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Electroconvulsive Therapy Part I: A Perspective on the Evolution and Current Practice of ECT

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Abstract

The concept of inducing convulsions, mainly through chemical means, to promote mental wellness has existed since the 16th century. In 1938, Italian scientists first applied electrically induced therapeutic seizures. Although electroconvulsive therapy (ECT) is employed in the treatment of several psychiatric disorders, it is most frequently used today to treat severe depressive episodes and remains the most effective treatment available for those disorders. Despite this, ECT continues to be the most stigmatized treatment available in psychiatry, resulting in restrictions on and reduced accessibility to a helpful and potentially life-saving treatment. The psychiatric and psychosocial ramifications of this stigmatization may include the exacerbation of the increasingly serious, global health problem of major depressive disorders as well as serious consequences for individual patients who may not be offered, or may refuse, a potentially beneficial treatment. The goal of this first article in this two-part series is to provide an overview of ECT's historical development and discuss the current state of knowledge about ECT, including technical aspects of delivery, patient selection, its side-effect profile, and factors that may contribute to underuse of ECT.

Keywords

electroconvulsive therapy; indications; mechanism of action; major depressive disorder; schizophrenia; bipolar disorder; mania; treatment-resistant depression; electrode placement; unilateral delivery; bilateral delivery side effects; cognitive effects

Introduction

In 2003, Ms. A, a teacher with a master's degree in education, was referred for electroconvulsive therapy (ECT) by her psychiatrist because she was experiencing a severe melancholic depression with profound agitation and had failed to respond to multiple medications. Ms. A. was screened for ECT, which was considered an appropriate option for her treatment. During the interview, she cried continuously and exhibited palpable fear. When asked to express the source of her fear, she replied, “The only ECT I've ever seen was in ‘Cuckoo's Nest.’” Following our

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explanation of the treatment in its present form and urging from her psychiatrist, therapist, and family, Ms. A. did agree to the treatment and signed consent.

The response of Ms. A., a woman with postgraduate education living in a metropolitan area in 2003 is emblematic of how influential, and potentially destructive, distorted views of ECT can be. The 1973 film Ms. A. referred to, *One Flew Over the Cuckoo's Nest*, based on Ken Kesey's 1962 novel, showed ECT used for the wrong purpose—coercion; for the wrong condition—a characterological problem, and delivered in an unmodified, outmoded fashion without anesthetic or muscle relaxant.[1] Although the treatment process and indications for use had changed by the time the film was released and have changed more profoundly still since that time, the public has only recently become cognizant of these developments.

Kerr et al.[2] identified four sources from which patients obtain information about ECT in order of frequency: friends, film and television, doctors, and print media. They found that people who obtained information from physicians had significantly fewer mistaken beliefs and were less frightened than others, while those whose primary source of information was friends or media were the most fearful. Unfortunately, as Hirshbein and Sarvananda stated, ECT has become a catalyst for the discourse on psychiatry's putatively coercive power and has been utilized by advocates and opponents alike to promulgate their views.[3] Popular accounts that portray ECT as coercive or barbaric can obviously interfere with treatment or cause patients to refuse treatment altogether. Ms. A. was fortunate to have an informed psychiatrist who understood the indications for ECT.

Ms. A. was treated with ECT, and remitted fully after seven treatments. Her response was assessed biweekly using the 24-item Hamilton Rating Scale for Depression (Ham-D).[4] Ms. A.'s scores dropped from 37 before ECT to 8 when she was evaluated 1 week after completing the course of ECT. In her case and many others, it was the support and education provided by members of the ECT team, including psychiatrists, nurses, and social workers, that enabled her to accept and complete her ECT treatment. Collaboration with and resilience within the patient's social support and family system were also major positive influences. After several weeks of recovery following completion of the course of ECT, Ms. A. returned to her family, working life, and psychiatrist. She remained well 1 year later.

This two-part series of articles provides an overview of ECT from a biopsychosocial perspective. The first article focuses on the history of and current state of the treatment, and includes topics of interest to the psychiatric community as well as the lay public regarding what ECT is, when it should be prescribed, what patients can expect, and why more people do not pursue the treatment. Case studies are used to illustrate some points.

Indications: When is ECT Recommended?

ECT involves the successive application of electrical current to the human brain for the purpose of alleviating symptoms of specific mental disorders. Approximately 80% of patients presenting for ECT treatment have a diagnosis of major depression. ECT also continues to be used, although less frequently, to treat schizophrenia, the condition in which it was originally applied, as well as catatonia and acute mania.[5] It is also indicated for the treatment of certain medical conditions but should be considered only in individuals who do not respond to other, more traditional treatments. These may include refractory Parkinson's disease, particularly with “on-off” syndrome (e.g., severe, unpredictable motor fluctuations), neuroleptic malignant syndrome, and intractable seizure disorders.[5] ECT is considered a first-line treatment when medical or psychiatric factors require a rapid and robust clinical response, when ECT poses less risk to a patient than medication (e.g., during pregnancy or in elderly patients), when there is a clear history of medication resistance or a history of favorable response to ECT, or when the patient prefers ECT to medication.[6]

Mechanism of Therapeutic Action

There is no definitive theory regarding the mechanisms of action that render ECT effective, although more than 100 theories have been proposed during the 70 years in which this treatment has been available. Generally speaking, the complexity of the central nervous system has made it a considerable challenge to distinguish the clinical and neurological phenomena associated with the use of ECT from findings that are conjectural or coincidental.[6,7] Some of the theories that were put forward were psychological in nature, and included patient expectation, placebo effects, forced regression, and the contribution of retrograde amnesia to clinical response, but these have been proved incorrect.[6,8] More recent biological theories have highlighted the neurophysiological alterations produced by the ECT stimulus, which are likely related to ECT's anticonvulsant effects. The anticonvulsant hypothesis proposes that the self-limiting capacity of ECT seizures and associated functional suppression of bioelectrical activity are associated with efficacy and positive clinical outcome.[6,7] ECT's anticonvulsant effects are perhaps most obvious in regard to its use in the clinical treatment of intractable seizure disorders and status epilepticus.[7] These effects also manifest during a course of ECT. They include changes that affect the ECT seizure, such as progressive increases in patients' seizure threshold, which has been associated with clinical response, and progressive decrease in seizure duration, independent of efficacy.[7] They also include increases in inhibitory neurotransmitters and decreases in excitatory neurotransmitters.[6–9] Brain imaging, including positron emission tomography (PET), has revealed increases in cerebral blood flow (CBF) and cerebral metabolic rate (CMR) with the ECT seizure, producing a hypermetabolic state. However, the ensuing post-ictal (i.e., post-seizure) state is characterized by decreases in CBF and CMR, indicating functional suppression.[8–11] In addition, scalp recordings of electroencephalographic (EEG) events have also been studied as a measure of cerebral changes and post-ictal bioelectric suppression associated with clinical response to ECT. The degree of post-ictal suppression, or decrease in EEG amplitude as well as the development of slow wave (delta) frequencies over the prefrontal cortex during and after the ECT course, both suggesting reductions in neural activity, have been associated with clinical improvements independent of specific technical aspects of treatment, including electrode placement and stimulus intensity.[7,11,12]

Recently, considerable attention has been focused on the role of the hippocampus in mood disorders and the effects of antidepressant treatments, including ECT, on this structure. The controversial finding published by Altman and Das in 1965[13] that new neurons can be generated in the dentate gyrus of the adult human hippocampus provided the impetus for further inquiry into the role of this structure in mood disorders. These inquiries have revealed that antidepressant treatments, particularly ECT, promote neurogenesis in the hippocampus, and that pathophysiologic reactions to environmental factors, such as stress, can reduce it.[14,15] Much of the work in this area has been conducted in rodents (e.g., see Madsen et al. 2000[16]). Perera et al. were the first to extend this work to primates.[15] They administered a course of 12 electroconvulsive seizures (ECS), the animal analog of ECT treatment, three times weekly for 4 weeks to macaque monkeys and found a striking increase in cell proliferation in the dentate gyrus of the hippocampus based on examination using bromodeoxyuridine (BrdU) labeling after ECS. They also found that this increase was maintained 4 weeks after the course of ECS was completed, consistent with the time frame within which most humans respond to antidepressant treatment.

This work is very relevant to the study of mood disorders, given that recent research utilizing magnetic resonance imaging (MRI) has revealed a reduction in hippocampal volume in patients with severe unipolar depression.[17-19] Of particular interest here is that patients with severe, particularly recurrent depression often experience disturbances of the hypothalamic-pituitary-adrenal (HPA) axis with resulting increases in glucocorticoid levels.

