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ELECTROCONVULSIVE THERAPY: SIXTY YEARS OF PROGRESS AND A COMPARISON WITH TRANSCRANIAL MAGNETIC STIMULATION AND VAGAL NERVE STIMULATION

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The science of electroconvulsive therapy (ECT) has progressed rapidly over the last 20 years, providing new insights into the mechanisms of action of ECT, improving both the acute and long-term efficacy of the treatments, and decreasing cognitive problems associated with the treatments. The anticonvulsant hypothesis unifies many of the scientific findings in electroencephalography, neuroimaging, and clinical studies to provide a coherent testable hypothesis of the therapeutic mechanism of ECT. This hypothesis assumes that ECT enhances the transmission of inhibitory neurotransmitters and neuropeptides and that the active process of inhibiting the seizure is essential to the therapeutic action of ECT. New data are presented on improvements in the acute efficacy of ECT with suprathreshold (eight to 10 times the seizure threshold) right unilateral ECT, and three NIMH-supported studies are discussed that examine the efficacy of maintenance therapies. Decreasing cognitive side effects of ECT is another area of active research; changes in techniques and medication treatments are highlighted. Finally, two new treatments using subconvulsive stimuli, repetitive transcranial magnetic stimulation, and vagal nerve stimulation are discussed and compared to ECT.

Cerletti and Bini (1) first investigated ECT as a treatment for psychosis in 1938, theorizing that epilepsy and schizophrenia were incompatible. They hypothesized that the artificial induction of seizures in nonepileptic persons with schizophrenia would relieve psychosis. ECT was developed at approximately the same time as frontal leukotomy (2) and insulin coma therapy (3), but these treatments carried a high morbidity, and were replaced by modern psychopharmacology in the 1950s and 1960s. The indications for ECT were established during this time, and its use in conditions other than mood disorders and schizophrenia diminished.

ECT has remained as an accepted medical treatment for depression and was one of the most significant medical advances in the twentieth century. However, in 1950 the mortality and morbidity from ECT were unacceptably high and most of the early research in ECT focused on the safety and efficacy of the treatments. The death rate was approximately 0.1% (4) and the risk of fractured bones estimated to be as high as 40% (5). Over the last half century, the mortality from ECT has decreased dramatically because of a number of advances, including the widespread use of modern anesthetic agents (e.g., methohexital) (5) and succinylcholine (6), the introduction of cardiac and electroencephalogram (EEG) monitoring during treatments (7), and medications used to decrease the acute hemodynamic response during ECT (8). Abrams put the risk of mortality from ECT into perspective in 1997. He noted that ECT was ten times safer than childbirth and an order of magnitude less that the spontaneous death rate in the population (9).

Today, ECT is recognized as a safe treatment for depression and, despite the advances in pharmacotherapy in the last four decades, ECT continues to be the most effective treatment for severe melancholic depression. Four areas of research are important as we move into the twenty-first century: developing a scientific understanding of the mechanisms of action of ECT, optimization of the efficacy of acute courses of ECT, treatment of the cognitive side effects

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of ECT, and continuing research into the efficacy of different ECT techniques, including novel electrode placements and continuation/maintenance ECT.

MECHANISM OF ACTION OF ECT

Salzman asserts that the psychiatric community continues to show ambivalence toward ECT and ECT research has suffered as a consequence (10). Although there are active steps within the NIMH to address these issues and provide more focused research in ECT (10), an understanding of the basic mechanisms by which ECT exerts its effect is still unclear. This fact is an irony given that ECT is one of the few treatments in psychiatry that was theoretically based (11). Although the original hypothesis that epilepsy and psychosis could not coexist in the same patient was later proven incorrect, the treatment of depression by inducing seizures in patients first with camphor monobromide and later by electrically induced convulsions is one of major medical breakthroughs of the past century.

One of the most confusing aspects of accepting ECT as a treatment for depression in the lay public and patients is the inability of clinicians to clearly explain how ECT is effective in relieving symptoms of depression. Patients have difficulty understanding how a treatment that is so seemingly toxic to the brain (i.e., causing a seizure) could actually be therapeutic. Patients readily accept that the therapeutic effect of antidepressants is to replete a serotonin deficit. However, the antidepressant medications have a number of other effects on a variety of neurotransmitters, regulatory hormones, and cellular mechanisms.

The mechanism by which a convulsive stimulus acts as one of the most powerful antidepressants is equally complex but the explanation may be as simplistic: ECT works by increasing natural brain substances that decrease the excitability of the brain. The unique therapeutic action of ECT is that the induced-seizures last only seconds and not minutes or hours. The physician's contribution to the ECT treatment is the induction of a seizure; the patient's contribution is turning the seizure off. Seizure termination is an active process that underlies the therapeutic mechanism of the treatment. This idea is elaborated on in the following but may give us a plausible explanation for patients on the mechanism of action of ECT.

The earliest attempts at understanding the importance of a convulsion in ECT focused on terminating the ECT-induced seizure with lidocaine to determine if the length of a seizure correlated with the efficacy of the treatment (12). The initial finding was that an ECT seizure had to continue for at least 25 seconds to be therapeutic (13) and the patient had to accumulate a minimal number of seconds of EEG seizure time during a course of ECT (14).

A popular theory of the mechanism of action of ECT, the diencephalic hypothesis (15,16), assumed that the degree of response to ECT was correlated with stimulation of the deep brain structures that regulate the hypothalamic pituitary–endocrine end axis activity. Stimulation of this system resulted in the release of pituitary hormones such as adrenocorticotropin hormone (ACTH), thyrotropin, prolactin, oxytocin, and vasopressin. Research using rodents administered electroconvulsive shock (ECS) and examining the CSF of patients receiving ECT has supported a relationship between increases in neuropeptides during the convulsive stimulus (17). According to the diencephalic hypothesis, ECT seizures that have a longer duration, and ECT parameters that are more effective at stimulating the diencephalic structures (i.e., bilateral [BL] greater than unilateral [UL] and high-dose greater than low-dose ECT), therefore, would be more effective in treating depression.

Both of these assumptions have been questioned recently. Sackeim and colleagues were the first to demonstrate that the therapeutic benefit of the ECT seizure was dependent on the amount above the individual patient's seizure threshold that the stimulus was administered and not simply the duration of the seizure (18). Although the acute release of neuroendocrine markers did correlate with the type of seizure administered and seizure duration, the expected correlation between the acute surge in plasma oxytocin, vasopressin (19), or prolactin (20), and clinical response to ECT was not shown in studies of depressed patients receiving a course of ECT.

Recent research on predicting a patient's response to ECT have focused less on the quantitative analysis of seizure duration and more on the relationship between a qualitative analysis of the ictal and postictal seizure morphology to therapeutic response (21,22). ECT-induced seizures have a characteristic pattern of hypersynchronous neuronal discharge with excitation of cortical neurons during the initial tonic phase, followed by alternating excitatory and inhibitory effects in the clonic phase, and finally postictal suppression owing to inhibition and neuronal hypoexcitability.

A number of treatment-related factors affect seizure morphology, including electrode placement, the percentage above the seizure threshold that the stimulus is administered, and the stimulus waveform (23). A number of features of the ictal EEG seizure that demonstrate a more intense seizure predict clinical response to ECT. (See ref. 24 for review.) Seizure intensity is measured by increased ictal EEG amplitude (high-voltage spikes and waves), symmetry or coherence of ictal EEG amplitude between the right and left hemispheres, and weaker postictal hemispheric coherence, longer duration of stereotypic ictal EEG pattern, and greater postictal suppression or flattening of the EEG. These seizure characteristics have been used to predict the efficacy of an ECT course (22,25–27), or more precisely these variables can be used to predict when a seizure is not adequate. Inadequate EEG seizures have low-amplitude waves and are not symmetric, with no clear ending of the seizure in the postictal period.

