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Non-pharmacological somatic treatments for bipolar depression

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Abstract

Non-pharmacological somatic treatments have a long history in the care of patients with bipolar disorder. 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 unipolar or bipolar depression or mania. This chapter discusses the therapeutic properties of ECT in the acute treatment of bipolar depression, mania, and unipolar depression. It also reviews the essential limitations of ECT – its adverse cognitive effects and high rates of relapse. The chapter introduces new developments in this field that have created forms of ECT administration 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, and the development of new forms of convulsive therapy, particularly Magnetic Seizure Therapy (MST) and Focal Electrically Administered Seizure Therapy (FEAST). Additional novel interventions such as repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS) are also reviewed.

Introduction

The pharmacological treatment of bipolar disorder has always presented key challenges. Results of the recent national study of unipolar depression, 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 [1]. 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, Systematic Treatment Enhancement Program for Bipolar Depression (STEP-BP) found disappointingly low rates of sustained recovery when paroxetine or buproprion were added to a mood-stabilizing agent, and these rates did not differ from the group receiving a mood-stabilizing agent and placebo [2].

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 bipolar 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-BP study retrospectively reported a switch to a hypomanic, manic, or mixed states within 12 weeks of starting antidepressant treatment [3]. This seemed 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 mainstays 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 [4]. 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 an especially great need for rapid and effective treatment.

Non-pharmacological somatic treatments have a long history in the care of patients with bipolar disorder. 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 unipolar or bipolar depression or mania [5]. That is a powerful statement, as it suggests 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, that it is likely the most effective acute treatment available for either condition. The essential limitations of ECT – its adverse cognitive effects and high rates of relapse – are discussed below [6–8]. However, new developments in this field have created forms of ECT administration 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 [9], and the development of new forms of convulsive therapy, particularly Magnetic Seizure Therapy (MST) [10] and Focal Electrically Administered Seizure Therapy (FEAST) [11].

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 one amp at the scalp surface and markedly less than that in neuronal tissue. Thus, a weak and remarkably transient electrical stimulus results in the most profound acute antidepressant and antimanic effects seen in bipolar disorder. Because the intensity of the electrical stimulus is known not to result in neuronal injury, and because 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 mechanisms 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 depends 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 initial 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, and highlights potential new developments.

Electroconvulsive therapy

Ladislas von Meduna, acting under a 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, von Meduna tested the bold concept that exogenously-induced seizures might reduce symptoms in patients with schizophrenia. 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 [12]. This assertion proved controversial, because 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, von Meduna lost his academic post. 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. Convulsive therapy was widely adopted worldwide.

In 1938, Cerletti and Bini in Rome demonstrated that electrical stimulation was the preferred method of seizure induction. It had the advantages of ensuring that only one seizure occurred, whereas recirculation was always possible with chemical induction; more critically, seizure induction was instantaneous after application of the electrical stimulus. This advantage was critical because

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 neural tissue. Subsequent developments during the 1950s introduced the use of muscle relaxants (first curare and then succinylcholine) to block the convulsive motor manifestations of seizures. 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 (for the most part, regardless of whether a seizure was induced), the pre-application of a muscle paralyzing agent, and the subsequent inability to breathe without assistance, necessitated for psychological reasons the use of general anesthesia.

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 in the middle of the 20th century, mood disorders were under-recognized and schizophrenia over-diagnosed in the US. Thus, the observation that mood disorders responded at remarkably high rates to ECT, and more so than 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 6–12 treatments with ECT [13].

This estimate, extending across unipolar and bipolar depressive conditions, has not been realized in recent years. Regardless of treatment methods, remission rates with ECT are somewhat more modest [8, 9, 14–16]. This shift is likely due to the fact that when ECT was introduced there were few, if any, competing 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 [15, 17]. 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 1 week following the end of the treatment course.

The extent of expected clinical improvement with ECT exceeds that of any other known antidepressant treatment [5]. 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 of patients with treatment resistance who receive ECT. For

example, in the STAR*D study, remission rates among unipolar depressed patients who had not achieved adequate benefit after two pharmacological treatments were roughly 10% [1]. Such patients would be expected to remit at substantially higher rates if treated with ECT.

There is no evidence that the distinction between bipolar and unipolar depression affects the 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 rates. However, there are two caveats to this claim. First, it has been shown that patients with bipolar depression require fewer treatments to achieve response or remission than patients with unipolar depression. 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 who responded or remitted required approximately 1.5 fewer treatments than unipolar patients meeting the same outcome criteria [18]. This observation was subsequently replicated in a very large naturalistic study of patients treated in community settings [19].