In animal studies, increases in glucocorticoid levels associated with stress, an animal model for depression, can decrease cell proliferation and neurogenesis in the dentate gyrus of the hippocampus [20,21] Regarding mechanism of therapeutic action, treatment with antidepressants, including ECT, may reverse the damaging effects of increased glucocorticoid levels on the proliferation of hippocampal neurons.[22] Hellsten et al.[21] investigated whether ECS might mitigate the noxious effects of cortisol on the hippocampal cells of rats. While exogenously introduced corticosterone decreased neurogenesis by 75% in this sample, this decrease was counteracted by a *single* administration of ECS, and multiple ECS increased neurogenesis. The mechanism of action here may involve the upregulation of the expression of brain-derived neurotrophic factor (BDNF) in this region. Increased levels of stress-induced or exogenously-introduced glucocorticoids lower the expression of mRNA for BDNF in the adult rat hippocampus; ECS have been shown to block the stress-induced downregulation of BDNF.[23] Altar et al. directly assessed the effect of ECS or tranylcypromine on BDNF protein in the hippocampus of adult mice. They found that, with varying schedules of ECS administration, BDNF protein was increased significantly in various brain regions, including the hippocampus, the structure in which the effect was most long lasting. Tranylcypromine yielded a smaller and less enduring increase in BDNF, which occurred in the frontal cortex and striatum, not in the hippocampus.[23] Hippocampal atrophy is not specific to severe depressive disorders;[18,22] nor do these findings of ECT-induced neurogenesis definitively explain how ECT exerts its therapeutic effects. However, they are compelling in that they may begin to clarify ECT's effects on brain regions putatively involved in the clinical presentation of depression.

ECT itself is consistently associated with brief acute elevations in blood levels of various hormones (e.g., prolactin, thyrotropin, oxytocin, vasopressin, and glucocorticoids),[11] as discussed in several comprehensive reviews.[24,25]These acute elevations are not necessarily associated with the antidepressant action of ECT per se; they are more closely associated with seizure expression and duration, and technical features of the ECT stimulus. It is in fact difficult to separate possible therapeutic aspects of neuroendocrine elevations from epiphenomena of seizure activity.[11] In addition, inter-individual variations in hormone levels at baseline vary widely.[25]. However, hormonal elevations in response to ECT have been studied in the hope that they may shed light on the pathophysiology of depression, seizure physiology, and ECT's method of action.[24-26] Since the quantities of hormones released from the brain are too small to measure, hormones that are released into the blood stream including prolactin and cortisol, are easier to study. For example, prolactin, with an elimination half-life of about 40 minutes leaves the bloodstream comparatively slowly. Therefore it is easier to assay and is known to reflect technical features of ECT treatment rather than illness severity.[26,27] Cortisol is widely investigated due to the association between depressive illness and abnormally high cortisol secretion.[28]

The intriguing relationship between depression, glucocorticoid levels, and memory impairment is relevant for a discussion of ECT's therapeutic as well as cognitive effects. It is known that depression is associated with memory impairment,[29] and disruptions of the HPA with resulting elevated glucocorticoid levels,[24;30] and that elevated cortisol is associated with impaired cognitive functioning.[28,30,31] Hence, the fact that ECT produces a sharp rise in serum cortisol directly following an individual treatment may result in an acute overstimulation of steroid receptors, superimposed on depression/stress-induced chronic overstimulation of steroid receptors, particularly in the hippocampus, and may contribute to cognitive deficits in the short term.[28] However, as mentioned above,[22] ECT often precipitates a *decrease* in overall serum cortisol over a course of treatment and may reverse the noxious effects of stress-related cortisol elevations. This effect is noted particularly in treatment responders and has been investigated by Schwartz and Chen.[26] These authors assumed that the abnormalities in cortisol regulation seen in many depressed patients would

result in larger ECT-induced cortisol releases early in a course of treatment, when the patient was still ill. They administered dexamethasone to attenuate base rates of cortisone production, to make changes in ECT-associated cortisol releases higher and easier to detect. In 10 of 12 male depressed patients, the average elevation in cortisol level was found to be 575% from baseline after the first ECT, compared to 181% after the last; three patients had no increases at all after the last treatment. These findings were corroborated in a small study of patients with previously medication-resistant depression who experienced remission with ECT. This study utilized the dexamthasone-suppressed corticotropin-releasing hormone stimulation test, reported to have greater sensitivity than standard dexamethasone suppression.[32] In sum, the acute and rapid elevation in a variety of hormones post ECT stimulus may be a byproduct of seizure activity, without clinical or cognitive manifestation of significance or duration. However, the normalizing of the HPA axis as an outcome of successful ECT provides impetus for continuing inquiry into the relationship between the ECT stimulus and the pathophysiology of depressive illness and associated cognitive effects.

Historical Overview

Origins of ECT

Although the specific mechanism of action of ECT has not been isolated, the notion that convulsions may promote wellness has existed for centuries. During the 16th century, the Swiss alchemist Paracelsus gave camphor by mouth to induce convulsions and “cure lunacy.” Several cases of convulsions induced by chemical means, specifically camphor in oil, were documented in the 18th and 19th centuries.[8,24] In 1934, Ladislaw Meduna, a Hungarian psychiatrist, investigated a hypothetical inverse relationship between seizures and schizophrenia. Drawing on neuropathologic studies and a review of work performed over the previous century, Meduna postulated a possible relationship between the lack of glial cells in individuals with schizophrenia and the overgrowth of these cells in people with epilepsy. Hoping to cure patients with schizophrenia by inducing epilepsy, he injected camphor in oil into a patient with catatonic schizophrenia, causing a 60 second grand mal seizure. The patient went into a full recovery after a short series of such treatments; five more patients were treated by the end of that year. Camphor was replaced by metrazol,[24] and the treatment spread throughout Europe.

The concept of applying electricity to the heads of people with mental problems developed as a result of the extremely unpleasant sensations experienced by patients treated with metrazol, which led scientists to seek alternate methods of inducing convulsions. Swiss scientists developed a method of inducing seizures in dogs using direct electrical current. The Italian scientists Cerletti and Bini subsequently succeeded in defining the parameters necessary for applying electricity directly to the human scalp. In 1938, they treated an unidentified 39-year-old man who was found delusional in a train station. His delusions receded after several treatments; he recovered fully after 11 treatments without adverse effects.[8,33] Thus “electroconvulsive” therapy was born.

A young German scientist, Lothar Kalinowsky, was present at the second ECT given by Cerletti and Bini and became involved with some of the early research on ECT. He might have been the first to introduce ECT in the United States, but in the process of leaving Rome and fleeing the Nazis, his equipment was delayed. In 1940, Renato Almansi and David Impastato introduced ECT at Columbus Hospital in Manhattan (which later became the now closed Cabrini Medical Center). Later that year, Kalinowsky obtained a post at the New York State Psychiatric Institute where he began treating patients with ECT.[24] From that time through the 1950s, ECT was extensively used in the United States where it joined a cadre of somatic therapies, including psychosurgery and insulin coma, that were being used to treat severely ill patients for a broad variety of symptoms.[34] ECT, introduced during a period of

unprecedented therapeutic optimism in psychiatry, became the mainstay of biological treatments for psychiatric disorders during the 1940s and 1950s. Other somatic treatments were introduced during this period, but ECT was the only treatment that flourished.[24,35] Although widely used, ECT's effectiveness specifically as an antidepressant was largely based on anecdotal reports and case studies. Standards for empirical research on treatment of depression would not emerge until later, when pharmacological trials were undertaken.[6,24]

Overview of Efficacy Research

ECT in the Treatment of Schizophrenia

Although major depression is the diagnosis for which ECT is now most frequently recommended in the United States and other western nations, research has continually been conducted on the effectiveness of ECT for the treatment of patients with schizophrenia and mania. Readers are referred to the American Psychiatric Association's (APA) publication *The Practice of ECT: Recommendations for Treatment, Training, and Privileging,* [5] published in 2001, as well as to Sackeim et al.,[6] Abrams,[24] and Prudic[8] for reviews of the history of research on ECT's general efficacy and appropriateness for schizophrenia, the diagnosis for which it was originally applied. These overviews highlight the design flaws and clinical and technical inconsistencies that characterized early studies in the United States.These included diagnostic over-inclusivity, resulting in inclusion of patients with schizoaffective disorder and psychotic depression, as well as lack of specified diagnostic criteria, failure to use standardized rating instruments, subjective definitions of outcome, diagnostic heterogeneity in the samples studied (e.g., data from patients with chronic and acute courses of illness analyzed together), inadequate descriptions of patient samples, small sample sizes, limitations of the ECT technique employed, inconsistent ECT procedures, variations in medication dosing and ECT schedules, and a preponderance of uncontrolled and retrospective studies.

