the benefit for periods of up to two years. Thus, this intervention may take a considerable time to show antidepressant effects and has a high capacity to maintain benefit if achieved. As yet, there is no evidence that MDD and BD patients differ in response to VNS.

Despite FDA approval, the absence of controlled data establishing the claims of late onset of action and strong durability of benefit has limited access to VNS in the USA, due to the reluctance of insurers to reimburse for the procedure. Recent developments in this field include the development of noninvasive techniques to stimulate the vagus nerve using peripheral electrical or magnetic stimulation.

11.1.7 Deep Brain Stimulation (DBS)

Stimulation through electrodes indwelling in specified locations in the brain offers unique opportunities to modulate specific pathways for therapeutic benefit. DBS is an FDA-approved treatment for dystonia, essential tremor, and tremor in Parkinson's disease. Therapeutic effects in Parkinson's disease may be marked and evident from first onset of stimulation and highly dependent on the contact placement within a small neural structure and stimulation parameters. In Parkinson's disease, long-term follow-up (five years) indicates that retention of benefit is remarkably high, especially in the context of a degenerative, medication-resistant disorder. In Parkinson's disease, DBS either in the subthalamic nucleus or the globus pallidus is effective, while this is not true for dystonia. Thus, there may be multiple entry points to modulate a network for therapeutic purposes, and these networks differ anatomically among the movement disorders (Hardesty and Sackeim 2007).

DBS in mood disorders is an experimental procedure with a small knowledge base. The morbidity/mortality risk of DBS is significant due to the invasive procedure. Therefore, DBS in mood disorder patients is only conducted in a research context with patients with markedly resistant and severe MDD. The initial experience was limited to open-label, pilot studies with small sample sizes that suggested impressive clinical effects. The targets for stimulation have been the subgenual anterior cingulate in the work led by Mayberg (Mayberg et al. 2005), the anterior limb of the internal capsule (Greenberg et al. 2006), and the nucleus accumbens and the medial forebrain bundle (Schlaepfer et al. 2008).

Mood and movement disorders may differ in how rapidly treatment paradigms are developed. First, knowledge of specific circuitry is less advanced in the case of

mood disorders. Second, the nuclei targeted within the striatum are relatively small in the case of movement disorders, and yet specific location within a nucleus is critical to outcome. In the case of MDD, the structures most often implicated as targets for modulation are large gray matter areas like the anterior cingulate or right orbital frontal cortex. However, the DBS signal does not broadcast well over wide regions of tightly packed gray matter. Thus, it is difficult to modulate over broad areas and, consequently, the work by Mayberg involved stimulating the white matter under the anterior cingulate, thus hoping to modulate activity within the cingulate itself (Mayberg et al. 2005). Similarly, the group stimulating in the internal capsule are also stimulating white matter tracts that may act at distant structures. Initial observations with this target suggested that therapeutic effects in MDD might be contingent on use of high intensity stimulation.

The initial experience with DBS in resistant MDD was largely positive. With the sample sizes small, the trials unblinded and uncontrolled, and many other caveats, the groups focusing on the anterior cingulate, internal capsule, accumbens, and medial forebrain bundle have been encouraged by the clinical outcomes observed, including effectiveness in MDD and bipolar depression and strong durability of benefit (Holtzheimer et al. 2012). However, two randomized controlled pivotal trials were conducted by industry to establish the safety and efficacy of DBS to the subgenual cingulate target (BROADEN trial) or to the ventral capsule/ventral striatum (Dougherty et al. 2015). Both trials were prematurely stopped due to lack of an efficacy signal. The negative findings have resulted in rethinking the role of DBS in the treatment of severe, treatment-resistant depression and in considerable discussion about the source of differences with the results of the original, open-label investigations.

References

American Psychiatric Association (2001) The practice of ECT: recommendations for treatment, training and privileging, 2nd edn. American Psychiatric Press, Washington, DC

Berman RM, Prudic J, Brakemeier EL, Olfson M, Sackeim HA (2008) Subjective evaluation of the therapeutic and cognitive effects of electroconvulsive therapy. Brain Stimul 1(1):16–26

Brakemeier EL, Berman R, Prudic J, Zwillenberg K, Sackeim HA (2011) Self-evaluation of the cognitive effects of electroconvulsive therapy. J ECT 27(1):59–66

Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, Giacopuzzi M, Barbieri S, Priori A (2011) Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 35(1):96–101

Burt T, Prudic J, Peyser S, Clark J, Sackeim HA (2000) Learning and memory in bipolar and unipolar major depression: effects of aging. Neuropsychiatry Neuropsychol Behav Neurol 13 (4):246–253

Burt T, Lisanby SH, Sackeim HA (2002) Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol 5(1):73–103

Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, Dunner DL, Lanocha K, Solvason HB, Demitrack MA (2012) Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 29(7):587–596

Cycowicz YM, Luber B, Spellman T, Lisanby SH (2008) Differential neurophysiological effects of magnetic seizure therapy (MST) and electroconvulsive shock (ECS) in non-human primates. Clin EEG Neurosci 39(3):144–149

Daly JJ, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Roose SP, Sackeim HA (2001) ECT in bipolar and unipolar depression: differences in speed of response. Bipolar Disord 3 (2):95–104

Deng ZD, Lisanby SH, Peterchev AV (2015) Effect of anatomical variability on electric field characteristics of electroconvulsive therapy and magnetic seizure therapy: a parametric modeling study. IEEE Trans Neural Syst Rehabil Eng 23(1):22–31

Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, Eskandar EN, Baltuch GH, Machado AD, Kondziolka D, Cusin C, Evans KC, Price LH, Jacobs K, Pandya M, Denko T, Tyrka AR, Brelje T, Deckersbach T, Kubu C, Malone DA Jr (2015) A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry 78(4):240–248

Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, Brock DG, Bonneh-Barkay D, Cook IA, Lanocha K, Solvason HB, Demitrack MA (2014) A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. J Clin Psychiatry 75(12):1394–1401

Folkerts HW, Michael N, Tolle R, Schonauer K, Mucke S, Schulze-Monking H (1997) Electroconvulsive therapy vs. paroxetine in treatment-resistant depression – a randomized study. Acta Psychiatr Scand 96(5):334–342

George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, Anderson B, Nahas Z, Bulow P, Zarkowski P, Holtzheimer PE III, Schwartz T, Sackeim HA (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67(5):507–516

Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, Rasmussen SA (2006) Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology 31 (11):2384–2393

Hardesty DE, Sackeim HA (2007) Deep brain stimulation in movement and psychiatric disorders. Biol Psychiatry 61(7):831–835

Heijnen WT, Birkenhager TK, Wierdsma AI, van den Broek WW (2010) Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. J Clin Psychopharmacol 30(5):616–619

Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, Wint D, Craighead MC, Kozarsky J, Chismar R, Moreines JL, Mewes K, Posse PR, Gutman DA, Mayberg HS (2012) Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry 69(2):150–158

Horvath JC, Forte JD, Carter O (2015) Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial Direct Current Stimulation (tDCS). Brain Stimul 8(3):535–550

Janicak P, Davis J, Gibbons R, Ericksen S, Chang S, Gallagher P (1985) Efficacy of ECT: a meta-analysis. Am J Psychiatry 142(3):297–302

Jelovac A, Kolshus E, McLoughlin DM (2013) Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. Neuropsychopharmacology 38(12):2467–2474

Kalinowsky LB, Hoch PH (1946) Shock treatments and other somatic procedures in psychiatry. Grune & Stratton, New York

Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, Mueller M, Bernstein HJ, O'Connor K, Smith G, Biggs M, Bailine SH, Malur C, Yim E, McClintock S, Sampson S, Fink M (2006) Continuation electroconvulsive therapy vs pharmacotherapy for

relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry 63(12):1337–1344
Lisanby SH, Schlaepfer TE, Fisch HU, Sackeim HA (2001) Magnetic seizure therapy of major depression. Arch Gen Psychiatry 58(3):303–305
Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA (2003) Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. Neuropsychopharmacology 28(10):1852–1865
Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. Neuron 45 (5):651–660
Meduna LJ (1935) Versuche über die biologische Beeinflussung des Abaufes der Schizophrenie: I. Campher und Cardiozolkrämpfe. Z Neurol Psychiatry 152:235–262
Mulsant BH, Haskett RF, Prudic J, Thase ME, Malone KM, Mann JJ, Pettinati HM, Sackeim HA (1997) Low use of neuroleptic drugs in the treatment of psychotic major depression. Am J Psychiatry 154(4):559–561
Nahas Z, Short B, Burns C, Archer M, Schmidt M, Prudic J, Nobler MS, Devanand DP, Fitzsimons L, Lisanby SH, Payne N, Perera T, George MS, Sackeim HA (2013) A feasibility study of a new method for electrically producing seizures in man: focal electrically administered seizure therapy [FEAST]. Brain Stimul 6(3):403–408
O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, Demitrack MA, George MS, Sackeim HA (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62(11):1208–1216
Pereira Junior Bde S, Tortella G, Lafer B, Nunes P, Bensenor IM, Lotufo PA, Machado-Vieira R, Brunoni AR (2015) The bipolar depression electrical treatment trial (BETTER): design, rationale, and objectives of a randomized, sham-controlled trial and data from the pilot study phase. Neural Plast 2015:684025
Perera TD, Coplan JD, Lisanby SH, Lipira CM, Arif M, Carpio C, Spitzer G, Santarelli L, Scharf B, Hen R, Rosoklija G, Sackeim HA, Dwork AJ (2007) Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. J Neurosci 27(18):4894–4901
Prudic J, Sackeim HA, Devanand DP (1990) Medication resistance and clinical response to electroconvulsive therapy. Psychiatry Res 31(3):287–296
Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA (2004) Effectiveness of electroconvulsive therapy in community settings. Biol Psychiatry 55(3):301–312
Rush AJ (2007) STAR*D: what have we learned? Am J Psychiatry 164(2):201–204
Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ, Rapaport MH, Zajecka J, Nierenberg AA, Husain MM, Ginsberg D, Cooke RG (2005) Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 58(5):347–354
Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME (2007) Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 356(17):1711–1722
Sackeim HA (1994) Magnetic stimulation therapy and ECT. Convulsive Ther 10:255–258
Sackeim HA (2000) Repetitive transcranial magnetic stimulation: What are the next steps? Biol Psychiatry 48(10):959–961
Sackeim HA (2003) Electroconvulsive therapy and schizophrenia. In: Hirsch SR, Weinberger D (eds) Schizophrenia, 2nd edn. Balckwell, Oxford, pp 517–551
Sackeim HA (2004) The convulsant and anticonvulsant properties of electroconvulsive therapy: towards a focal form of brain stimulation. Clin Neurosci Rev 4:39–57
Sackeim HA (2014) Autobiographical memory and electroconvulsive therapy: Do not throw out the baby. J ECT 30(3):177–186

Sackeim HA, Prudic J (2005) Length of the ECT course in bipolar and unipolar depression. J ECT 21(3):195–197

Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR (1983) Anticonvulsant and antidepressant properties of electroconvulsive therapy: a proposed mechanism of action. Biol Psychiatry 18 (11):1301–1310

Sackeim HA, Decina P, Kanzler M, Kerr B, Malitz S (1987) Effects of electrode placement on the efficacy of titrated, low-dose ECT. Am J Psychiatry 144(11):1449–1455

Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990) The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. J Clin Psychopharmacol 10(2):96–104

Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM (1993) Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med 328(12):839–846

Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J (2000) A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 57 (5):425–434

Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Cooper TB, Prudic J (2001a) Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA 285(10):1299–1307

Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, Johnson CR, Seidman S, Giller C, Haines S, Simpson RK Jr, Goodman RR (2001b) Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacology 25(5):713–728

Sackeim HA, Brannan SK, John Rush A, George MS, Marangell LB, Allen J (2007a) Durability of antidepressant response to vagus nerve stimulation (VNSTM). Int J Neuropsychopharmacol 10:817–826

Sackeim HA, Prudic J, Fuller RB, Keilp J, Lavori PW, Olfson M (2007b) The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology 32:244–254

Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N, Berman RM, Brakemeier EL, Perera T, Devanand DP (2008) Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimul 1(2):71–83

Sackeim HA, Dillingham EM, Prudic J, Cooper T, McCall WV, Rosenquist P, Isenberg K, Garcia K, Mulsant BH, Haskett RF (2009) Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. Arch Gen Psychiatry 66(7):729–737

Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, Joe AY, Kreft M, Lenartz D, Sturm V (2008) Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology 33(2):368–377

Schoeyen HK, Kessler U, Andreassen OA, Auestad BH, Bergsholm P, Malt UF, Morken G, Oedegaard KJ, Vaaler A (2015) Treatment-resistant bipolar depression: a randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. Am J Psychiatry 172(1):41–51

Shiozawa P, Fregni F, Bensenor IM, Lotufo PA, Berlim MT, Daskalakis JZ, Cordeiro Q, Brunoni AR (2014) Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int J Neuropsychopharmacol 17(9):1443–1452

Sienaert P, Vansteelandt K, Demyttenaere K, Peuskens J (2009) Ultra-brief pulse ECT in bipolar and unipolar depressive disorder: differences in speed of response. Bipolar Disord 11 (4):418–424

Tor P-C, Bautovich A, Wang M-J, Martin D, Harvey SB, Loo C (2015) A systematic review and meta-analysis of brief versus ultrabrief right unilateral electroconvulsive therapy for depression. J Clin Psychiatry 76(9):e1092–e1098

Truman CJ, Goldberg JF, Ghaemi SN, Baldassano CF, Wisniewski SR, Dennehy EB, Thase ME, Sachs GS (2007) Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry 68(10):1472–1479

Wehr TA, Goodwin FK (1979) Rapid cycling in manic-depressives induced by tricyclic antidepressants. Arch Gen Psychiatry 36(5):555–559