Analysis of the EEG morphology has been used to determine seizure intensity (26). Clinicians can be trained to visually inspect the EEG strips during ECT and determine the adequacy of the seizure by evaluating the amplitude of the ictal EEG relative to baseline, symmetry of right and left hemispheric EEGs, distinct spike and wave pattern, and degree of postictal suppression (28). Both the Thymatron DGx ECT device (Somatics Inc., Pine Bluff, IL) and the MECTA 5000Q ECT device (MECTA Corp., Lake Oswego, OR) provide measures of the quality of the EEG. Although further testing of the clinical use of the computer-assisted EEG analysis provided with these machines is necessary, these devices may add to stimulus dosing, particularly in patients administered UL ECT, in determining if a seizure is adequate (24,27,29).

Another promising area of investigation into the mechanism of ECT is research correlating functional brain imaging with response to ECT. Studies have shown an increase in cerebral blood flow (CBF) up to 300% of baseline values with an accompanying increased permeability of the blood–brain barrier and increased cerebral metabolic rate (CMR) up to 200% during the ictal period (30). In contrast, CBF decreased to levels below baseline (31) or returned to baseline (32) and PET scans showed a marked decrease in CMR in the postictal period (33).

Although there have not been any clinical studies correlating the increase in CBF/CMR during the ictal period with clinical response, Nobler and colleagues (34) found a correlation between decreased CBF in the immediate postictal period and clinical response. This well-designed study included 54 depressed patients imaged using the Xenon inhalation technique. Patients showed a low baseline CBF compared to matched controls, and their response to ECT was correlated with the further decrease in CBF from baseline. These changes were greatest in the anterior cortical regions and the degree of change was correlated with clinical improvement on the Hamilton Depression Rating Scale. Moreover, these reductions in CBF persisted for the 2-month follow-up in responders, was correlated with improvement in depression scores and the nonresponders continued to have an increase in CBF compared to baseline. Nobler and Sackeim (35) point out that decreased CBF in the anterior cortex supports earlier findings by Max Fink (36,37) and their own group (38) of a relationship between frontal delta activity on EEG and response to ECT. There are additional data suggesting that the reductions in cerebral blood flow that occur immediately after ECT may persist for days (39) to months (40) after the treatments and the most dramatic reductions occurred in the frontal cortex.

Sackeim has unified many of these EEG, CBF, and CMR findings with preclinical research in the anticonvulsant hypothesis as the mechanism of action of ECT (40). During a course of ECT, the patient's seizure threshold is increased and seizure duration decreases during the first several treatments (41,42). ECT seizures usually are limited to less than 1 minute and there is an active inhibitory process in the interictal and postictal states evident by the development of slow or delta waves and decreases in the CBF and metabolic uptake of glucose. The anticonvulsant properties of ECT are hypothesized to occur because of enhanced transmission of inhibitory neurotransmitters and neuropeptides (e.g., GABA and endogenous opioid concentrations) and are an essential element of the therapeutic effect of ECT in mania and depression.

The magnitude of the seizure threshold increase is greater in more effective methods of administering ECT (i.e., high-dose UL and low-dose BL versus low-dose UL) and is correlated with clinical response (18,43). Clinically, Sackeim cites unpublished data that the patients who return to an acute course of ECT after relapsing have the same seizure threshold that they had at the start of treatment. However, it is unclear whether the return of the seizure threshold to baseline occurs after an acute course of ECT in all patients or only in patients who relapse. The duration of the seizure is also decreased over a series of treatments and is another indication of the anticonvulsant effect of ECT. However, seizure duration is not related to efficacy unlike seizure threshold (43).

The EEG of the patient during and immediately following therapeutic ECT treatments indicate that there is an ongoing active process in which the brain is inhibiting the seizure process. Inhibitory processes include the early onset of high amplitude slow-wave activity after the tonic phase of the seizure and bioelectric postictal suppression processes (21,22,27,44–46). The efficacy of ECT has been correlated with the early onset of these inhibitory processes, a fact that supports the anticonvulsant hypothesis. Two elements of seizure expression, seizure strength and peak amplitude of slow-wave activity, were inversely correlated with seizure threshold and the third element, postictal bioelectric suppression, was not related to seizure threshold (40). Because the seizure threshold is increasing during the treatment course, two of the essential elements of a therapeutic seizure (seizure strength and peak amplitude of slow-wave activity) are deteriorating, thereby limiting the effectiveness of subsequent seizures. This finding provides the rationale for developing EEG algorithms (see the preceding), increasing the stimulus dosing or retitrating the seizure threshold during a course of ECT in patients who are not responding.

During a course of ECT, as in epilepsy, CBF/ CMR increase dramatically during the seizure and decrease below baseline in the interictal and postictal states (35). Patients responding to ECT show a more marked global decrease in CBF as well as specific reductions in the anterior frontal cortex (34). These changes were correlated with an increase in the seizure threshold. Finally, increasing slow-wave activity in the frontal cortical regions after ECT was also associated with clinical improvement (38). Both these finding support the anticonvulsant hypothesis.

The anticonvulsant hypothesis unifies many research

findings and provides important new leads that have the potential for improving clinical outcomes and predicting patients who are at risk of relapsing after ECT. The anticonvulsant properties of ECT related to clinical outcome include an increase in the seizure threshold during a course of ECT, early onset of slow-wave activity interictally, distinct postictal suppression, and decreases in CBF/CMR and increased slow-wave activity after a series of treatments.

An anticonvulsant mechanism for ECT would be unique when compared to the antidepressant medications (which are rarely associated with seizures) and anticonvulsant medications (e.g., valproic acid and carbamazepine), which have only moderate antidepressant efficacy (47). However, there is evidence that newer anticonvulsant medications, including lamotrigine, may be more effective in the depressed phase of bipolar illness (48). The mechanism by which the anticonvulsants exert their antidepressant effects is poorly understood and is hypothesized to occur through a number of neurotransmitters, including inhibiting the presynaptic release of excitatory amino acids (e.g., glutamate) and enhancing the effect of inhibitory neurotransmitters and neuropeptides.

New research should focus on testing the anticonvulsant hypothesis and determining the neurotransmitters essential for the antidepressant properties of ECT. Examining the relationship of the anticonvulsant effects of ECT to the efficacy of the treatments by blocking or augmenting the anticonvulsant properties of ECT can test this hypothesis. For example, CSF neuropeptides associated with the anticonvulsant effects of electroconvulsive shock (ECS) have been isolated in laboratory animals (49). These neuropeptides could be given in conjunction with ECS to determine if the coadministration of these neuropeptides would block the therapeutic efficacy of ECS (50). Although ethical considerations may limit this type of research in humans, studies could be designed to investigate the relationship of the acute rise in endogenous anticonvulsant substances (including GABAergic and endogenous opioids) in the CSF of ECT responders versus nonresponders.

Clinical research should continue to concentrate on developing algorithms to determine the relationship of ECT treatment variables (e.g., seizure threshold) to ECT response or the loss of seizure efficacy during a course algorithms can test the anticonvulsant clinicians in administering effective treatments. variables (e.g., diminished CBF in the anterior may also be investigated to predict relapse.