Schizophrenia is one of the most debilitating of psychiatric disorders, affecting 1%-2% of the world's population and about 2.4 million Americans over the age of 18.[36] The total annual cost of schizophrenia in the United States in 2002 was estimated to be $62.7 billion. [37] It is also the most controversial diagnosis for which ECT is prescribed. The initial reports on the efficacy of ECT in schizophrenia consisted of case studies of individual patients; several of which are discussed in the APA publication mentioned above.[5] Abrams[24] reviewed a series of older, randomized, single or double-blind trials, in which ECT was employed to treat chronic schizophrenia, prior to the introduction of antipsychotic medications. For example, in a study published in 1953, Miller et al.[38] assigned 30 patients with chronic catatonic schizophrenia to ECT or sham ECT involving the administration of pentothal anesthesia alone. In a study published in 1959, Brill et al.[39] treated 67 male patients with chronic schizophrenia with ECT or pentothal alone. In a third study published in 1964, Heath et al.[40] compared ECT to sham ECT involving pentothal anesthesia alone in 45 patients with chronic schizophrenia. None of these studies found any appreciable differences between treatment groups in clinical outcome. However, later studies that allowed treatment with conventional antipsychotic medications (e.g., Brandon et al.[41] Abraham & Kulhara[42]) found a short-term clinical advantage when ECT was added to existing pharmacologic treatment regimens. Generally, factors that seemed to alter clinical outcome in acute treatment included the level of chronicity of the illness and the *concurrent* use of antipsychotic medications.[5,43,44] In 1971, based on four case studies, Weinstein and Fisher[44] made a compelling case for the dual synergism of ECT and antipsychotic medications, and they advocated the introduction of ECT into existing treatment paradigms for patients with less chronic illness. In 1995, Sackeim et al.[6] discussed multiple trials that had investigated the use of ECT in the treatment of schizophrenia and provided evidence for the synergistic effect of ECT and antipsychotic medications; they suggested that the

combination of ECT and antipsychotic medication was a particularly promising strategy for patients with treatment-resistant schizophrenia and shorter illness duration, as well as for relapse prevention.

The controversy over the efficacy of ECT for the treatment of schizophrenia has more recently been embodied in the opposing recommendations of a number of different groups. The recommendations of the American Psychiatric Association[5] are some of the most positive. They state that "The introduction of effective antipsychotic medications markedly reduced the use of ECT in patients with schizophrenia. However, ECT remains an important treatment modality, particularly for patients with schizophrenia who do not respond to pharmacologic treatment" (p. 16). The recommendations provided by the National Institute for Clinical Excellence (NICE),[45] the World Federation of Societies for Biological Psychiatry (WFSBP),[46] and the Royal College of Psychiatrists[47] in the United Kingdom were not as sanguine. For example, the most recent NICE Guidelines, published in 2003,[45] stated:

> The evidence for the effectiveness of ECT in schizophrenia in general was not conclusive and therefore ECT is not recommended for this population. Further research is required to establish clearly the benefits in subgroups of individuals with schizophrenia, for example those with severe symptoms of depressive illness or catatonia (p. 16).

The WFSBP guidelines, published in 2005, specifically stated that "apart from catatonia, ECT should only be used in exceptional cases in treatment-refractory schizophrenia, as no advantages have been consistently demonstrated compared to pharmacologic treatments" (p. 151).[46] Finally, the Royal College of Psychiatrists' special guidelines on the use of ECT also published in 2005[47] stated that "the treatment of choice for acute schizophrenia is antipsychotic drug treatment. ECT may be considered as a fourth line option, that is, for patients with schizophrenia for whom clozapine has already proven ineffective or intolerable" (p. 4). This publication also reiterates and endorses the NICE guidance in stating that "the current state of the evidence does not allow for general use of ECT in the management of schizophrenia to be recommended" (p. 5).

A number of rejoinders to these recommendations have refuted their conclusions and presented evidence supporting the use of ECT in combination with antipsychotic medication in treating patients with treatment-resistant schizophrenia. They have also supported the use of continuation and maintenance ECT treatment (C-ECT and M-ECT) in this population. In 2006, in a direct rejoinder to the NICE report, Chanpattana and Andrade presented evidence from studies done in Thailand.[43] They pointed out that, while there is little evidence that ECT has greater efficacy from direct comparisons with antipsychotic medications, there is evidence that combined treatment involving ECT plus clozapine, when warranted, may produce a more rapid response and may facilitate relapse prevention when used after the acute episode. These authors reported the results of a randomized controlled trial (RCT) that was the first to date to evaluate the effectiveness of combined ECT and antipsychotic medication in C-ECT. In this study, 93% of patients receiving monotherapy with antipsychotic medication relapsed within 6 months compared with 40% who were receiving a combination of antipsychotic medication and C-ECT. In addition, none of the eight patients receiving long-term (17 months) M-ECT relapsed, providing impetus for conducting methodologically sound trials to evaluate the utility of combination treatment in patients with treatment-resistant schizophrenia in acute treatment as well as relapse prevention. These authors have also focused on the short-term effects of combinations of ECT and antipsychotic medications (e.g., flupenthixol) in patients with treatment-resistant schizophrenia, and they have examined characteristics that distinguished responders from nonresponders, an understudied area.[48,49] Based on this work, they found that responders

were less likely to have positive family histories for schizophrenia and were more likely to be younger, to have the paranoid subtype of schizophrenia, to have fewer negative symptoms, and most significantly, to have had a shorter index episode and a shorter duration of illness. This latter finding led the authors to recommend introducing ECT into pharmacologic paradigms earlier in an acute exacerbation of illness.

In a Cochrane review published in 2005, Tharyan and Adams performed an extensive meta-analysis of relevant databases from 1974 to 2004 to assess the extent to which ECT contributes to improved clinical outcomes in schizophrenia, including general clinical improvement, hospitalization, and level of functioning.[50] Based on this review, which included 26 randomized controlled trials, they concluded that when compared to sham ECT, ECT produced greater improvement, with fewer patients relapsing in the short term and more patients likely to be discharged from the hospital. When ECT was compared directly with antipsychotic medications, the group receiving medication fared better. However, when ECT was *combined* with antipsychotic medications, the combination was superior to either treatment used alone on a variety of measures. In addition, the introduction of C-ECT to customary relapse prevention paradigms (e.g., continuation antipsychotic medication) yielded superior results compared with medication alone.[50]

In 2006, Painuly and Chakrabarti published the results of a meta-analysis of evidence from Indian studies that had investigated combined use of ECT and antipsychotic medications.[51] The meta-analysis, which included four controlled trials (n = 113) in which the Brief Psychiatric Rating Scale (BPRS)[52] was the standard measure, found significantly greater short-term improvement (i.e., during the first 4 to 8 weeks of treatment) with combinations of ECT and antipsychotic medications than with medication alone. When these investigators compared mean treatment effects, they found that the combination of antipsychotic medication and ECT had approximately a 5 point advantage on the BPRS compared with medication alone, which was a statistically significant difference. Finally, in 2005, Braga and Petrides[53] published a systematic review of the use of combinations of ECT and antipsychotic medications in patients with schizophrenia, in which they examined efficacy, side effects, and the ECT techniques that were used. They reviewed 19 open- and single-blind studies that included over 1,000 patients; of these reports, only two (n = 15) did not find that the augmentation strategy produced greater clinical improvement than medication alone.

It is evident that the use of ECT as a treatment modality for schizophrenia has historically been burdened with methodological problems and remains controversial. Although the debate regarding ECT's usefulness in treating this debilitating illness continues, it is also apparent that recent research has yielded promising findings, particularly considering the significant clinical improvements obtained when ECT is utilized to augment an existing medication regimen. Recent evidence from clinical studies and meta analyses alike illustrate why these debates persist but also demonstrate that there may be an appropriate place for ECT in treatment algorithms for schizophrenia.

