

C H A P T E R 4 4

Electroconvulsive Therapy

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Since electroconvulsive therapy (ECT) was first developed over 70 years ago, it has proved to be consistently effective in the treatment of affective disorders (Abrams, 1992). Although the serendipitous discovery of psychotropic medications such as chlorpromazine and iproniazid in the 1950's revolutionized psychiatric treatment, clinicians and researchers soon recognized the limitations in the effectiveness of psychotropic medications and ECT remained an important therapeutic alternative. This has provided impetus for continued research related to ECT, including exploration of its clinical indications, techniques to maximize its efficacy and minimize its toxicity (especially cognitive and cardiac side effects), and its therapeutic mechanisms of action. In this chapter, we review the relevant literature and provide practical guidelines for the administration of ECT, including the efficacy of ECT in various psychiatric disorders as well as appropriate patient selection, stimulus settings and electrode placement, pretreatment medical evaluation, and management of the patient during acute, continuation, or maintenance courses of ECT. Finally, we examine putative mechanism of action of ECT and provide an overview of some recent developments to treat depression with nonconvulsive stimuli such as transcranial magnetic stimulation (TMS).

History of ECT

The development of ECT occurred at a time when few somatic treatments were available for psychiatric disorders and physicians were desperately attempting to find treatments for severely ill, psychotic patients. The first attempts at inducing therapeutic seizures for such patients were performed chemically. In 1935, Manfred Sakel (1900–1957) induced hypoglycemic episodes in psychiatric patients (i.e., insulin shock therapy), while in the same year Lazlo Meduna (1896–1964) injected patients with pentylenetetrazol to induce convulsions in order to treat psychosis. Three years later, the Italian psychiatrists Ugo Cerletti (1877–1963) and Lucio Bini (1908–1964) used electroshock treatments to induce seizures. This method proved safer and easier to administer than chemically induced seizures and replaced other forms of inducing seizures.

Modern psychopharmacology developed with the discovery of lithium (1949) and iproniazid (1957) for the treatment of mood disorders and the synthesis of the first antipsychotic, chlorpromazine (1952); the first tricyclic antidepressant, imipramine (1959); and the first benzodiazepine, chlordiazepoxide (1960). The development of psychotropic medications was associated with a decline in the use of ECT from the 1960s to the 1980s. However, in the 1980s, the use of ECT began

to increase, and more than 36,000 patients received ECT in 1986, the last year a national survey on the use of ECT was conducted (Thompson, Weiner, & Myers, 1994). Recent studies in Canada and Denmark have demonstrated relatively stable rates of ECT utilization over the last 15-30 years (Munk-Olsen, Laursen, Videbech, Rosenberg, & Mortensen, 2006; Rapoport, Mamdani, & Herrmann, 2006). Since the 1980s, the safety of ECT has improved significantly with the introduction of sophisticated cardiopulmonary and electroencephalographic monitoring, better anesthetic agents, and the adoption of the brief-pulse stimulus machine. Today, ECT is arguably the fastest, most effective treatment for mood disorders. ECT is possibly the safest procedure performed under general anesthesia, with a mortality rate reported at 0.002% (Abrams, 1997).

Yet, despite these advances, the availability and use of ECT varies dramatically in different parts of the United States. A 1988 study of ECT usage rates in 317 metropolitan areas reported that there was a wide variation in the use of ECT (from 0.4 to 81.2 patients per 10,000 population), and 36% of the sampled areas did not have ECT available as a treatment (Hermann, Dorwart, Hoover, & Brody, 1995). The strongest predictors of ECT use were the number of psychiatrists, number of primary care physicians, and number of private hospital beds per capita. The stringency of state regulations restricting ECT was negatively associated with ECT use.

Other countries, including Great Britain, Spain, and Ireland, have shown a similar pattern of variation in rates of ECT use (Bertolin-Guillen, Peiro-Moreno, & Hernandez-de-Pablo, 2006; Latey & Fahy, 1985; Pippard, 1981). Although it is unclear whether such differences represent overuse of ECT in some areas or underuse of ECT in other areas, wide variability in the use of other medical and surgical procedures has been hypothesized to result from a lack of consensus in the medical community regarding the appropriate use and efficacy of a particular medical procedure (Wennberg, Barnes, & Zubkoff, 1982). ECT is clearly one of the most controversial procedures in medicine, with widely varying beliefs about the safety and efficacy of the procedure among the lay public and medical students (Walter, McDonald, Rey, & Rosen, 2002), as well as psychiatrists and other mental health professionals (Janicak, Mask, Trimakas, & Gibbons, 1985). In the Irish study, one of the most important variables in the availability of ECT was whether the psychiatrist had a favorable attitude toward ECT (Latey et al., 1985). The availability of ECT was more closely related to the physician's perceptions of the procedure rather than to the data indicating the potential benefits of the somatic treatment. Unfortunately, this often leads to a significant lack of access to ECT. Ongoing education of physicians and the public will improve the availability of ECT to all who might benefit from it (Sackeim, 1995).