This observation reflects a large effect, given that 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 dosage exceeds seizure threshold, with higher dosage leading to more rapid improvement [14]. However, multiple studies have failed to find a difference in initial seizure threshold in bipolar and unipolar 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. Bipolar patients appeared to improve more rapidly regardless of whether they received right unilateral or bilateral ECT or the particular dosage that was applied. This would suggest that the neurophysiological response to exogenous seizure induction may differ in bipolar and unipolar 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 [20], while others have noted that ECT results in remarkably rapid onset of neuroplastic changes, including neurogenesis [21]. Thus, there are a variety of avenues needing exploration to account for the more rapid onset of benefit in bipolar depression.

The second area in which efficacy in 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 over-represented in patients with bipolar relative to unipolar depression, 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 [5]. 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; the dosage of antipsychotic medication considered adequate was often intolerable, especially in the elderly, and especially when combined with the available antidepressant medications [22]. Relatively low rates of established medication resistance continue to characterize patients whose depression has psychotic features, as treatment with 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 United States 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 [5]. 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, multi-site study randomized unipolar and bipolar depressed patients to concomitant treatment with placebo, nortriptyline, or venlafaxine during the course of ECT (unpublished data). 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 319 participants in this study had bipolar depression and there was no evidence that these results differed with polarity. Thus, this recent evidence may lead to a 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 unipolar 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 substantial outcome enhancement.

Research in schizophrenia has supported the safety and clinical utility of combining antipsychotic medications and ECT, with evidence for synergistic clinical effects [23]. However, as regards mood disorders, 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, thus confounding these observations. Nonetheless, it is prudent to limit both benzodiazepine and anticonvulsant use during ECT. Because ECT has profound anticonvulsant properties, often leading to a decrease in anticonvulsant dosage in epilepsy patients, and because improvement is usually marked and rapid in psychic anxiety, these dosage limitations are usually well tolerated. Another problematic issue is exposure to lithium during ECT. 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 [5].

The major limitations associated with 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 show that such reactions occurred at remarkably small rates. The reasons for this are unknown, 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 the symptoms are mild, but others terminate the ongoing course of ECT, institute a new pharmacological regimen, and observe the patient for the emergence of severe manic symptoms.

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 may substantially differ in their impact on the degree of retrograde amnesia observed 6 months following treatment [7, 9]. Indeed, recent work has, for the first time, shown that the objective findings can co-vary with patients' subjective reports of deficits [24]. It has become evident that *how* ECT is administered can radically alter the likelihood of long-term negative effects. For instance, the introduction of an ultrabrief form of stimulation, when coupled with the right unilateral electrode placement, substantially reduces cognitive effects at all time points [9]. There is evidence that older bipolar patients may at baseline have greater cognitive impairment, especially memory deficits, than similarly aged unipolar patients, presumably because of their history of more frequent episodes [25]. However, there is no evidence that bipolar patients are more at risk than unipolar patients with respect to ECT's cognitive side effects.

ECT is one of the only psychiatric treatments that is discontinued once 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; not surprisingly, medication resistance is a strong predictor of relapse [9, 15, 16, 26]. However, as the STAR*D study highlighted, durability of benefit appears to be a significant and general problem in the management of depression, regardless of which treatment patients receive. Furthermore, and although sample sizes have been generally small, there is no evidence that relapse risk following ECT differs in unipolar and bipolar depression.

Magnetic Seizure Therapy (MST)

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 [14, 15, 27]. 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 offers superior control over anatomic distributions of the current, and greater precision in intracerebral dosing (current densities) should be a major advance. Sackeim (1994) proposed that use of a time-varying train of magnetic pulses might achieve these goals, and termed the intervention, Magnetic Seizure Therapy (MST) [10]. Theoretically, the transparency of the scalp and skull to the magnetic field would allow for greater anatomic precision, and the fact that dosage was primarily determined by distance from the coil would limit deep stimulation and allow for greater dosing precision.

The future of this modality is uncertain. Preliminary studies are underway and have generally shown a relatively low level of cognitive side effects but uncertain efficacy [28, 29]. From an engineering standpoint, the major limitation to MST is that it has not been possible 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 because the extent that dosage is substantially above seizure threshold can be a critical determinant of efficacy.

Focal Electrically Applied Seizure Therapy (FEAST)

FEAST is a new intervention that also offers the possibility of greater anatomic precision in the site of seizure initiation. Sackeim (2004) reasoned that by using unidirectional current flow, thus having a consistent anode and cathode, and by altering the geometry of the electrodes, one could achieve greater precision in the anatomic distribution of currents paths [11]. The basic principles underlying FEAST have been validated in limited research with non-human primates and in a small open pilot investigation.