ECT in the Treatment of Mania

Prior to the introduction and increased availability of pharmacologic agents, particularly lithium, ECT was the treatment of choice for manic states.[6,8,54] The early literature on the use of ECT in mania included case studies, uncontrolled trials, naturalistic studies, and retrospective reviews and suffered from some of the same methodological concerns that were discussed above in the context of schizophrenia. However, ECT has shown consistent promise in the treatment of acute as well as treatment-refractory mania.[5,55-57] In 1994, Mukherjee et al. reviewed 50 years of research on the utility of ECT for treatment of patients with mania.[54] They described a number of prospective studies as well as retrospective

reviews conducted during the 1940s (i.e., after the introduction of electrically-induced seizures), involving 589 patients with mania. They reported that, although the studies were methodologically disparate, generally speaking, 80% of the patients with mania (470/589) obtained marked clinical improvement with ECT,[54] although what constituted clinical improvement was not standardized across studies. In 1959, Langsley et al. published results of the one early randomized controlled trial, which involved 106 patients with mania or schizophrenia. In this study, ECT produced results that were equivalent to chlorpromazine; however, results for the two diagnoses were not reported separately.[58] Mukherjee et al. discussed six retrospective studies done since 1976.[54] While four of these studies were naturalistic and involved case reviews, two were controlled and used similar strategies for selecting patients. In one of these studies, ECT alone was compared with subsequent treatment with chlorpromazine alone,[59,60] while the other study compared ECT to chlorpromazine and lithium separately.[61] In both studies, the introduction of ECT resulted in marked clinical improvement or remission in 100% of cases. Two individual case reports published in 2006 also offered compelling examples of ECT's efficacy for recurrent refractory mania[62] and medication-resistant bipolar disorder.[63]

Very few prospective controlled trials concerning the use of ECT for mania have been conducted. Two such studies, although not without methodological concerns, compared the antimanic effects of ECT with those of lithium or a antipsychotic medication. In a study published in 1988, Small et al. randomized patients with mania either to ECT (three electrode placements) or to treatment with lithium and haloperidol.[64] Another study by Mukherjee et al., also published in 1988, used a similar design.[65] All of the 17 patients treated in the Small et al. study remitted after 8 weeks of treatment, while 13 of 22 (59%) of the patients in the Mukherjee et al. study showed complete remission. Differences in study parameters, including patients' exposure to antipsychotic medications during ECT in the Small et al. study, may have explained the differences in outcomes. The Mukherjee et al. study may also have used stricter diagnostic criteria and included only patients who failed to respond to adequate pharmacotherapy prior to ECT. More recently, in a double-blind controlled study published in 1994, Sikdar et al. compared real and simulated ECT in 30 demographically and clinically matched patients who were in an acute manic state.[66] Two groups of 15 patients received actual or simulated ECT. All patients also received 600 mg of chlorpromazine daily until the sixth session, followed by a modified dosage or an alternate antipsychotic medication, as warranted by each patient's clinical presentation. The group of patients receiving real ECT experienced significantly greater and faster resolution of their manic symptoms; 12 patients in the real ECT group recovered completely by the end of the eighth session, compared to one patient in the simulated group. Patients randomized to simulated ECT also required higher doses of antipsychotic medication to recover.

The most recent guidance from the NICE and the WFSBP Guidelines was somewhat more favorable regarding use of ECT in acute and refractory mania than in schizophrenia. For example, the NICE guidance[45] stated:

> There is less robust RCT evidence [than in depression] to suggest that it is effective in the acute treatment of catatonia and mania. However, the committee considered that the data appraised taken in conjunction with the strength of clinical opinion and the experiences of users, provide sufficient basis on which to recommend the use of ECT in restricted circumstances when the alternative treatment options have proven ineffective (p. 16).

WFSBP more liberally stated that “electroconvulsive therapy is regarded as the most efficacious treatment modality for mania, frequently chosen (and anecdotally found effective) when other approaches have failed….accordingly, it should be considered in patients accepting this treatment and who have not responded to previous drug treatments”

(p. 10).[67] The APA guidelines[5] reviewed the earlier literature as well as the three prospective comparative studies discussed above and acknowledged that, given the availability and ease of use of both anticonvulsant and pharmacologic agents, ECT has been rather a treatment of last resort for patients who are refractory to medications. They also acknowledged that patients who are medication refractory respond at a lower rate than those for whom ECT is a first-line treatment, as is the case with depressive disorders. In sum, although there is a dearth of rigorous research in this area, just as for schizophrenia, the combination of ECT and antipsychotic medications shows promise in promoting speed of recovery and maintaining wellness in the long term. Additional research is warranted, particularly regarding the clinical features of mania that appear to be most responsive to ECT, and the technical features of ECT that appear to be most effective in treating mania.

ECT in the Treatment of Depression: Efficacy and Technical Features

Since depression is the condition for which ECT is prescribed most often, information on its effectiveness in treating depression compared to other treatment regimens will only be briefly summarized here. Rather, this section will focus on technical features of the treatment, recent research, and ECT for specific issues within the treatment of depression. As mentioned earlier, a great majority (i.e., 80%-85%)[5,8] of patients receiving ECT in the United States or “first world” countries have a diagnosis of major depressive disorder. Randomized trials conducted from the 1960s to the 1980s found ECT to be more consistently effective for major depression than other available treatments. The majority of studies involved patients with a diagnosis of endogenous depression, although some studies also included subgroups of patients with delusional depression. In the 1960s, with the introduction of antidepressant medication, the bulk of these studies involved comparisons of these new medications to ECT, the standard treatment at that time. Patients were generally randomly assigned to ECT or medication, particularly imipramine, and monoamine oxidase inhibitors (MAOIs).[68-70] In 1985, Janicak et al.[71] published the results of a meta-analysis of findings from studies that had compared the effectiveness of ECT and medication regimens and reported that the average response rate to ECT was 20% higher than response to tricyclic antidepressants and 45% higher than response to MAOIs. Later, the general efficacy of ECT was investigated by comparing real ECT to sham ECT (i.e., anesthesia alone).[72–77] A number of randomized trials found significant differences favoring ECT in response rates between groups receiving real and sham ECT, as defined by between-group differences in scores on the Ham-D. Although many of these studies would not meet standards for modern clinical trials for various reasons, including antidepressant dosage, non-blinded raters, inconsistent response criteria, and diagnostic heterogeneity,[24] all of these studies found a clear and significant advantage for ECT over medication. In fact, no study has found any treatment, including other forms of brain stimulation currently in development, to be superior to ECT in the treatment of major depression.[6]

The Electrical Stimulus

The technical properties involved in ECT, in particular the electrical stimulus and electrode placement, can profoundly affect treatment outcomes and side-effect profiles. These properties have been researched extensively since the 1940s. ECT was initially delivered using a sinusoidal waveform. This pattern of electrical stimulation is less efficient because it delivers a significant amount of electricity below the threshold required to depolarize neuronal tissue, which does nothing to improve clinical outcome and produces significant cognitive side effects.[24] Early research on the electrical stimulus investigated means of altering its properties to ameliorate the degree of memory loss. The brief pulse stimulus, initially investigated by Merritt and Putman (1938, cited in Abrams[24]), delivers full current amplitude “instantaneously.” Thus it is both more efficient and produces a more favorable side-effect profile.[24,78-80] The prototype for modern brief pulse devices was not developed

until 1976. Fox et al.,[81] Valentine et al.,[82] Weaver et al.,[83] and Welsh et al.[84] investigated the efficacy and side-effect profile of sine wave versus brief pulse ECT. The Fox et al. study was retrospective, while the other studies were prospective. In their publication, Weaver et al. also provided an overview of eight studies conducted prior to their own research. They noted that those earlier studies to varying degrees were characterized by variations in or unspecified stimulus parameters, different electrode placements, and failure to change one of these variables at a time, as well as different standards used for selection criteria, blinding of raters, and clinical response. However, none of the studies comparing brief pulse versus sine wave found any statistically significant difference in clinical response, while all of the studies found a more favorable side-effect profile with brief pulse stimulation. Randomized trials[85,86] have also found that brief pulse waveforms have efficacy equivalent to sine wave. Based on the inherent inefficiencies and the less favorable side-effect profile of the sine wave stimulus, by the early 1980s it had (for the most part) been replaced in Western nations by ECT devices that produce a brief pulse waveform.[5,87]

Electrode Placement

ECT was initially delivered bilaterally. In 1949, Goldman[88] introduced unilateral electrode placement in order to avoid delivering the ECT seizure over speech areas. Since this researcher was also using a brief pulse stimulus, it is difficult to separate the effects related to each factor. Nevertheless, Goldman did note a marked diminution in post-ECT confusion using unilateral compared with bilateral placement. Research into the efficacy and side-effect profile of unilateral electrode placement continued throughout the 1950s[89-91] although it was not until 1958 that controlled trials were done comparing post-ECT deficits in patients receiving unilateral versus bilateral ECT.[8,24] Until the results of those trials became known, bilateral electrode placement, which produces more short- and long-term cognitive effects than unilateral placement[82,92,93]continued to be the standard.

Recent Research

Over the past three decades, research has focused on qualities of the brief pulse electrical stimulus in combination with variations in electrode placement, in order to determine the optimal conditions for retaining efficacy while reducing adverse effects. Practitioners had assumed that it was the elicitation of a generalized grand mal seizure of adequate duration that was both “necessary and sufficient” for antidepressant effects.[86,93,94] Sackeim et al. established that the intensity of the electrical stimulus, delivered *with respect to an individual's' seizure threshold*, has an impact on both the efficacy of right unilateral (RUL) ECT and on the adverse effects associated with both RUL ECT and bilateral ECT (BL ECT).[95] This discovery stimulated additional research aimed at determining to what extent the electrical stimulus should exceed an individual's seizure threshold.[93,96] Sackeim et al. developed and employed a method of seizure threshold approximation, involving the application of incrementally repeated stimulations. This incremental method was utilized to determine the smallest electrical dose necessary for brief-pulse ECT to produce a grand mal seizure of sufficient duration, in a particular individual. The work that extended from this had the goal of preventing patients from receiving a fixed electrical dosage that might either be insufficient to produce desired clinical effects for RUL ECT or else might exceed optimal stimulus dosing and thus intensify unfavorable cognitive effects.