In the United States, middle and upper socioeconomic groups receive ECT more frequently than do lower socioeconomic groups (Babigian & Guttmacher, 1984; Kramer, 1985), possibly because ECT is used more often in private than in public hospitals (Thompson & Blaine, 1987). Private hospitals have fewer regulations governing ECT, improved financial reimbursement, and a higher percentage of patients with mood disorders that respond to ECT (Hermann et al., 1995). As with many medical treatments, financial incentives have shifted ECT toward the outpatient setting, although this is also due to improved safety and increased use of maintenance and continuation ECT courses.

Older adults receive ECT more often than do younger patients (Kramer, 1985; Thompson et al., 1994), although a 1992 National Institutes of Health consensus panel found that ECT was underused as a treatment for late-life depression (anonymous, 1992). A survey of older adults using Medicare insurance showed that the overall rate of ECT use increased nearly 30% from 1987 to 1992, particularly among women, Caucasians, and the disabled (Rosenbach, Hermann, & Dorwart, 1997). There are several reasons that women may be overrepresented in ECT populations including the increased prevalence of depression in women and the fact that women live longer than men. Racial differences in patients receiving ECT may be related to the above mentioned socioeconomic factors or to differing cultural beliefs about ECT or psychiatric illnesses. Caucasians are more likely to receive ECT than African-Americans (Breakey & Dunn, 2004), while the paucity of information on ECT use in the growing Hispanic-American population has been recently highlighted (Euba & Saiz, 2006; Major, 2005).

Mechanism of Action of ECT

Despite extensive clinical use for more than 60 years and unequivocal documented efficacy, the mechanisms underlying the mechanism of action for ECT remain poorly understood. Theories have ranged from psychological and psychodynamic concepts to neurotransmitter changes, neuroendocrine effects, alterations in intracellular signaling pathways and changes in gene expression (Sackeim, 1994). Some theories are easy to discard. For example, there is no convincing evidence that

ECT causes structural brain damage or that the memory-impairing effects of ECT are associated with clinical improvement (Devanand, Dwork, Hutchinson, Bolwig, & Sackeim, 1994; Weiner, 1984).

Most serious efforts to understand the mechanisms of ECT have focused on changes in neurotransmitter systems and intracellular biochemical processes (for reviews see (Fochtmann, 1994; Newman, Gur, Shapira, & Lerer, 1998; Nutt, 1993)). Researchers have identified changes leading to therapeutic benefits at cellular and systems levels using neurochemical information about ECT from studies of electroconvulsive shock (ECS) in rodents. Repeated seizures, whether electrically induced or spontaneous, clearly result in short and long-term changes in brain function. The assumption is that repeated generalized seizures in animals reflect effects in patients with psychiatric disorders (Lerer, 1984).

An alternative strategy is to examine the effects of ECT on CNS processes for which there is better mechanistic understanding. The assumption is that the effects of ECT on CNS systems are related to the known antidepressant effects of other treatments including psychotherapy, pharmacotherapy and newer brain stimulation techniques such as deep brain stimulation and transcranial magnetic stimulation. Importantly, advances in understanding the neurocircuitry and cellular changes associated with major psychiatric disorders offer hope in defining the effects of ECT that are likely to be important. While all of these strategies have weaknesses, the anticonvulsant hypothesis explains both the effects of ECT on an intracellular level as well as the efficacy of ECT in relation to the anticonvulsant medications used to treat mood disorders.

Anticonvulsant Hypothesis

One of the most popular theories defining the mechanism of action of ECT is that the antidepressant efficacy is directly correlated with the anticonvulsant effect of ECT. That is, the therapeutic effect of ECT is proportional to an increase in the seizure threshold during ECT and a course of ECT results in an increase in seizure threshold and a decrease in seizure duration (Sackeim, 1999). This theory focuses on changes in neurotransmitter systems and intracellular biochemical processes and is supported by the preclinical data of the effect of ECT in modulating seizure threshold.