OPTIMIZATION OF ACUTE EC

ECT is widely cited to have an antidepressant greater than 80% (51). More recently, tients achieving remission after an acute conservatively estimated at between 50%

reason for this apparent decline in efficacy is the increasing resistance to treatment among the patients referred for ECT in the last 15 years. Prior to the development of the serotonin reuptake inhibitors (SSRIs), the most common reason for referral for ECT was intolerance of available antidepressant medications, chiefly tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Intolerance to antidepressant pharmacotherapy was particularly important in the elderly who constitute the majority of patients referred for ECT. The elderly are also the patient group most susceptible to the side effects of TCAs and MAOIs. The advent of SSRIs, serotonin, and norepinephrine reuptake inhibitors (SNRIs), 5-HT_{2A} blockers, and other novel antidepressants in the last 15 years has radically changed the medication histories of the patients referred for ECT. These newer agents are remarkably well tolerated, and a majority of patients receiving ECT have had at least one complete trial of an antidepressant without improvement. These patients who are refractory to antidepressant medications are also more refractory to ECT. The ECT response rate in antidepressant medication-refractory patients is probably no better that 50%, whereas the response rate in medication naive patients is closer to the historically quoted 80% to 90% (52). The problem of decreased acute response to ECT in this growing population of medication-refractory patients has led to new interest in the technical factors that control the response to acute ECT. Among these factors are electrode placement, stimulus dose, and possibly concurrent medications.

Despite 60 years of clinical application, the ECT field has only recently come to appreciate the relative contributions of stimulus electrode placement and stimulus intensity to the therapeutic and adverse effects of ECT. As previously discussed, clinical wisdom prior to 1987 taught that as long as the EEG seizure during ECT was ≥25 seconds, then the treatment was maximally effective. This belief was refuted by Sackeim and colleagues' report that when ECT is delivered with right unilateral (RUL) electrode placement and a stimulus just barely above the patient's seizure threshold, then the antidepressant response rate was approximately 20%, despite seizure durations ≥25 seconds (18). Further work by this group clarified that the efficacy of right unilateral (RUL) ECT was exquisitely sensitive to the magnitude

TABLE 76.1. ANTIDEPRESSANT RESPONSE RATE BY ELECTRODE PLACEMENT AND STIMULUS DOSE

	Barely Suprathreshold	2.5-Times Threshold
RUL	17%	43%
BL	65%	63%

This work demonstrated that, within the stimulus dose studied, the efficacy for RUL was sensitive to dose, whereas the efficacy of bilateral (BL) ECT was insensitive to dose. Also, RUL ECT appeared inferior to BL ECT at any dose. Subsequent work confirmed that the efficacy of RUL ECT is dose dependent and that RUL ECT administered at six times the initial seizure threshold is as effective as BL ECT with fewer cognitive side effects than BL ECT (54). McCall and colleagues found a dose–response relationship in patients receiving RUL ECT that extended to 12 times the seizure threshold and, as predicted, cognitive side effects were increased as the stimulus dose increased relative to the seizure threshold (55). The response rate for RUL ECT at eight to 12 times threshold was about 70%, approximately the rates typically quoted for BL ECT.

Based on this new information, it seems reasonable to recommend that ECT be delivered with either BL electrode placement at a stimulus dose just above threshold, or with RUL placement at a stimulus dose markedly above threshold. Less intensive strategies (i.e., RUL at 2.5 times threshold) should probably be avoided for routine use. Although it is clear that the lower intensity RUL strategies have less acute amnesia side effects, this advantage is probably offset by poorer efficacy and consequently poorer quality of life (QOL), because depression severity is among the best predictors of QOL in severely depressed patients (56,57).

There remain three important considerations in the routine use of titrated unilateral ECT. First, many psychiatrists are hesitant to determine the seizure threshold because they feel that the procedure is medically dangerous. There is a potential risk to stimulating the vagus nerve with subconvulsive stimuli without adequate compensatory adrenergic discharge from a seizure and the possibility of prolonged asystole. However, a controlled operative setting with cardiac monitoring decreases the possibility of brief periods of bradycardia causing any significant risk for a majority of patients.

Second, some would argue that the initial treatment in a series of titrated seizures is a ''wasted'' seizure, adding to costs and potential cognitive side effects without any significant therapeutic benefit to the patient. The unilateral seizure at or near the seizure threshold used during the initial treatment setting to determine seizure threshold probably adds little benefit. However, the potential advantages of determining the seizure threshold and adjusting the subsequent seizures to the threshold has advantages in maximizing benefit and decreasing the potential for future ineffective treatments (if the energy delivered is too low) and cognitive side effects (if the energy is too high).

Finally, fixed high dose RUL ECT is an effective treatment for depression (55,58) and this data could obviate the need to determine seizure threshold. Because the majority of patients treated with ECT are older and older patients have very high seizure thresholds, dose titrations at eight to ten times threshold are generally at or above the 400-mC range used by McCall and associates. In fact, in some older patients even a suprathreshold stimulus set at 400 mC may be too low to achieve antidepressant efficacy.

Continued support for the efficacy of suprathreshold RUL ECT has raised some concern about the fact that ECT machines in the United States are restricted in the amount of energy they can deliver per treatment (504 to 576 mC maximal output). Abrams argues that the FDA mandated maximum output for ECT machines used in this country often does not allow for the administration of effective suprathreshold treatments and has called for a reexamination of these guidelines (59).

The question of whether or not to continue, discontinue, or initiate antidepressant medication during a course of acute ECT is also pertinent to the issue of improving the response rate among patients with a history of antidepressant medication resistance. Clinically, physicians are divided in their practice regarding antidepressant medications during ECT, and there are no good data to support any position. One of the developments in ECT practice in the 1990s was the occurrence of SSRI-resistance in ECT patients, and the virtual lack of TCA trials in these same patients before coming to ECT. This is especially important because there are some data to suggest that TCAs (i.e., nortriptyline) may be more effective than SSRIs in the severely depressed or hospitalized elderly (60). Possibly, the addition of an antidepressant (i.e., nortriptyline) may improve the antidepressant response to ECT in patients with a history of novel-antidepressant resistance.

PREVENTION OF RELAPSE AFTER ECT

In general, patients who receive an acute course of ECT are either subsequently resistant or intolerant of antidepressant medications. Patients diagnosed with psychotic depression are particularly susceptible to relapse after an acute course of ECT. Two studies found a relapse rare of approximately 70% in 1 year for a total of 53 patients with a diagnosis of psychotic depression (61,62). These studies were retrospective and could not examine compliance rates or the adequacy of either the initial (pre-ECT) or continuation medication trial.

In a prospective study, Sackeim and co-workers (63) followed 58 patients for 1 year after ECT. They examined a number of clinical variables including a retrospective review of the adequacy of the pre-ECT medication trial. The most important factor in determining relapse on maintenance medication after an acute course of ECT was the adequacy of the pre-ECT medication trial. Patients (with and without psychotic features) who were rated as receiving a therapeutic medication trial(s) prior to their acute course of ECT relapsed at a rate that was twice the rate found in patients who did not receive an adequate pre-ECT medication trial (64% versus 32%). The maintenance medication was not standardized but the results indicated that the adequacy of

the post-ECT medication trial was only marginally related to the relapse rate and then primarily in patients who did not have an adequate pre-ECT medication trial. The patients who were not determined to be medication resistant prior to ECT had a lower relapse rate when they received an adequate maintenance medication trial. Sackeim and associates argue that many of these patients may have responded to antidepressant medication prior to ECT if they had received an adequate trial. The overall relapse rate remained very high (approximately 50%) and most of the patients who relapsed did so in the first 4 months of this 1-year follow-up study. This finding indicates that the efficacy of ECT may be relatively transient. Given the increasing medication resistance found in most ECT patient populations, the clinical challenge is increasingly to determine the most effective maintenance treatments and increasingly physicians are utilizing maintenance ECT.

The American Psychiatric Association's (64) clinical guidelines for continuation ECT (C-ECT) include patients who: (a) have recurrent depressive episodes responsive to ECT; (b) demonstrate resistance/intolerance or noncompliance with antidepressant medications; (c) can comply with the overall treatment plan including behavioral restrictions (i.e., limiting driving) and providing informed consent. Continuation and maintenance ECT strategies are being used increasingly in the treatment of patients with major depression who are felt to have a high-risk for relapse (65). The guidelines for the use of C-ECT have been actively discussed but there are little prospective data on which to base recommendations on frequency of treatments and how long they should be continued or the nature of the potential cognitive side effects. A majority of the studies are case reports and many predate antidepressant medication (66). More recent reports in patients with depression (66–74), mania (75,76), and schizophrenia (77) describe a marked decrease in the number of hospitalizations, hospital days, depressive symptoms, increased functional status, and stable cognitive functioning for the period of continuation ECT.