A series of studies performed from the 1980s to the present investigated the effects of manipulating electrical stimulus and electrode placement on clinical efficacy and side effects. For example, Sackeim et al.[93,96] demonstrated in a series of studies that brief pulse RUL ECT at seizure threshold is ineffective and that a dose-response relationship exists for this electrode placement, while they found that brief pulse BL ECT is effective once seizure threshold is reached. They also reported that brief pulse RUL ECT had a superior side-effect

profile. Sackeim et al.[96] also demonstrated that the combination of RUL electrode placement with a more physiologic stimulus waveform, ultrabrief pulse at 6× seizure threshold, maintained efficacy and further improved the side-effect profile to the point where it was difficult to distinguish patients who received ECT from a control population who had never been ill on cognitive measures 2 months after ECT. This study also confirmed that ultrabrief pulse BL ECT at 2.5× seizure threshold was ineffective, while earlier studies had not examined seizure threshold relationships.

More recently, Sackeim et al.[97] expanded on these findings in a random assignment, double-masked trial. Ninety depressed patients received RUL ECT at 6× seizure threshold and BL ECT at 2.5× seizure threshold, at either a pulse width of 1.5 ms, or an ultrabrief pulse width of 0.3 ms. At the time this study was conducted, 1.5 ms was a standard pulse width; since these findings were made public circa 2004, practice has in fact shifted in the direction of narrower, more efficient pulse widths. The study confirmed that RUL ECT at a pulse width of 1.5 ms had efficacy rates that were comparable to standard BL ECT. Ultrabrief RUL treatment, however, showed robust therapeutic effects—remission rates were 75% compared with 35% for ultrabrief BL ECT, which was the least efficacious treatment; 65% for standard BL ECT, and 59% for standard RUL ECT. In addition, ultrabrief RUL ECT produced a significantly more favorable acute (post-ictal), short- (post-treatment course), and long-term (2 and 6 months post-ECT) cognitive profiles. In fact, the group who received ultrabrief RUL treatment did not show impairment on any cognitive measures taken during or after ECT, relative to their own baselines. Loo et al.[98] confirmed the efficacy and favorable side-effect profile of standard and ultrabrief RUL ECT; however, differences in treatment technique produced some variation in outcome. Their 3-year, prospective, naturalistic study included 96 depressed patients who were referred for ECT and received an acute course of ECT in an inpatient setting. Seventy-four patients received ultrabrief RUL ECT at 6× seizure threshold, and 22 patients received standard RUL ECT at 5× seizure threshold. Although response and remission rates for those patients who completed treatment with RUL ECT in both pulse widths without crossover to BL ECT were high (i.e., 79% and 57% in the standard group, and 97% and 61% in the ultrabrief group), this study crossed patients over for nonresponse after only 6 treatments compared with the 10 treatments allowed in the Sackeim et al. study,[97] so that overall response rates for the RUL ultrabrief group were lower. Patients who received ultrabrief RUL ECT did show less impairment than those receiving standard pulse widths on a variety of cognitive tests that assessed both anterograde and retrograde memory, particularly those which assessed retention of information over a time delay. However, the authors noted that patients who received ultrabrief RUL ECT did show greater impairment in neuropsychological functioning than patients in the Sackeim et al. study. An explanation for this involves differences in treatment parameters between these studies, and emphasizes the importance of such technical variation. For example, in the study by Loo et al.,[98] the average number of ECT treatments administered was greater, ECT was given at a higher dosage relative to threshold, and doses were increased over the treatment course compared with the study by Sackeim et al.[97] Thus it is evident that variations in treatment parameters can affect cognitive outcomes.

The findings of this progression of studies underscore that the efficacy and side-effect profile of ECT differs markedly as a function of technical variations in treatment. Although systematic research over the past several decades on treatment techniques has identified strategies that can potentially reduce cognitive deficits, these techniques, developed and tested in clinical trials, are not necessarily being incorporated into ECT treatment in the community.[87]

To investigate how variation in treatment technique and setting might affect patients' cognitive profiles after ECT, Sackeim et al.[99] conducted a prospective, observational study to assess the cognitive outcomes of 347 patients receiving ECT at seven medical facilities in the New York City area, both immediately following ECT and 6 months after the course of treatment. In this study, the investigators administered a neuropsychological battery of nine tests designed to assess global cognitive status, psychomotor function, attention, anterograde learning and memory, and autobiographical memory. They found significant differences between patients treated at different facilities on 7 of the 11 measures immediately after ECT, with differences persisting at 6 months on measures of global cognitive status and autobiographical memory. Sackeim et al. determined that study site effects were largely attributable to differences in treatment technique, particularly type of electrical waveform and electrode placement. Sine wave stimulation, for the use of which there is no justification at this point,[5] and bilateral electrode placement, produced the most persistent long-term deficits. Given that high dose, ultrabrief pulse RUL ECT is as clinically effective as BL ECT with minimal retrograde amnesia, there does not seem to be any justification for the continued use of sine-wave ECT.[96,99] The point is that, like so many other medical procedures, ECT can be delivered safely and effectively, or sub-optimally, with poor clinical results and adverse side-effect profiles for patients.

Research efforts to refine ECT continue to focus on enhancing efficacy and minimizing side effects. Unfortunately, results of this work are slow to make their way into practice or public awareness.[87] Treatment approaches that are less than state of the art, combined with a general lack of understanding of ECT, can contribute to how the treatment is perceived by clinicians as well as the lay public and thus to underutilization of ECT to treat severe psychiatric illness.

Clinical Urgency and Diagnostic Subtypes

ECT is often recommended as a “treatment of last resort.” According to Abrams,[24] Sackeim et al.,[6] and Prudic,[8] ECT should be considered under circumstances of increased clinical urgency, intolerance to psychotropic drugs, failure of drug therapy, or patient preference. Clinical urgency would include the presence of depressive hallucinations or delusions, catatonia, suicidality, and co-existing medical disorders (e.g., cardiac risk in patients receiving tricyclic antidepressants, pregnancy) for which treatment with antidepressant medication poses a risk. Kellner et al.[100] and Prudic and Sackeim[101] proposed that ECT can have a profound short-term benefit in suicidal patients. In cohorts of 148 and 44 patients, respectively, both research groups found rapid and robust reductions on item 3 of the HAM-D, which rates suicidal thoughts and acts. They recommended that ECT be considered earlier in the course of treatment for patients at risk for suicide.

Other researchers have examined effects in different subtypes of depression. In a study involving 253 patients (176 with nonpsychotic major depression and 77 with psychotic major depression), Petrides et al.[102] found that psychotic patients who received bilateral ECT at 50% above seizure threshold improved earlier in the course of treatment and had a more robust remission rate (95%) than the nonpsychotic patients in the sample (remission rate of 83%). Remission was defined as achieving a score ≤ 10 on the 24-item Ham-D scale and showing a 60% drop in Ham-D scores from baseline; Ham-D ratings were conducted within 24-72 hours of each treatment. Although the majority of patients in this study achieved remission within eight ECT treatments, remission rates differed between the groups, and the authors concluded that psychotic depression may be a phenomenologically separate entity from nonpsychotic depression. This hypothesis is supported by neuroendocrine and neurocognitive studies that have shown greater abnormalities and different deficit patterns in patients with psychotic depression compared with patients with nonpsychotic depression. These researchers proposed, as did Fink[103] and Levin,[104] that

early prescription of ECT rather than a standard treatment algorithm (i.e., at least two courses of medication for 6 to 8 weeks each) might spare psychotically depressed patients unnecessary suffering. The following case illustrates this point.

> Ms. B. was a successful professional woman in her late 60s who lived in the metropolitan region of our hospital. Following a business setback, to the surprise of her family, she became increasingly hopeless, agitated, and finally delusional. Upon admission to the psychiatric unit of a general hospital, she was diagnosed with a severe, first-episode depression with psychotic features, including somatic and guilty delusions. She was administered antipsychotic and antidepressant medications for 10 weeks but showed no clinical improvement. She was then referred for ECT. Her HAM-D score before ECT was 48. After 13 ECT treatments, Ms. B. was in complete remission, with a Ham-D score of 5 at 1 week post ECT. She returned to her life and work, and remained well at 1-year follow up.

Although a limited number of studies have directly investigated differences in response between patients with unipolar and bipolar depression,[105,106] these studies have demonstrated similarity in response rates. For example, retrospective reviews of naturalistic ECT treatment in community settings[107-110] have found no differences in response rates among unipolar and bipolar depressed patients, despite differences in patient demographics, technical aspects of treatment, and illness histories. Three prospective studies,[106,111,112] which utilized the HAM-D, also found that unipolar and bipolar patients had similar response rates to ECT. However, Medda et al. found that unipolar and bipolar II patients fared best, while patients with bipolar I disorder exhibited residual manic and psychotic symptoms.[111] Two of these studies[106,112] investigated speed of response, and found that patients with bipolar disorder required significantly fewer treatments to respond than patients with unipolar depressive disorder.