γ -Aminobutyric acid (GABA) is the predominant inhibitory transmitter in the brain and is a target for multiple anticonvulsant drugs (e.g., barbiturates, benzodiazepines). Data from animal studies demonstrate increases in the threshold for bicuculline- and pentylenetetrazole-induced seizures following a series of ECS (Nutt, Cowen, & Green, 1981; Plaznik, Kostowski, & Stefanski, 1989). Because bicuculline and pentylenetetrazole act by inhibiting GABA_A receptors, these findings suggest that ECT results in changes in GABAergic inhibition. Additionally, GABA levels increase in certain CNS regions after ECS (Green, Sant, Bowdler, & Cowen, 1982), and there is evidence from magnetic resonance spectroscopy that ECT increases GABA levels in occipital cortex in humans (Sanacora et al., 2003). These changes in GABA levels suggest that there may be an increase in tonic inhibition after repeated seizures and effects on GABA-mediated tonic inhibition is increasingly recognized as an important effect of several neuroactive drugs (Farrant & Nusser, 2005). Changes in the GABA_A receptor-chloride channels that are the primary postsynaptic GABA receptors are less certain (Fochtmann, 1994) although it is clear that different receptor subtypes contribute to tonic and phasic (synaptic) inhibition. There is also evidence that ECS enhances the function of GABA_B receptors that mediate pre- and postsynaptic inhibition (Lloyd, Thuret, & Pilc, 1985) and this is likely to contribute to an overall depression of CNS excitation.

An interesting finding in rodents is that repeated seizures cause the release of an anticonvulsant substance into cerebrospinal fluid. Anticonvulsant activity can be transferred to naive animals by intracerebroventricular injections of cerebrospinal fluid from animals that have experienced seizures (Tortella & Long, 1985; 1988). Tortella et al. (Tortella, 1989) found that the anticonvulsant substance is likely to be an endogenous opioid and that treatment with naloxone, an opiate receptor antagonist, blocked anticonvulsant effects of ECS. There is also evidence for upregulation of δ opiate binding sites (e.g., sites for D-alanine-D-leucine enkephalin) after repeated seizures (Hitzemann et al., 1987). Whether similar changes occur in humans is speculative and, to date, efforts to lengthen ECT-induced seizures using naloxone have not been successful (Prudic, Fitzsimons, Nobler, & Sackeim, 1999; Rasmussen, 1998).

Efforts to identify anticonvulsant mechanisms in ECT must account for changes in both seizure threshold and duration, because different mechanisms may govern the two processes. Of note is the finding that adenosine is released extracellularly during seizures and may play a role in seizure termination. Adenosine is an important inhibitory neuromodulator that acts at several receptor types. Adenosine A₁ receptors are upregulated by ECS in the cortex, but not the hippocampus or striatum (Gleiter, Deckert, Nutt, & Marangos, 1989). Clinically, adenosine receptor antagonists like caffeine and theophylline prolong ECT-induced seizures (Hinkle, Coffey, Weiner, Cress, & Christison, 1987) with less effect on seizure threshold (McCall, Reid, Rosenquist, Foreman, & Kiesow-Webb, 1993a). Furthermore, theophylline has been associated with prolonged seizures and status epilepticus during ECT (Rasmussen & Zorumski, 1993). These observations suggest that release of adenosine, and perhaps increased sensitivity of certain adenosine receptors, may contribute to decreases in seizure duration during ECT, although caffeine and theophylline have other effects that could influence excitability, including phosphodiesterase inhibition and release of calcium from intracellular stores (Sawynok & Yaksh, 1993).

Much of the focus in studying anticonvulsant mechanisms of ECT has centered on changes in neural inhibition after repeated seizures. It is also important to consider how ECT influences excitation, particularly the glutamate system that serves as the predominant mode of fast excitatory transmission in the CNS. Seizures are accompanied by acute release of glutamate, but there is less information about the effects of repeated seizures on glutamate release, uptake, and receptors. Although the brain damage that accompanies status epilepticus appears to result, in part, from excessive activation of *N*-methyl-D-aspartate (NMDA) type glutamate receptors (Clifford, Zorumski, & Olney, 1989), seizure-related brain damage typically requires more than 20 minutes of continuous activity and is therefore unlikely to be relevant to ECT (Devanand et al., 1994; Gruenthal, Armstrong, Ault, & Nadler, 1986). Furthermore, there is evidence that repeated ECS actually prevents seizure-related brain damage in some models of status epilepticus (Kondratyev, Sahibzada, & Gale, 2001). Repeated ECS increases mRNA for NR2A and NR2B subunits of the NMDA receptor and decreases the metabotropic receptor, mGluR5b, in dentate gyrus and the CA1 hippocampal region (Watkins, Pei, & Newberry, 1998). These effects are transient and return to control levels within 48 hours. Other studies suggest that repeated ECS decreases NMDA receptor function by altering the potency of glycine for its regulatory site on NMDA receptors, an effect that could diminish the ability of glycine to promote opening of the NMDA ion channel by glutamate (Paul, Nowak, Layer, Popik, & Skolnick, 1994; Petrie, Reid, & Stewart, 2000).