Theoretically, there are several potential theories that may explain the efficacy of maintenance ECT over maintenance medication. First, maintenance ECT may be effective because the ECT treatments are gradually tapered rather than abruptly discontinued. During this taper, most clinical protocols decrease the interval between the maintenance treatments if the patient shows signs of relapse. A tapering schedule over this period may be critical because most patients relapse within 3 months of stopping the treatments. In 1954, prior to the use of antidepressant medications as maintenance treatment, Bourne and Long (78) coined the term ''convulsion dependence'' to describe psychotic patients who relapsed unless they were tapered from their ECT treatments.

The second potential therapeutic benefit may be the fact that ECT has a different mechanism of action than the antidepressant medications. Increasingly patients are presenting for ECT after multiple failed medication trials and there may be little benefit from yet another trial of an SSRI. In fact the one medication regimen that has been shown to be effective in maintenance therapy is a combination of lithium and nortriptyline (discussed in the following). The benefit of this combination therapy may be owing to the fact that few patients had been given lithium augmentation prior to their acute course of ECT.

Finally, maintenance ECT is similar to depot haloperidol in the treatment of schizophrenia and may provide prophylactic benefit from improved compliance in patients who might otherwise not comply with their maintenance medication. Most studies of maintenance ECT only report patients who complied with the treatment regimen. The experience at the Emory University Outpatient ECT program is similar to the data reported by Clarke and colleagues (67). When patients do not complete the scheduled 6-month maintenance ECT program, we found that more than half of the patients relapsed.

In 1991, Monroe (79) discussed the need for increased research into continuation and maintenance ECT. There is clear evidence that these treatments are being used increasingly in clinical practice, yet there is a lack of guidelines to establish the optimal treatment frequency, the type of patient who would benefit from maintenance ECT versus medication, or an understanding of the potential long-term side effects. The NIMH is presently funding three studies that will add significantly to our understanding of maintenance ECT. Two multicenter trials are examining the efficacy of different maintenance strategies after an acute response to ECT. Sackeim and colleagues are comparing maintenance placebo, nortriptyline versus nortriptyline and lithium after an acute response to ECT. Preliminary results from this line of investigation show that nortriptyline provides only marginally greater protection against relapse during the post-ECT period than does placebo, with relapse rates of approximately 70% during the first year. The addition of lithium to nortriptyline resulted in a further significant reduction in relapse to approximately 40% during that interval. Charles Kellner is the principal investigator on a trial comparing maintenance medication and maintenance ECT. The authors are currently examining the cost effectiveness of maintenance medication compared to maintenance ECT in elderly patients with recurrent major depression. These last two trials do not yet have preliminary data available, but together they will provide prospective data on the relative effectiveness and costs of different maintenance strategies used after an acute course of ECT.

COGNITIVE PROBLEMS ASSOCIATED WITH ECT

The one significant remaining ECT-related morbidity is the potential for cognitive side effects. Although there is little

scientific literature supporting permanent brain damage after ECT (80–82), memory disturbances continue to be a serious side effect after an acute course of ECT. Clearly, there have been significant advances over the last 50 years. Delirium was a clinical goal in some early protocols (so called ''regressive ECT'') that equated the development of delirium with therapeutic response. This technique provided no advantage over more conservative forms of ECT and has been abandoned. Replacement of sine wave stimuli with machines that provide a brief pulse stimuli, and the elucidation of the appropriate stimulus parameters that increase the efficacy of safer treatments (suprathreshold right unilateral versus threshold bilateral ECT) have both been important contributions to the decrease in the ECT associated memory loss over the past few decades. The potential development of ultrabrief pulse ECT and research into pharmacologic treatments such as physostigmine (83), naloxone (84), and thyrotropin releasing hormone (TRH) (85) all hold promise for further decreasing ECT-associated memory loss. Double-blind placebo controlled trials using with intranasal vasopressin (86,87), ACTH (88,89), dexamethasone (90), and nimodipine (91) have not shown the active drug to be more effective than placebo.

The frequency of ECT administration is yet another way of controlling ECT-related memory loss. Twice-weekly ECT is associated with an antidepressant response as good as thrice-weekly ECT, but with less adverse memory effects (and a slower rate of antidepressant response) (92,93). Recently, the issue of optimal electrode placement has been reopened with isolated enthusiasm for bifrontal stimulating electrode placement or an asymmetric placement (a right fronto-temporal electrode referenced to a left frontal electrode). Preliminary reports suggest that these novel electrode placements are associated with an antidepressant efficacy comparable to standard bilateral placement, with fewer cognitive side effects, but there are insufficient data thus far to recommend them as a replacement for standard BL or RUL placements (94,95).

NONCONVULSIVE STIMULI IN THE TREATMENT OF DEPRESSION

Repetitive transcranial magnetic stimulation (rTMS) and vagal nerve stimulation (VNS) are two new treatments for depression that, unlike ECT, use subconvulsive stimuli to treat depressive symptoms. Compared to ECT, these treatments have the potential for targeting specific brain regions and stimulating areas that are thought to be involved in depression while sparing areas such as the hippocampus and thus reducing potential cognitive side effects.

rTMS was first used in 1985 as a noninvasive method of stimulating brain neurons (96). rTMS produces pulses of electromagnetic currents conducted by the brain that have different effects on neuronal firing, depending on the frequency in which it is administered. In general, rTMS acts by inducing action potentials in neuronal elements, but at high frequency (>5 Hz) the net effect of a stimulus train is excitatory (97); similarities have been drawn between the effects of fast rTMS and long-term potentiation (LTP) produced by high frequency electrical stimulation (98). At low frequencies (1 Hz) the net effect of a stimulus train is usually inhibitory (99,100). In animal studies, rTMS has been demonstrated to cause down-regulation of *B*-adrenoreceptors (101) and, as has been shown in ECS, rTMS up-regulates astroglial gene expression in the CNS (102). Preliminary data support rTMS in the treatment of a number of psychiatric disorders including depression, schizophrenia, obsessive-compulsive disorder, and posttraumatic stress disorder (103).

This chapter focuses on the use of rTMS in depression and compares rTMS to ECT. From the outset it should be stressed that the efficacy of rTMS in the treatment of depression is modest and much of the research has been focused narrowly on a relatively restricted group of treatment parameters. The majority of rTMS studies use set parameters: high frequency or fast stimulations (≥10 Hz) over the left dorsolateral prefrontal cortex (DLPFC) at or around the motor threshold (e.g., 80% to 110% MT). These parameters are based on PET data (104) and ECT data (34) demonstrating hypofunctioning of the left prefrontal cortex in depression as well as two pivotal early studies demonstrating an antidepressant effect of fast left DLPFC rTMS (105,106). Although one recent parallel group sham controlled study found no treatment effect (107), most open (105,108,109) and double-blind studies (106,110,111) have confirmed a relatively modest antidepressant response for fast left DLPFC. When directly compared to ECT, 4 weeks of rTMS appears to be as effective as ECT in nonpsychotic, but not psychotic, depression (112). In this study there may have been a bias for the ECT group because over half of the patients in the ECT group and none of the patients in the rTMS group remained on antipsychotics and/or antidepressants. Two weeks of either RUL ECT or one ECT treatment followed by four rTMs sessions were also shown to be equivalent in the treatment of 22 depressed outpatients (113).

To date there have been no seizures reported using fast rTMS within the established safety guidelines (114) and no cognitive side effects in patient populations (109). The most common side effects are pain at the treatment site and headaches usually relieved by acetaminophen.