Treatment-Resistant Depression

The increasing number of patients with treatment-resistant depression (TRD) who are being referred for ECT may affect potential ECT outcomes, both with respect to short-term response[113-115] and relapse rates.[116] Although earlier studies reported ECT response rates of 70%-90%,[5,115], the cohorts of patients now being treated with ECT include an increasing number of patients who have failed to respond to adequate trials of antidepressants (i.e., patients with treatment-resistant illness). While there is debate about how to define “treatment resistance,” there has been increasing evidence, and thus increasing concern, that failing to respond to a number of adequate trials of antidepressant medications can foster treatment resistance and chronicity in depressed patients. The increasing prevalence of treatment resistance poses significant clinical challenges, considering the potential deterioration of patients' psychosocial functioning.[32] Data in this area began to emerge in early studies, such as Avery and Lubrano's 1979 reanalysis[117] of DeCarolis et al's. large prospective trial of ECT in medication-resistant patients (i.e., patients who had failed to respond to a 30-day trial of imipramine).[118] The purpose of this reanalysis was to determine how likely it was for depressed patients to respond to ECT if they had not responded to adequate treatment with antidepressant medication. In this study, endogenous depression was defined according to the DSM-II as a depressive subtype in which the depression is the result of an intrinsic biological or somatic process rather than an environmental influence, in contrast to a reactive depression. The reanalysis found that patients with both endogenous and psychotic subtypes of depression who had not responded to imipramine did respond to ECT. However, the adequacy of the imipramine trials by present-day standards and hence the true medication-resistance of the patients prior to ECT treatment was not established. Moreover, response was not clearly defined, raters were not blinded, and a broad variety of subtypes was included.

In a rigorous four-site study of the effects of medication resistance on ECT outcome, Prudic et al.[119] assessed medication resistance in 100 patients with unipolar, nonpsychotic depression before they received ECT. Medication histories from all patients were evaluated using the Antidepressant Treatment History Form (ATHF),[116] which allows for a highly comprehensive assessment of prior treatment. Prudic et al. evaluated treatment history in the index episode only, in a final sample of 54 patients who had not previously been treated with ECT, and found significant differences in response rates immediately after and 1 week after the course of ECT. Predictors of ECT response were medication resistance, longer duration of the index episode, and higher baseline Ham-D scores. Resistance to heterocyclic antidepressants (e.g., imipramine, nortriptyline, amitriptyline) was associated with lower rates of response to ECT than resistance to SSRIs or previous inadequate trials of any other medication. The authors concluded that response to ECT is *not* independent of a patient's prior response to specific classes of medication, and that differential response rates can be expected for patients who failed an adequate trial of a heterocyclic antidepressant.[119] However, these investigators still obtained response rates of 63% at immediate assessment and 47% at 1 week after the course of ECT, which should not preclude prescription of ECT in this population.

Side Effects: Perception and Reality

The pervasive fear of ECT, a product of poor treatment practices and inaccurate portrayals by the media, has been a stumbling block that has hindered people from pursuing the treatment. The fear of serious medical and psychiatric consequences and the stigma attached to ECT seem counterintuitive given its demonstrated efficacy and safety,[120] and the documented successful treatment of well-known entertainers, authors, musicians, and politicians.[121] The notion that ECT causes brain damage or “fries the brain” has been promulgated since the inception of this treatment. However, there are no data to support this idea and research, in fact, refutes it. For example, in 1994, Devanand et al. published a systematic review of virtually all of the research and general literature regarding this question, reviewing cognitive effects, imaging, autopsies on former ECT patients, human epilepsy studies, and over 20 animal studies, and found no evidence that ECT produces any damage to the brain on a structural or cellular level.[122]

Serious Medical Outcomes and Counterindications

Serious medical outcomes associated with ECT are quite rare. The Texas Department of Mental Health, due to its stringent reporting requirements, provides data on this subject. Shiwach et al.[123] reviewed this database, which contains information on 8,148 patients who received 49,048 ECT treatments over a 5-year period. The database describes causes of death for the 30 patients who died within 14 days of ECT. No deaths occurred during ECT treatment. Of the 30 patients who died within 14 days of ECT, 10 died from cardiac complications, 8 by suicide, 4 by automobile accident. Three patients died from sepsis, which was unlikely to be related to ECT (1 from peritonitis due to a burst diverticulum, 1 from generalized organ failure, while the cause was not reported for the third). Three additional patients died from neurological problems (supranuclear palsy, stroke, and ruptured aneurism) unrelated to ECT. One patient died from laryngospasm, likely related to intubation required in this case for anesthesia. Another patient died of pneumonitis secondary to the aspiration of vomitus, which may have been indirectly related to ECT. One patient died from cancer, and two from unknown causes.[123] Of interest is that death rates from cardiac disease are higher among people suffering from severe depression, regardless of treatment type.[124]

Special considerations arise in using ECT to treat patients with coexisting medical conditions, particularly certain cardiovascular disorders such as recent myocardial

infarction, congestive heart failure, or valvular heart disease. Other conditions of concern are neurological disorders such as space-occupying lesions or venous malformations, diabetes, obstructive pulmonary disease, and osteoporosis. Pre-ECT medical evaluation should identify coexisting medical illnesses and evaluate their potential interaction with and impact on ECT treatment. Issues related to using ECT in patients with coexisting medical conditions are reviewed comprehensively in Prudic[8] and in the American Psychiatric Association's recommendations concerning ECT treatment.[5] As mentioned above, Shiwach et al.[123] reported one death that occurred on the day of ECT, which was due to laryngospasm that was attributable to anesthesia. The deaths that occurred within 48 hours of ECT included 5 from cardiac complications, 3 from sepsis, 1 by suicide, and 1 from unknown causes. It is not possible to know definitively whether or not these deaths were due directly to complications from ECT; however, with these broad inclusion criteria, a mortality rate of 2 to 10 in 100,000 is obtained. It is generally estimated that this death rate is comparable to that for anesthesia alone, about 3.3 to 3.7 deaths in 100,000.[123]

Cognitive Side Effects: Four Types of Memory Disturbance

Memory disturbances remain the most problematic effect of ECT. Since the introduction of ECT in 1938, patients who have received the treatment have reported cognitive side effects.[125] These effects remain a source of concern. Numerous neurobiological, technical and patient-related factors can contribute to the cognitive side effects associated with ECT, and profound variations can occur among patients both in objective effects and subjective reactions. Clarifying the neurobiology of ECT's amnestic effects has posed significant challenges, and remains a goal for continuing research [8,126]. Although a detailed review of this work is beyond the scope of this paper, it is important to note here that ECT is known to produce physiologic effects on brain regions which may be integrally involved in short- and long-term declarative memory. For example, ECT affects memory systems associated with the medial temporal lobe, which contains the hippocampus, implicated in the consolidation of new information (anterograde memory).[126-128] ECS in animal models has been shown to interfere with hippocampal long-term potentiation (LTP), proposed as mechanism that may subserve the neural substrates of new learning.[127,128] A salient finding here is that the duration of the reduction in hippocampal LTP mirrors the duration of anmestic effects following ECT.[127] However, medial temporal lobe changes do not explain ECT-related long term (retrograde) memory deficits, which may be associated with physiologic changes in the prefrontal cortex caused by ECT.[9] A resolution of these issues may change conceptions of, and translate into alterations in, the technical aspects of treatment.[126]

Generally speaking, technical aspects of treatment such as stimulus waveform, electrode placement, stimulus intensity, dosage relative to threshold, and number and spacing of treatments can significantly affect the nature and extent of cognitive deficits following a course of ECT.[5,11,86,96-99] Patient-related factors such as gender, age, cognitive functioning at baseline, and concomitant psychotropic medications may also play a role. As discussed above, in the prospective longitudinal study by Sackeim et al.[99] that investigated clinical and cognitive outcomes at seven facilities, significant differences in treatment technique were found to be associated with differences in patients' short- and long-term cognitive deficits. However, these investigators also found that specific patient factors (the covariates age and premorbid IQ) increased the likelihood that patients would experience more severe cognitive deficits when assessed immediately after and 6 months after ECT. Specifically, they found that older patients and patients with lower estimated premorbid IQ evidenced the most significant deficits in functioning. In addition, gender had quite strong effects on the assessment of autobiographical memory, with women showing marked deficits on this measure that persisted over time. These findings indicate that adverse cognitive effects following ECT are associated with a multitude of factors related not only to treatment

parameters but also to certain patient characteristics and that, under very specific circumstances, these adverse effects may persist over time.