Antidepressant Medication and the Effects of ECT on Mood Disorders

The efficacy of anticonvulsants as mood stabilizers supports the anticonvulsant hypothesis and this hypothesis is appealing in that it can explain the therapeutic effects of ECT in both mania and depression (Sackeim, 1994; 1999). Yet most antidepressants are not anticonvulsants and researchers have investigated other common mechanisms for ECT and antidepressant medication to determine the therapeutic effect of ECT.

There are a number of common threads in the neurotransmitter changes induced by ECT and antidepressant medication. ECT, like antidepressant pharmacotherapy, has been reported to normalize hypothalamic-pituitary-adrenal (HPA) axis perturbations associated with major depression (Yuuki et al., 2005). However, a more productive area of research has focused on determining how a course of ECT affects biogenic amines. Of interest is the finding that certain antidepressants cause β_1 -adrenergic receptor subsensitivity, and similar effects are observed with ECS (Nutt, 1993). ECS has multiple other effects on the adrenergic system, including increased norepinephrine turnover, increased α_1 -adrenergic receptor sensitivity and possibly decreased presynaptic α_2 -adrenergic receptor sensitivity. ECS also enhances the function of the serotonin system, producing increased behavioral responses to serotonin agonists and possibly increases in 5-hydroxytryptamine-type 2 (5-HT₂) receptor binding in the cerebral cortex (Fochtmann, 1994; Nutt, 1993; Sackeim, 1994). The latter effect was initially observed in rodents and differs from changes induced by chronic antidepressant drugs. Studies in nonhuman primates question the rodent results and provide evidence that ECS diminishes 5HT-2 binding in cortex (Strome, Clark, Zis, & Doudet, 2005). Thus, 5-HT₂ receptor downregulation, like β -adrenergic receptor subsensitivity, may be a common mechanism for several antidepressant treatments.

An emerging trend in antidepressant mechanisms is the effect of antidepressants on glutamatergic and GABAergic neurotransmission. In particular, a decrease in the function of NMDA receptors appears to be a mechanism shared by several antidepressant treatments, including ECS (Petrie et al., 2000). In the case of ECS, effects on NMDA receptors appear to be mediated by changes in the glycine regulatory site on these channels. There is also evidence that ketamine, a non-competitive NMDA receptor antagonist, has acute antidepressant properties (Berman et al., 2000; Zarate et al., 2006). Coupled with the possibility that untimely NMDA receptor activation may contribute to ECT-induced anterograde memory problems, the antidepressant effects of ketamine raise the possibility that ketamine or other NMDA receptor blocking anesthetics may be preferred agents for use during ECT.

One of the more intriguing avenues for understanding the effects of ECT is the literature on the neurocircuitry of mood regulation and depression. This circuitry involves connections between and within regions of prefrontal cortex, the anterior cingulate gyrus, subgenual prefrontal cortex, anterior thalamus and more traditional limbic structures (hippocampus and amygdala) (Drevets, 2000; Seminowicz et al., 2004). There is now evidence for structural changes including cell loss (glia and possibly neurons) in several of these regions in subtypes of depression (Harrison, 2002). It also appears that different antidepressant treatments may differentially affect metabolism in this circuit. Effective treatment with paroxetine appears to increase metabolism in frontal regions while decreasing metabolism in hippocampus while cognitive-behavioral therapy results in the opposite effects (Goldapple et al., 2004; Seminowicz et al., 2004). ECT, in contrast, diminishes metabolism in both prefrontal cortex and hippocampus (Nobler et al., 2001). Although it is too early to draw firm conclusions about these observations, it is intriguing that chronic deep brain stimulation (DBS) targeted toward the subgenual prefrontal region appears to be effective in a small sample of chronic, treatment-resistant depressed patients (Mayberg et al., 2005), further implicating changes in this circuitry in the biology of depression.