Realizing the potential benefits of rTMS, however, is dependent on expanding the treatment parameters including research on the variable effects of slow versus fast stimulation. Although early studies using slow TMS demonstrated poor outcomes (115–117), and are often cited as rationale for using fast rTMS, the stimulation site was the vertex in these three studies. More recent trials of *slow* rTMS over the *right* DLPFC have shown benefit. Klein and col-

leagues (118) randomized 71 depressed patients to 2 weeks of slow, active or sham treatment over the right prefrontal cortex and 41% of active-treatment subjects had a 50% or greater drop in Hamilton depression scores compared to only 17% of sham-treatment subjects. Similarly, Tormos and associates (119) showed a significant antidepressant response to *fast left* DLPFC stimulation and *slow right* DLPFC stimulation, but not fast right DLPFC stimulation or sham. Slow left stimulation was not administered. Trials of slow TMS over the left DLPFC have also shown promise. Padberg and colleagues (120) randomized 18 nonpsychotic patients to treatment over the left DLPFC using fast, slow, or sham treatments. They showed a statistically significant (but clinically insignificant) response to fast and slow stimulation compared to placebo. In two small studies, George and Nahas demonstrated that lower frequency stimulation (5 Hz) might be more effective at 20 Hz TMS. Patients who were administered 5 Hz rTMS over the left DLPFC had a higher response rate (50% decline in the HDRS) than those administered 5 Hz rTMS over the right DLPFC (6/10 versus 3/10 responders, respectively) and placebo (0/10 responders) (121,122). Slow TMS (<1 Hz) has never been associated with seizures or any other adverse consequences in neurologically normal individuals; therefore, it is potentially safer than fast stimulations (114).

There are two basic clinical problems associated with rTMS. First, although half the patients respond to the treatments (defined as a 50% improvement in the HDRS), a much smaller percentage obtains remission (HDRS $\leq$10). Second, and perhaps of more concern, is the fact that a majority of patients (up to 100% in some studies) relapse in the month after treatment. Both the antidepressant response (M. Szuba, personal communication) and relapse rate (109) are improved by increasing the number of weeks of treatments but, as with ECT, the most severely ill patients may respond partially and relapse quickly. Combination treatment strategies (slow right and fast left) and maintenance rTMS strategies are being employed to improve response and keep patients in remission.

Beyond simply stimulation of the right or left cortex, techniques are being developed to assist in focusing the magnetic impulse on specific cortical structures. The development of new more focal coils and neuroimaging techniques to guide the placement of the rTMS stimulation (123) hold promise on targeting specific brain regions.

Using these techniques, rTMS can help in elucidating the neuronal pathways involved in depression. Initial studies using functional neuroimaging and rTMS have shown that many of the effects of rTMS occur at brain regions distant from the site of stimulation including the caudate, orbitofrontal cortex bilaterally, and cerebellum (124). These studies have also called into question the hypothesis that fast rTMS increases neuronal excitability (125,126) and slow rTMS inhibits neuronal firing (127,128).

However, it may be possible to determine if rTMS is effective in given individuals by evaluating the functional neuroimaging before and after rTMS stimulation. Speer and associates have shown that patients with hypometabolism on baseline PET scans utilizing [^{18}F]-Fluorodeoxyglucose in the left prefrontal cortex responded preferentially to 2 weeks of fast rTMS (20 Hz) as compared with patients with hypermetabolism who responded at a higher rate to slow (1Hz) rTMS (129). Individual characteristics may be a key factor in determining treatment response.

Vagal nerve stimulation (VNS) is another new and promising treatment for major depression. VNS has been successfully used to treat patients with intractable seizures since 1994 and was noticed to have positive effects on mood that were not simply secondary to the decrease in seizure frequency (130). The VN has both parasympathetic efferent fibers to the heart and GI tract and sensory afferent fibers (approximately 20% and 80% of the fibers, respectively). The afferent fibers connect the nucleus tractus solitarius to the orbital and lateral frontal cortices, and parabrachial nucleus (PN) and locus ceruleus (LC). The fibers passing through the PN/LC (which are adjacent to one another) connect to the hypothalamus and thalamus and, central to the antidepressant properties of VNS, the bed nucleus of the stria terminalis and amygdala. George and associates (131) detail the rationale for the use of VNS in treatment-resistant depression, including these VN afferent connections to the limbic system as well as PET data showing activation of limbic structures (132) and increases in CNS monoamines with VNS (133–135).

The first open trial of VNS by Rush and colleagues included 30 nonpsychotic patients with treatment-resistant unipolar or bipolar depression (136). As in the treatment of epilepsy, the stimulator was attached to the left vagal nerve, which can be accessed peripherally in a procedure similar to implanting a cardiac pacemaker, and compared to the right VN has fewer afferent fibers to the autonomic system controlling cardiac and gastric physiologic functions (137). Twelve of 30 patients (40%) met criteria for treatment response ($\geq$50% decrease in HDRS) and 5 patients had a final HDRS $\leq$10. None of the patients discontinued treatment because of adverse events. The most common adverse events (which were similar to the AE's in the epilepsy trials) were hoarseness (60%) and throat pain (27%). Ten percent of the patients had abnormal wound healing.

VNS may be an effective treatment in resistant depression. The two variables that predicted clinical response to VNS included previous response to ECT (only one of 19 patients who had received ECT had a sustained response to VNS) and decreased stimulator output. Encouragingly, of the ten responders with available follow-up data over 4 to 9 months, all have demonstrated continued response.

VNS has been shown to be safe in the treatment of over 6,000 patients with epilepsy and may also provide relief to the 10% to 20% of depressed patients who fail or have an inadequate response to available somatic treatments. The

adverse side effect profile and costs could be dramatically reduced if a method of stimulating the VN could be achieved without surgery. The cost of the device and electrodes is $9,200, and the additional cost of the surgical procedure raises the total costs to approximately $12,000 to $25,000 (131). These costs are comparable to what might be expected for acute and 1-year maintenance treatment for ECT; however, insurance coverage may depend on the results of the pending placebo-controlled study and FDA approval for the treatment of depression. VNS is approved for the treatment of epilepsy.

Some researchers have questioned the benefit of electrical stimulation, which does not produce a seizure (138), arguing that subconvulsive seizures in ECT have not been shown to provide any clinical benefit (139). However, the anticonvulsant hypothesis assumes that the beneficial effects from ECT derive not from the convulsion, but the anticonvulsant effects of the seizure. VNS has documented anticonvulsant effects. Slow rTMS dampens neuronal excitability (100) and theoretically may be useful in treating epilepsy (140). There is also research underway at Columbia University using fast rTMS to precipitate a convulsion in animal models to determine the efficacy of TMS seizures in depression. Further investigations using animal models could potentially cause focal convulsions of specific brain regions (e.g., limbic structures) and spare brain sensitive structures that cause side effects but are not integral to the therapeutic effect (e.g., hippocampus). Together rTMS and VNS have the potential of providing valuable insight into the pathophysiology of depression and may potentially add to the treatment of resistant depression.