Common cognitive side effects fall into four basic categories. The first type of cognitive effect is the ***stereotypical and transient postictal disorientation*** that patients experience immediately after ECT treatment, which is a function of the seizure itself and of the anesthesia that was administered. This can range from mild, clearing within minutes to a few hours, to severe organic syndromes in rare cases. Factors in the administration of ECT, including electrode placement and number of treatments, can affect recovery time.[96] However, patients subjectively experience this period quite differently. Some patients awaken rapidly and are able to resume their regular activities. Others may sleep for several hours, following which they are able to eat and resume their day. However, there are patients who experience notable disorientation, and these effects can produce greater subjective distress. This is demonstrated in the following case.

> Ms. C., a 43-year-old woman with recurrent major depression, received her first course of ECT treatment in our hospital during 2005. She experienced considerable disorientation following her first and second treatments. After 1 hour spent in the post-ECT recovery area, she found she was unable to return to her room in our inpatient unit without assistance and had to use a wheelchair. This made her feel very personally vulnerable; she considered stopping treatment unless she could be escorted through the nursing area so that she could avoid being seen by other patients. Her request was granted and she continued her course; the disorientation attenuated over time.

A second type of cognitive effect is ***anterograde amnesia***, the inability to retain information learned during and shortly after a course of ECT treatment, which also varies in severity. Anterograde amnesia can contribute significantly to a patient's inability to retain important information, both in general and specifically about the treatment. Patients may feel that clinicians are prevaricating or simply not providing information, when, in fact, they may not have retained it. The use of a daily log or diary is highly recommended for this reason, as illustrated in the following case.

> Mr. D. experienced a profound melancholic depression, which was treated with ECT. He responded after 10 treatments but then quickly relapsed; he was then provided with 6 additional bilateral treatments. He eventually remitted fully; however, he experienced notable difficulties with memory retention. It was suggested that Mr. D. try keeping a diary, but he resisted, stating that he was “not much of a writer.” Toward the end of his treatment, Mr. D. would ask staff members the same questions about his treatment multiple times a day, even on days when he did not receive treatment. With considerable support, he was eventually able to use a diary and began recording the results of meetings with clinical staff, visits and calls from family, and proposals for discharge plans. He began reviewing these each day and stated that this activity did make him feel more empowered about his treatment. Mr. D. was discharged to his home, family, and job. His cognitive problems cleared within about 2 months of his ECT course.

A third type of cognitive effect is ***short-term retrograde amnesia***, which involves memory gaps for events that occurred within a few weeks or possibly months *before the course of ECT*. Retrograde amnesia usually improves during the first few months after the acute ECT course, but recovery can be incomplete for some patients. This can be upsetting, particularly if patients place particular value on their personal memories and experiences. Lisanby et al. investigated whether memory for personal, autobiographical events or public, impersonal events is more vulnerable to the effects of ECT.[129] In a randomized controlled trial involving 55 patients with major depression who received RUL ECT or BL ECT at two

different stimulus intensities, they found that patients' recall was more acute for autobiographical memories, particularly the most salient of those memories. At 2-month follow up, patients treated with RUL ECT returned to baseline levels for impersonal memory, while those who received BL ECT maintained deficits for recent impersonal events. However, it is the value placed on memories versus the subjective experience of wellness that seems to determine patients' views of these deficits, as illustrated in the following case.

> Mr. E., a 35-year-old patient with a history of intermittent depressive episodes and anxiety, developed a severe agitated depression. He received ECT and remitted after 14 treatments, relapsed quickly, and was provided with 8 bilateral treatments after which he experienced a full and lasting remission. Mr. E. thoroughly enjoyed “feeling like himself again” and “getting his personality back.” However, he had taken a work-related trip to China about 8 months before receiving the course of ECT. He noted that he was unable to recall much of this trip, but stated that he “didn't care because he had not felt this well in years.” During the next 6 months of post-discharge follow-up, Mr. E. stated that his recall was indeed improving for the trip and other events, and that he remained unconcerned as his wellness took precedence.

In some cases, however, short-term retrograde amnesia is not just a nuisance, but can have deleterious effects, as illustrated in the following case.

> Ms. F. was treated for a severe melancholic depression with profound retardation. As she began to improve with ECT, she discussed her work and boasted acute recall of all her clients' medical information prior to her depression. She experienced a remission after receiving 20 treatments, and her Ham-D score dropped from a 42 before ECT to a 9 1 week after treatment. At that point, she began thinking about returning to work. Ms. F. was experiencing difficulty with recall in general and realized that she had not written down the password for a grant on which she had been working, nor had she given it to anyone else; the information was thus irrevocably lost. This led the staff to develop an ECT Pre-Treatment Information Log for patients, particularly those who, like Ms. F., have few if any friends or family members involved in their treatment (See Part II of this series for a more detailed discussion of this tool).

The fourth type of cognitive impairment, which is fortunately rare, involves more extensive ***retrograde memory loss*** in which the patient experiences severe, persistent memory deficits dating back several months or even years.[126] This phenomenon was described in an article by Anne Donahue,[130] Representative from 2002 to the present in the Vermont State House of Representatives,. Ms. Donahue had ECT in the fall of 1995 and spring of 1996 for a total of 33 treatments, involving a switch from unilateral to bilateral delivery. She stated that the treatment saved her mental health and possibly her life, and that, if necessary, she would elect to undergo another course of ECT. However, in her personal account of her post-ECT experience, she reported subjectively significant loss of specific personal memories. While expecting her memory deficits to clear within 6 months, as she had been told, she experienced profound memory loss that extended back at least 5 years. She added that her deficits “exceeded anything the doctors anticipated” or that she was advised about. For example, she reported having the following conversation with a friend. After informing the woman that she had had “a treatment which affected her memory,” the conversation went roughly as follows:

> Anne: Well, it's great to run into you here. What brings you to Burlington?
>
> Friend: I live in Burlington, remember?

> Anne: No, actually I never knew that.
>
> Friend: Well actually, you did know that. We've had lunch together here several times over the past few years, and I've been out to visit you. It must be that treatment you mentioned. (p. 139).[130]

While acknowledging that patients who experience such pronounced effects are in the minority, Ms. Donahue felt the need to conduct her own investigation into the gap between anecdotal evidence of significant memory loss and the scientific community's official position. She concluded that patients deserve more complete explanations of possible long-term cognitive effects, and that the scientific community had not expressed adequate support for controlled research to determine which patients may be particularly at risk for such adverse effects and for providing definitive explanations for such effects.

Common Physical Side Effects: What Patients May Experience

Most patients do not report that ECT is a subjectively stressful experience.[131] However, some patients may experience physical side effects following ECT including headache, nausea, and muscle pain, particularly early in the course of treatment. These effects may be the result of the seizure, the anesthesia, or some combination of the two and are not medically serious. Patients may also experience a rare but unpleasant side effect from the combination of anesthesia and muscle relaxant, known as “anesthesia awareness” (discussed below), in which they may regain consciousness prior to the muscle relaxant wearing off. However, there is no way for patients to know which side effects, if any, they will experience until they have started treatment. It is therefore important to inform patients of the possible side effects, however unusual, and that treatment for the specific symptoms they experience is available and will be provided if necessary.

Post-ictal headache—It has been reported that up to 45% of patients experience post-ictal headache.[5] This headache characteristically has a frontal throbbing character; it is usually mild, and occurs more frequently in younger patients. Although its etiology is not known, it appears to have a marked vascular component and may be associated with technical aspects of the treatment.[132,133] Post-ictal headaches usually respond to common analgesics; however some patients experience more severe headaches and require prophylactic treatment with a non-steroidal anti-inflammatory agent (NSAID) or specific anti-migraine treatment.

Nausea—Patients may experience nausea following ECT, with reported rates of nausea ranging from 1% to 23%.[134,135] Nausea may be associated with headache or with its treatment, or it may occur independently as a side effect of anesthesia. While nausea may resolve with treatment of the headache, prophylactic treatment with agents such as ondansetron may be used.