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 will be determined mainly by coil geometry and detectable current densities can generally reach two centimeters deep. A large number of open and blinded studies have raised the possibility that repetitive stimulation at high frequency (>5 Hz) over the left dorsolateral prefrontal cortex (DLPFC) has antidepressant effects. A smaller number of studies suggest that slow stimulation (≤1 Hz) over the right DLPFC may have similar effects. Several meta-analyses have concluded that randomized sham-controlled trials have shown consistent antidepressant effects [30], and a large industry-sponsored multi-site trial also reported generally positive findings [31].

Despite this evidence, there is controversy about the role of rTMS as an antidepressant treatment, and it has yet to be approved by the FDA for routine clinical use. The evidence is convincing that rTMS has a very strong safety profile, with transient pain at site of stimulation. However, some question whether the magnitude of the antidepressant effect is of clinical consequence, and there have been methodological concerns regarding the adequacy of blinding and other technical issues. Fundamentally, there is a need to amplify rTMS's antidepressant effects. This may occur through patient selection factors. For instance, in the industry trial, patients with the lowest levels of medication resistance showed a robust clinical effect that was much diminished in more resistant patients. Alternatively, there has been very little work optimizing rTMS stimulation parameters to amplify the clinical signal. As yet there is no evidence that patients with bipolar depression differ in response to rTMS from patients with unipolar depression.

Vagus Nerve Stimulation (VNS)

VNS is approved by the FDA specifically for treatment-resistant depression (either unipolar or bipolar). 80% 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. In 1997, VNS was approved as a treatment for epilepsy due to its anticonvulsant properties. Subsequently, an initial pilot study in 60 patients suggested that VNS had clinically significant long-term effects for depressed patients with marked medication resistance [32]. A subsequent randomized, sham-controlled, multi-site study failed to detect a difference between active and sham VNS after a 10-week treatment period [33]. However, as in the pilot study, a substantial number of patients were improved after a year. Notably, it also seemed that VNS had remarkable durability of benefit [34]. A surprisingly large percentage of patients who showed clinical benefit after starting VNS maintained that benefit for periods of up to 2 years. Thus, it is possible that this intervention may take a considerable amount of time to show antidepressant effects, and a high capacity to maintain benefit when achieved. As yet, there is no evidence that unipolar and bipolar depressed patients differ in response to VNS.

The absence of controlled data establishing the claims of late onset of action and strong durability of benefit have limited patient access to VNS, due to the reluctance of insurers to reimburse for the procedure. New studies are being planned to address these challenges.

Deep Brain Stimulation (DBS)

Stimulation through electrodes indwelling in specified locations in the brain offers unique opportunities to modulate specific pathways for therapeutic ben-

efit. DBS is a FDA-approved treatment for dystonia, essential tremor, and tremor in Parkinson's disease. Evidence gleaned from the treatment of these disorders suggest that there may be multiple entry points to modulate a network for therapeutic purpose, and that these networks differ anatomically among the movement disorders [35].

DBS in mood disorders is an experimental procedure with a small knowledge base. The morbidity/mortality risk of DBS is significant due to the invasiveness of the procedure. Therefore, DBS in individuals with mood disorders is only conducted in a research setting in patients with markedly resistant and severe major depression. The experience so far has been limited to small, open-label pilot studies. The targets for stimulation have been the anterior cingulate in the work led by Mayberg [36], and the anterior limb of the internal capsule in the work led by Greenberg [37].

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 major depression, the structures most often implicated as targets for modulation are large gray matter areas like the anterior cingulate or right orbital frontal cortex. However, in most contexts the DBS signal does not broadcast well over wide regions of tightly packed grey matter. Thus, it is difficult to modulate over broad areas and there is little knowledge to guide targeting to lower volume areas. Consequently, the work by Mayberg and colleagues [36] has involved stimulating the white matter under the anterior cingulate, hoping to modulate activity within the cingulate itself. Similarly, the group stimulating in the internal capsule [37] are also stimulating white matter tracks that may act at distant structures. Indeed, initial observations with this target suggest that therapeutic effects in major depression may be contingent on use of high intensities of stimulation.

The initial experience with DBS in treatment-resistant major depression has been largely positive. Despite small sample sizes, unblinded and uncontrolled trials, and many other caveats, both groups conducting this research have achieved encouraging clinical outcomes, including the durability of the treatment response. Other pilot studies of DBS have implicated the accumbens as a target to specifically modulate anhedonia in depression. Randomized, blinded, sham-controlled trials of DBS in treatment-resistant depression are now being planned.

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