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REFERENCES

1. Endler NS. The origins of electroconvulsive therapy (ECT). *Convulsiv Ther* 1988;4:5–23.
2. Freeman W, Watts JW. *Psychosurgery in the treatment of mental disorders and intractable pain* Springfield, IL: Charles C Thomas, 1952.
3. Sakel M. *Pharmacologic treatment of schizophrenia* New York: Nervous and Mental Disease Publishing, 1938.
4. Impastato D. Prevention of fatalities in electroshock therapy. *Dis Nerv Syst* 1957;18(Suppl):34–75.
5. Bennett AE. Curare: a preventive of traumatic complications in convulsive shock therapy. *Am J Psychiatry* 1941;97:1040–1060.
6. Holmberg G, Thesleff S. Succinyl-choline-iodide as a muscular relaxant in electroshock therapy. *Am J Psychiatry* 1952;108: 842–846.
7. Blachy P, Gowing D. Multiple monitored electroconvulsive treatment. *Compr Psychiatry* 1966;7:100–109.
8. Figiel GS, McDonald WM, McCall WV, et al. Electroconvulsive therapy. In: Schatzberg AF, Nemeroff CB, eds. *Textbook of psychopharmacology.* Washington, DC: American Psychiatric Press, 1995:523–543.
9. Abrams R. The mortality rate with ECT. *Convuls Ther* 1997; 13(3):125–127.
10. Salzman C. ECT, research, and professional ambivalence [editorial] [see comments]. *Am J Psychiatry* 1998;155(1):1–2.
11. Rudorfer MV, Goodwin FK. Introduction. In: Coffey CE, ed. *The clinical science of electroconvulsive therapy,* vol. 38. Washington, DC: American Psychiatric Press, 1993:xvii–xxi.
12. Ottosson J-O. Experimental studies of the mode of action of electroconvulsive therapy. *Acta Psychiatr Neurol Scand* 1960;35: 1–141.
13. Fink M, Johnson L. Monitoring the duration of electroconvulsive therapy seizures: 'cuff' and EEG methods compared. *Arch Gen Psychiatry* 1982;39(10):1189–1191.
14. Maletzky BM. Seizure duration and clinical effect in electroconvulsive therapy. *Comp Psychiatry* 1978;19(6):541–550.
15. Abrams R, Taylor MA. Diencephalic stimulation and the effects of ECT in endogenous depression. *Br J Psychiatry* 1976;129: 482–485.
16. Fink M, Ottosson JO. A theory of convulsive therapy in endogenous depression: significance of hypothalamic functions. *Psychiatry Res* 1980;2(1):49–61.
17. Mathe AA. Neuropeptides and electroconvulsive treatment. *J Ect* 1999;15(1):60–75.
18. Sackeim HA, Decina P, Kanzler M, et al. Effects of electrode placement on the efficacy of titrated, low-dose ECT. *Am J Psychiatry* 1987;144(11):1449–1455.
19. Devanand DP, Lisanby S, Lo ES, et al. Effects of electroconvulsive therapy on plasma vasopressin and oxytocin. *Biol Psychiatry* 1998;44(7):610–616.
20. Lisanby SH, Devanand DP, Prudic J, et al. Prolactin response to electroconvulsive therapy: effects of electrode placement and stimulus dosage [see comments]. *Biol Psychiatry* 1998;43(2): 146–155.
21. Krystal AD, Weiner RD, McCall WV, et al. The effects of ECT stimulus dose and electrode placement on the ictal electroencephalogram: an intraindividual crossover study. *Biol Psychiatry* 1993;34(11):759–767.
22. Nobler MS, Sackeim HA, Solomou M, et al. EEG manifestations during ECT: effects of electrode placement and stimulus intensity. *Biol Psychiatry* 1993;34(5):321–330.
23. Weiner RD, Krystal AD. EEG monitoring of ECT seizures. In: Coffey CE, ed. *The clinical science of electroconvulsive therapy,* vol. 38. Washington, DC: American Psychiatric Press, 1993: 93–109.
24. Krystal AD. The clinical utility of ictal EEG seizure adequacy models. *Psychiatric Ann* 1998;28(1):30–35.
25. Krystal AD, Zaidman C, Greenside HS, et al. The largest Lyapunov exponent of the EEG during ECT seizures as a measure of ECT seizure adequacy. *Electroencephalogr Clin Neurophysiol* 1997;103(6):599–606.
26. Krystal AD, Coffey CE, Weiner RD, et al. Changes in seizure threshold over the course of electroconvulsive therapy affect therapeutic response and are detected by ictal EEG ratings. *J Neuropsychiatr Clin Neurosci* 1998;10(2):178–186.
27. Krystal AD, Weiner RD, Coffey CE. The ictal EEG as a marker of adequate stimulus intensity with unilateral ECT. *J Neuropsychiatr Clin Neurosci* 1995;7(3):295–303.
28. McCall WV, Farah A, Reboussin D. Can we teach psychiatric residents to rate seizure regularity? *Convuls Ther* 1995;4: 248–252.