Muscle soreness—Muscle soreness may follow ECT, most often after the initial treatment. This soreness is most likely due to intense fasciculation (muscle twitching) associated with the administration of depolarizing muscle relaxants such as succinylcholine. Patients may also experience jaw pain, due to direct stimulation of muscles near the jaw by the ECT stimulus. Firm closure around a bite block can minimize the development of jaw pain, which can later be treated with aspirin or NSAIDs. While depolarizing muscle relaxants are usually tolerated in later treatments, in cases of more persistent soreness, a non-depolarizing agent such as curare which blocks muscle fasciculations may be used as a treatment modification. Curare or more modern nondepolarizing muscle relaxants may also be administered in patients with neuromuscular degenerative disorders who might experience deleterious effects from the potassium releasing and muscle-depolarizing action

of agents such as succinylcholine. However, most patients do not experience muscle soreness to an extent that would warrant the use of this modification.[5,8]

Anesthesia awareness—The ability to produce muscle relaxation independently from anesthesia has permitted anesthesiologists to adjust the two effects as needed to ensure that their patients are safely unconscious and sufficiently relaxed to permit treatment. However, as mentioned, "anesthesia awareness," resulting from unanticipated individual differences in anesthesia requirements, can occur, albeit infrequently.[136] In this situation, the patient may be unable to move and feels unable to breathe, but is unable to alert staff to his or her state of consciousness. Although not dangerous to the patient, since oxygen is being provided, it is extremely disturbing subjectively and requires both an adjustment in analgesic provision and a solid *psychoeducational intervention*. The case of Mr. G. illustrates this clinical situation:

> Mr. G., a patient in his mid-30s with agitated depression and obsessive-compulsive disorder, was responding well to a course of ECT when he regained consciousness during recovery from (ECT) anesthesia. He felt he was unable to breathe and panicked and stated that he would not return to treatment, despite his clinical improvement. He then proceeded to speak about his experience incessantly with staff and other patients. He missed two treatments; however, repeated interventions by the ECT psychiatrist and clinical staff convinced him to complete his course of treatment, which he was able to do successfully after appropriate adjustments were made to his analgesia.

Patients receiving ECT are being treated for a potentially life-threatening psychiatric condition. ECT, like most serious medical treatments, has a range of possible physical side effects, which can be unpleasant and subjectively disturbing, but not dangerous. As mentioned earlier, patients complain more about not being provided with information about potential side effects than about the subjective experience of these effects. It is ethically, medically, and psychologically necessary to provide education and support to both patients and families—before, during, and after ECT. Patients should be given honest and open information so that they can make provisions for any cognitive deficits or discomfort that might affect their functioning during and after the course of ECT. The informed consent process, a legal doctrine introduced with the APA Task Force guidelines of 1978, provides an initial opportunity for the ECT psychiatrist, and other involved clinicians who are involved, to impart comprehensive information about ECT, to patients who are capable of comprehending and acting on such information.[5] The successful use of ECT requires a significant degree of medical and psychosocial intervention. The treatment team can substantially vary the technical aspects of the ECT administration to suit the clinical picture and specific symptoms of the individual patient (e.g., suicidality, psychosis, retardation). Such variations have ramifications for both efficacy and side effects.[5] The practitioner overseeing the ECT treatment should take responsibility for educating the clinical team as well as patients and families about why specific types of ECT administration were chosen, post-ECT treatment regimens, and likely side-effect profiles. A more detailed discussion of patient and family education for patients receiving ECT is provided in Part II of this two-part series. For a full review of management of post-ECT side effects, see the APA's recommendations,[5] Devanand et al.,[132] and Sackeim et al.[135]

Factors Affecting Utilization: Where are we now?

The usual clinical treatments for depression often produce disappointing results, with only about 35%-40% of patients experiencing a complete remission of symptoms,[137,138] a rate of response that may not be significantly different from placebo. The chronicity of depression that results from treatment-resistance contributes to the global burden of depressive illness

and deserves increased attention. This can have significant ramifications for both the depressed individual and for the larger community, as depression is associated with a growing global mental health burden. Major depression is the leading cause of disability in the United States among people between 15 and 44 years of age. It affects 14.8 million American adults, or 6.7% of the general population in a given year [139] Estimates of the ten leading causes of disability worldwide indicate that major depression is the second highest cause of disability after ischemic heart disease.[35]

While ECT remains the most effective treatment for depression, its use has waxed and waned over the past 70 years. Use of ECT was widespread during the 1950s and 1960s, with approximately 300,000 people per year receiving the treatment in the United States. However, provision of ECT dwindled significantly during the 1970s and early 1980s with the ascendancy of pharmacological approaches and in response to increased public protest. Once it became apparent that medication was not a panacea, ECT experienced a resurgence during the late 1980s and 1990s. Currently, approximately 100,000 people per year receive ECT treatment in the United States.[139] However, availability of ECT nationwide is at best uneven, and ECT can be seen as underutilized when considered in the context of the burden of severe depressive illness. Numerous factors contribute to the underutilization of ECT in the United States, including the following.

- Organized and vocal anti-ECT activity that is not countered by a public education campaign;
- Continued distortions in the media;
- Restrictive reimbursement schedules, which may hinder patients from obtaining or completing courses of ECT;
- Lack of availability, particularly for the poor and uninsured;
  - Public facilities have traditionally been unwilling, from a policy standpoint, to bear the stigma or the cost of providing ECT.
  - Only approximately 8% of psychiatrists in the United States offer ECT as a treatment
- Poor regard for the treatment;
- Psychiatrists' unwillingness to prescribe ECT due to concern that the recommendation will not be well received or because they have outdated information about the treatment;
- Inaccurate perception of costs: A common perception is that the duration of inpatient stays for patients receiving ECT is longer than for patients being treated with medications. However, studies have found that average stays are actually shorter and less costly for patients receiving ECT than for those being treated with medication, as long as the length of stay is calculated based on the day ECT began. [140,141]

From a global perspective, it is estimated that at least 1,000,000 people receive ECT annually.[24] Ottosson and Fink[35] presented an overview of ECT utilization in western and developing countries, including Canada, the United Kingdom, and other European nations including Italy, the Netherlands, and the Baltic nations, as well as Australia, New Zealand, and China, They pointed out wide variability in availability and technique in all of these nations. Of interest, in Nordic countries, known for high rates of depression, ECT is fairly consistently available particularly in regions where high consumption of antidepressant medication has been noted. In developing countries, ECT is marred by administration the “old fashioned way,” without anesthesia, muscle relaxants, or oxygenation. In sum, the

common denominator that characterizes ECT provision worldwide is variability—in the availability of trained physicians, appropriate facilities, and equipment. Each of these factors is heavily influenced by public opinion and political climate, as they are in each state of the United States.

Public Revelations

Public perceptions of and revelations about ECT abound, and range from highly positive to intensely negative. There is indeed a subset of ECT patients who have experienced either negligible benefits from ECT, or memory loss following ECT that may have been unanticipated, as in the case of Anne Donahue,[130] or anticipated as with public figures such as Kitty Dukakis[142] and psychologist Martha Manning.[143] Examples of these experiences and concerns will be elaborated on in the second paper in this two-part series. However, several well-known health care educators and providers have recently disclosed that they have experienced depression and received ECT. These disclosures have been very helpful in changing the image of the treatment for the lay public by providing personal accounts of the potential effectiveness of this treatment. The point of these disclosures is that ECT is more effective and safer when it is administered in a medically sound manner, incorporating empirically derived knowledge and state of the art technology.

Reid[121] presents a compelling series of case studies, in which psychiatrists described family members' positive experiences with ECT. Several professionals have elaborated on their personal stories, including Norman Endler, a Canadian professor of psychology,[144] Martha Manning,[143] Sherwin Nuland, a Yale professor of surgery,[145] Leon Rosenberg, former dean of Yale Medical School,[146] as well as one “anonymous” psychiatrist.[147] All of these accounts described severe depressive illnesses and positive, possibly life-saving experiences with ECT. However, many individuals have also discussed the highly stigmatizing responses they received from family, friends, and colleagues upon going public. Manning's experience is a case in point:

> Telling people I've had ECT is a real conversation killer. People seem more forthright these days about discussing depression. Hell, the cashier in the grocery store told me yesterday that she's on Prozac. But ECT is in a different class. For months I have glossed over ECT's contribution to the end of my depression with most people. But lately I've been thinking, “Damn it. I didn't rob a bank. I didn't kill anybody. I have nothing to be ashamed of.” I've started telling people about ECT. My admission is typically met with uncomfortable silences and abrupt shifts in topics. An acquaintance at a party is outraged. “How could you let them do that to you?” I bristle and answer, “I didn't let them do it to me. I asked them to do it” (p. 164).[143]

Manning also noted that the idea of applying an electrical stimulus to the human brain conjures up very different feelings than the idea of electricity used to save a life during a cardiac episode:

> No one bats an eye when electricity is delivered to a stalled heart. There is no outcry; in fact, it's considered a miracle. A person passes from life to death to life again through the application of electric current to the heart. But try talking about the same thing with the brain, and it's no miracle. Suddenly, words like torture and mind control populate the descriptions (p. 165).[143]

Conclusion

How did the concept of using electricity to relieve the suffering associated with certain mental disorders, while generally effective, become so tainted? The fact that ECT is

recommended to treat a potentially life-threatening condition cannot be overstated; thus it behooves the psychiatric community to help overcome misperceptions within its own ranks and within the lay public, so that prospective patients can receive the benefit of this underused but effective treatment. These issues, as well as a consideration of psychosocial interventions that can enhance patients' experience of this treatment, will be addressed in Part II of this two-part series.

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