29. Krystal AD, Weiner RD. ECT seizure therapeutic adequacy. *Convuls Ther* 1994;10(2):153–164.
30. Ingvar M. Cerebral blood flow and metabolic rate during seizures. Relationship to epileptic brain damage. *Ann NY Acad Sci* 1986;462:194–206.
31. Silfverskiold P, Rosen I, Risberg J. Effects of electroconvulsive therapy on EEG and cerebral blood flow in depression. *Eur Arch Psychiatry Neurol Sci* 1987;236(4):202–208.
32. Saito S, Yoshikawa D, Nishihara F, et al. The cerebral hemodynamic response to electrically induced seizures in man. *Brain Res* 1995;673(1):93–100.
33. Ackermann RF, Engel J Jr, Baxter L. Positron emission tomography and autoradiographic studies of glucose utilization following electroconvulsive seizures in humans and rats. *Ann NY Acad Sci* 1986;462:263–239.
34. Nobler MS, Sackeim HA, Prohovnik I, et al. Regional cerebral blood flow in mood disorders, III. Treatment and clinical response. *Arch Gen Psychiatry* 1994;51(11):884–897.
35. Nobler MS, Sackeim HA. Mechanisms of action of electroconvulsive therapy. *Psychiatr Ann* 1998;28(1):23–29.
36. Fink M, Kahn RL. Quantitative studies of slow wave activity following electroshock. *Electroenceph Clin Neurophysiol* 1956;8: 158.
37. Fink M, Kahn RL. Relationship of electroencephalographic delta activity to behavioral response in electroshock. *Arch Neurol Psychiatry* 1959;78:516–525.
38. Sackeim HA, Luber B, Katzman GP, et al. The effects of electroconvulsive therapy on quantitative electroencephalograms. Relationship to clinical outcome [see comments]. *Arch Gen Psychiatry* 1996;53(9):814–824.
39. Wilson WP, Schieve JP, Scheinberg P. Effect of series of electroshock treatments on cerebral blood flow and metabolism. *Arch Neurol Psychiatry* 1952;68:651–654.
40. Sackeim HA. The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. *J Ect* 1999;15(1):5–26.
41. Sackeim H, Decina P, Prohovnik I, et al. Seizure threshold in electroconvulsive therapy. Effects of sex, age, electrode placement, and number of treatments. *Arch Gen Psychiatry* 1987; 44(4):355–360.
42. Shapira B, Lidsky D, Gorfine M, et al. Electroconvulsive therapy and resistant depression: clinical implications of seizure threshold [see comments]. *J Clin Psychiatry* 1996;57(1):32–38.
43. Sackeim HA, Decina P, Prohovnik I, et al. Dosage, seizure threshold, and the antidepressant efficacy of electroconvulsive therapy. *Ann NY Acad Sci* 1986;462:398–410.
44. Krystal AD, Weiner RD, Coffey CE, et al. Effect of ECT treatment number on the ictal EEG. *Psychiatry Res* 1996;62(2): 179–189.
45. McCall WV, Robinette GD, Hardesty D. Relationship of seizure morphology to the convulsive threshold. *Convuls Ther* 1996;12(3):147–151.
46. Suppes T, Webb A, Carmody T, et al. Is postictal electrical silence a predictor of response to electroconvulsive therapy? *J Affect Disoord* 1996;41(1):55–58.
47. McElroy PEKaSL. Antiepileptic drugs. In: Nemeroff AFSaCB, ed. *Textbook of psychopharmacology,* second ed. Washington, DC American Psychological Press, 1998:431–454.
48. Bowden CL, Calabrese JR, McElroy SL, et al. The efficacy of lamotrigine in rapid cycling and non-rapid cycling patients with bipolar disorder [see comments]. *Biol Psychiatry* 1999;45(8): 953–958.
49. Tortella FC, Long JB. Endogenous anticonvulsant substance in rat cerebrospinal fluid after a generalized seizure. *Science* 1985; 228(4703):1106–1108.
50. Post RM. ECT: the anticonvulsant connection [see comments]. *Neuropsychopharmacology* 1990;3(2):89–92; discussion 97–99.
51. Abrams R. ECT technique: electrode placement, stimulus type, and treatment frequency. In: Coffey CE, ed. *The clinical science of electroconvulsive therapy,* vol. 38. Washington, DC: American Psychiatric Press, 1993:17–28.
52. Prudic J, Haskett RF, Mulsant B, et al. Resistance to antidepressant medications and short-term clinical response to ECT [see comments]. *Am J Psychiatry* 1996;153(8):985–992.
53. Sackeim HA, Prudic J, Devanand DP, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy [see comments]. *N Engl J Med* 1993;328(12):839–846.
54. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities [see comments]. *Arch Gen Psychiatry* 2000;57(5):425–434.
55. McCall WV, Reboussin DM, Weiner RD, et al. Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects [see comments]. *Arch Gen Psychiatry* 2000;57(5):438–444.
56. McCall WV, Cohen W, Reboussin B, et al. Effect of mood and age on quality of life in depressed inpatients. *J Affect Disord* 1999;55:107–114.
57. McCall WV, Reboussin BA, Cohen W, et al. Electroconvulsive therapy is associated with superior symptomatic and functional change in depressed patients after psychiatric hospitalization. *J Affect Disord* 2001;63:17–25.
58. Abrams R, Swartz CM, Vedak C. Antidepressant effects of high-dose right unilateral electroconvulsive therapy. *Arch Gen Psychiatry* 1991;48(8):746–748.
59. Abrams R. Electroconvulsive therapy requires higher dosage levels: Food and Drug Administration action is required [comment]. *Arch Gen Psychiatry* 2000;57(5):445–446.
60. Roose SP, Glassman AH, Attia E, et al. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *Am J Psychiatry* 1994;151(12): 1735–1739.
61. Spiker DG, Stein J, Rich CL. Delusional depression and electroconvulsive therapy: one year later. *Convuls Ther* 1985;1: 167–172.
62. Aronson TA, Shukla S, Hoff A. Continuation therapy after ECT for delusional depression: a naturalistic study of prophylactic treatments and relapse. *Convuls Ther* 1987;3(4):251–259.
63. Sackeim HA, Prudic J, Devanand DP, et al. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol* 1990;10(2):96–104.
64. Association AP. *American Psychiatric Association Task Force on Electroconvulsive Therapy. The practice of electroconvulsive therapy: recommendations for treatment, training and privileging.* Washington, DC: American Psychiatric Press, 1978.
65. Levy SD, Albrecht E. Electroconvulsive therapy: a survey of use in the private psychiatric hospital. *J Clin Psychiatry* 1985;46: 125–127.
66. Thienhaus OJ, Margletta S, Bennet JA. A study of the clinical efficacy of maintenance ECT. *J Clin Psychiatry* 1990;51: 141–144.
67. Clarke TB, Coffey CE, Hoffman GW, et al. Continuation therapy for depression using outpatient electroconvulsive therapy. *Convuls Ther* 1989;5(4):330–337.
68. Decina P, Guthrie EB, Sackeim HA, et al. Continuation ECT in the management of relapses of major affective episodes. *Acta Psychiatr Scand* 1987;75(6):559–562.
69. Thornton JE, Mulsant BH, Dealy R, et al. A retrospective study of maintenance electroconvulsive therapy in a university-based psychiatric practice. *Convuls Ther* 1990;2:121–129.
70. Matzen TA, Martin RL, Watt TJ, et al. The use of maintenance

electroconvulsive therapy for relapsing depression. *Jefferson J Psychiatry* 1988;6:52–58.
71. Grunhaus L, Pande A, Haskett R. Full and abbreviated courses of electroconvulsive therapy. *Convuls Ther* 1990;6:130–138.
72. Jaffe R, Dubin W, Shoyer B, et al. Outpatient electroconvulsive therapy: efficacy and safety. *Convuls Ther* 1990;6:231–238.
73. Loo H, Galinowski A, De Carvalho W, et al. Use of maintenance ECT for elderly depressed patients [letter; comment]. *Am J Psychiatry* 1991;148(6):810.
74. Dubin WR, Jaffe R, Roemer R, et al. The efficacy and safety of maintenance ECT in geriatric patients. *J Am Ger Soc* 1992; 40(7):706–709.
75. Husain MM, Meyer DE, Muttakin MH, et al. Maintenance ECT for treatment of recurrent mania [letter]. *Am J Psychiatry* 1993;150(6):985.
76. Bonds C, Frye MA, Coudreaut MF, et al. Cost reduction and maintenance ECT in refractory bipolar disorder. *J Ect* 1998; 14:36–41.
77. Chanpattana W. Continuation electroconvulsive therapy in schizophrenia: a pilot study. *J Med Assoc Thailand* 1997;80(5): 311–318.
78. Bourne H, Long MB. Convulsion dependence. *Lancet* 1954;2: 1193–1196.
79. Monroe RRJ. Mantenance electroconvulsive therapy. *Psychiatr Clin NA* 1991;14:947–960.
80. Weiner RD. Does electroconvulsive therapy cause brain damage? *Behav Brain Sci* 1984;7:1–53.
81. Devanand DP, Dwork AJ, Hutchinson ER, et al. Does ECT alter brain structure? [see comments]. *Am J Psychiatry* 1994; 151(7):957–970.
82. Coffey CE, Weiner RD, Djang WT, et al. Brain anatomic effects of electroconvulsive therapy. A prospective magnetic resonance imaging study. *Arch Gen Psychiatry* 1991;48(11):1013–1121.
83. Levin Y, Elizur A, Korczyn AD. Physostigmine improves ECT-induced memory disturbances. *Neurology* 1987;37(5):871–875.
84. Prudic J, Fitzsimons L, Nobler MS, et al. Naloxone in the prevention of the adverse cognitive effects of ECT: a within-subject, placebo controlled study. *Neuropsychopharmacology* 1999;21(2):285–293.
85. Stern RA, Nevels CT, Shelhorse ME, et al. Antidepressant and memory effects of combined thyroid hormone treatment and electroconvulsive therapy: preliminary findings. *Biol Psychiatry* 1991;30(6):623–627.
86. Lerer B, Zabow T, Egnal N, et al. Effect of vasopressin on memory following electroconvulsive therapy. *Biol Psychiatry* 1983;18(7):821–824.
87. Mattes JA, Pettinati HM, Stephens S, et al. A placebo-controlled evaluation of vasopressin for ECT-induced memory impairment. *Biol Psychiatry* 1990;27(3):289–303.
88. d'Elia G, Frederiksen SO. ACTH4-10 and memory in ECT-treated and untreated patients. I. Effect on consolidation. *Acta Psychiatr Scand* 1980;62(5):418–428.
89. Small JG, Small IF, Milstein V, et al. Effects of ACTH 4-10 on ECT-induced memory dysfunctions. *Acta Psychiatr Scand* 1977;55(4):241–250.
90. Horne RL, Pettinati HM, Menken M, et al. Dexamethasone in electroconvulsive therapy: efficacy for depression and post-ECT amnesia. *Biol Psychiatry* 1984;19(1):13–27.
91. Cohen MR, Swartz CM. Absence of nimodipine premedication effect on memory after electroconvulsive therapy. *Neuropsychobiology* 1990;24(4):165–168.
92. McAllister DA, Perri MG, Jordan RC, et al. Effects of ECT given two vs. three times weekly. *Psychiatry Res* 1987;21(1): 63–69.
93. Shapira B, Tubi N, Lerer B. Balancing speed of response to ECT in major depression and adverse cognitive effects: role of treatment schedule. *J Ect* 2000;16(2):97–109.
94. Bailine SH, Rifkin A, Kayne E, et al. Comparison of bifrontal and bitemporal ECT for major depression. *Am J Psychiatry* 2000;157(1):121–123.
95. Swartz CM. Asymmetric bilateral right frontotemporal left frontal stimulus electrode placement for electroconvulsive therapy. *Neuropsychobiology* 1994;29(4):174–178.
96. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex [letter]. *Lancet* 1985; 1(8437):1106–1107.
97. Pascual-Leone A, Valls-Sole J, Wassermann EM, et al. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* 1994;117(Pt 4):847–858.
98. George MS, Wassermann EM, Post RM. Transcranial magnetic stimulation: a neuropsychiatric tool for the 21st century. *J Neuropsychiatr Clin Neurosci* 1996;8(4):373–382.
99. Wassermann EM, Grafman J, Berry C, et al. Use and safety of a new repetitive transcranial magnetic stimulator. *Electroencephalogr Clin Neurophysiol* 1996;101(5):412–417.
100. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997;48(5):1398–403.
101. Fleischmann A, Sternheim A, Etgen AM, et al. Transcranial magnetic stimulation downregulates beta-adrenoreceptors in rat cortex. *J Neural Transm (Budapest)* 1996;103(11):1361–1366.
102. Fujiki M, Steward O. High frequency transcranial magnetic stimulation mimics the effects of ECS in upregulating astroglial gene expression in the murine CNS. *Brain Res Mol Brain Res* 1997;44(2):301–308.
103. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry [comment]. *Arch Gen Psychiatry* 1999;56(4):300–311.
104. George MS, Ketter TA, Post RM. Prefrontal cortex dysfunction in clinical depression. *Depression* 1994;2:59–72.
105. George MS, Wassermann EM, Williams WA, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport* 1995;6(14):1853–1856.
106. Pascual-Leone A, Catala MD, Pascual-Leone Pascual A. Lateralized effect of rapid-rate transcranial magnetic stimulation of the prefrontal cortex on mood. *Neurology* 1996;46(2):499–502.
107. Loo C, Mitchell P, Sachdev P, et al. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J Psychiatry* 1999; 156(6):946–948.
108. Figiel GS, Epstein C, McDonald WM, et al. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *J Neuropsychiatr Clin Neurosci* 1998;10(1): 20–25.
109. Greene Y, McDonald W, Epstein C, et al. An open trial of repetitive transcranial magnetic stimulation in treatment-resistant depression. 1998 Annual Meeting New Research Program and Abstracts, Washington, DC: American Psychiatric Association, 1998, p. 90.
110. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial [see comments]. *Am J Psychiatry* 1997; 154(12):1752–1756.
111. Berman RM, Narasimhan M, Sanacora G, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biol Psychiatry* 2000;47(4): 332–337.
112. Grunhaus L, Dannon P, Schrieber S. Effects of transcranial magnetic stimulation on severe depression: similarities with ECT (abstract). *Biol Psychiatry* 1998;43(76s):254.

113. Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. *Depress Anxiety* 2000;12: 118–123.
114. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol* 1998;108(1):1–16.
115. Hoflich G, Kasper S, Hufnagel A, et al. Application of transcranial magnetic stimulation in the treatment of drug-resistant major depression. *Hum Psychopharmacol* 1993;8:361–365.
116. Grisaru N, Yarovslavsky U, Arbarbanel J, et al. Transcranial magnetic stimulation in depression and schizophrenia. *Eur Neuropsychopharmacol* 1994;4:287–288.
117. Kolbinger HM, Hoflich G, Hufnagel A, et al. Transcranial magnetic stimulation (TMS) in the treatment of major depression: a pilot study. *Hum Psychopharmacol* 1995;10:305–310.
118. Klein E, Kreinin I, Chistyakov A, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study [see comments]. *Arch Gen Psychiatry* 1999;56(4):315–20.
119. Tormos J, Pascual-Leone AP, Catala MD, et al. Antidepressant effects of repetitive transcranial magnetic stimulation to dorsolateral prefrontal cortex: (1) Hemispheric asymmetry. *Arch Gen Psychiatry* in press.
120. Padberg F, Zwanzger P, Thoma H, et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res* 1999;88(3):163–171.
121. George MS, Speer AM, Molloy M, et al. Low-frequency daily left prefrontal rTMS improves mood in bipolar depression: a placebo-controlled case report. *Hum Psychopharmacol* 1998;13: 271–275.
122. Nahas Z, Speer AM, Molloy M, et al. Preliminary results concerning the roles of frequency and intensity in the antidepressant effect of daily left prefrontal rTMS [abstract]. *Biol Psychiatry* 1998;43:94.
123. Bohning DE, Percheny AP, Epstein CM, et al. Mapping transcranial magnetic stimulation (TMS) fields in vivo with MRI. *Neuroreport* 1997;8:2535–2538.
124. Kimbrell TA, et al. Changes in cerebral metabolism during transcranial magnetic stimulation (abstract). *Biol Psychiatry* 1997;41:1085.
125. Paus T, Jech R, Thompson CJ, et al. Dose-dependent reduction of cerebral blood flow during rapid-rate transcranial magnetic stimulation of the human sensorimotor cortex. *J Neurophysiol* 1997;79:1102–1107.
126. Stallings LE, Speer AM, Spicer KM, et al. Combining SPECT and repetitive transcranial magnetic stimulation (rTMS): left prefrontal stimulation decreases relative perfusion locally in a dose-dependent manner (abstract). *Neuroimage* 1997;5:S521.
127. Fox P, Ingham R, George MS, et al. Imaging human intracerebral connectivity by PET during TMS. *Neuroreport* 1997; 8(12):2787–2791.
128. Bohning DE, Shastri A, McConnell KA, et al. A combined TMS/fMRI study of intensity-dependent TMS over motor cortex. *Biol Psychiatry* 1999;45(4):385–394.
129. Kimbrell TA, Little JT, Dunn RT, et al. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biol Psychiatry* 1999;46(12): 1603–1613.
130. Harden CL, Pulver MC, Nikolov B, et al. Effect of vagus nerve stimulation on mood in adult epilepsy patients. *Neurology* 1999; 52(Suppl 2):A238–P03122.
131. George MS, Sackeim HA, Rush AJ, et al. Vagus nerve stimulation: a new tool for brain research and therapy [see comments]. *Biol Psychiatry* 2000;47(4):287–295.
132. Henry TR, Bakay RA, Votaw JR, et al. Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy. I. Acute effects at high and low levels of stimulation. *Epilepsia* 1998;39(9):983–990.
133. Ben-Menachem E, Hamberger A, Hedner T, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. *Epilepsy Res* 1995; 20(3):221–227.
134. Krahl SE, Clark KB, Smith DC, et al. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia* 1998;39(7):709–714.
135. Walker BR, Easton A, Gale K. Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius. *Epilepsia* 1999;40(8):1051–1057.
136. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: a multicenter study [see comments]. *Biol Psychiatry* 2000;47(4):276–286.
137. Schachter SC, Saper CB. Vagus nerve stimulation. *Epilepsia* 1998;39(7):677–686.
138. Swartz CM. Subconvulsive magnetic brain stimulation no replacement for ECT [letter]. *Am J Psychiatry* 1997;154(5): 716–717.
139. Fink M, Kahn RI, Green MA. Experimental studies in the electroshock process. *Disord Nerv Syst* 1958;19:113–118.
140. Epstein CM. TMS in epilepsy. In: George MS, Belmaker RH, eds. *Transcranial magnetic stimulation in psychiatry.* Washington, DC: American Psychiatric Press, 2000:173–184.