Coupled with the imaging results noted above, there is evidence that several antidepressant treatments, including ECS, have neurotrophic effects and result in neurogenesis in the dentate gyrus of adult rodents (Madsen et al., 2000; Malberg,

Eisch, Nestler, & Duman, 2000; Scott, Wojtowicz, & Burnham, 2000). These effects may result from changes in brain-derived neurotrophic factor (BDNF) and the Trk-B receptors through which BDNF exerts its actions, as well as effects on the adenylate cyclase intracellular signaling system including the downstream effector, cyclic-AMP response element binding protein (CREB) (Duman & Vaidya, 1998; Nestler et al., 2002; Schloss & Henn, 2004). Other evidence suggests that the new neurons produced in the dentate gyrus of adult rodents have the properties of functional neurons and participate in synaptic transmission (Song, Stevens, & Gage, 2002), suggesting that antidepressant treatments, including ECT, may ultimately enhance hippocampal function. These changes appear to be accompanied by increases in local angiogenesis and possibly blood flow in specific subregions of hippocampus (Hellsten et al., 2005; Newton, Girgenti, Collier, & Duman, 2006). Whether effects on neurogenesis are important for the therapeutic effects of ECT and other antidepressant treatments remains speculative, although elegant studies in rodents provide evidence that neurogenesis is important for at least some behavioral effects of medications (Santarelli et al., 2003). It is uncertain whether similar neurotrophic effects occur with ECT in humans. However, studies using magnetic resonance spectroscopy to monitor regional changes in the glutamate to glutamine ratio (called Glx), a marker of local intracellular excitatory transmitter metabolism (Hasler et al., 2007), indicate that depressed subjects have low Glx values that increase to normal with effective ECT (Michael et al., 2003; Pfliederer et al., 2003). Changes in Glx in depression and ECT may reflect alterations in glial function in the circuitry underlying depression.

Recent efforts to identify mechanisms contributing to the effects of ECS and antidepressant drugs have included the use of microarrays to study gene expression in multiple brain regions. While these studies are in their infancy, there is some evidence that rapidly acting treatments like ECS result in changes primarily in the catecholaminergic system while slower acting treatments, like fluoxetine, act predominantly on the serotonergic system. These studies also show strong effects of ECS on BDNF and transcripts encoding proteins involved in hippocampal synaptic plasticity (Conti et al., 2007). Follow up studies examining protein expression and downstream functional effects will be important in determining relevance to clinical actions.

Efficacy of ECT

Major Depression

Indications

The summary statement by the American Psychiatric Association Task Force on Electroconvulsive Therapy (Association, 2001) and research over the past thirty years (Abrams, 1992; Fink, 1979; O'Connor et al., 2001; Petrides et al., 2001) have confirmed that ECT is an effective treatment in more than 80% of patients with treatment-resistant unipolar or bipolar major depression. A meta-analysis of randomized controlled trials (RCTs) performed by the UK ECT Review Group (2003) confirmed the following related to the efficacy of ECT for major depression: (1) ECT is more effective than sham ECT (6 RCTs, effect size 0.91); (2) ECT is more effective than antidepressant pharmacotherapy (18 RCTs, effect size 0.80); and (3) aspects of ECT associated with positive response included higher total dose and bilateral electrode placement (although many studies likely underdosed unilateral ECT). It is noteworthy, however, that several of these studies compared the response rates in patients receiving ECT to patients on subtherapeutic doses of antidepressants.

Given this data, ECT should no longer be considered a treatment of last resort but a potential first-line treatment when a rapid clinical response is essential in severely ill patients (e.g. those with active suicidal ideation, malignant catatonia or medical compromise related to depression such as dehydration/malnutrition), when the patient has a history of a positive response to ECT, or when the patient and family request ECT over other treatment options. ECT generally exerts its antidepressant effects more rapidly than pharmacotherapy, and recent research has confirmed a rapid resolution of suicidal ideation with ECT (Kellner et al., 2005; Patel, Patel, Hardy, Benzies, & Tare, 2006). Beale and Kellner (Beale & Kellner, 2000) argued that the use of ECT after multiple failed medication trials does not take into account the tolerability and efficacy of modern ECT and may lead to needless suffering on the part of the patient. They pointed out that antidepressant algorithms use ECT as a tertiary treatment (see, e.g., Rush et al. (Rush & Thase, 1997)) instead of involving ECT practitioners early in the treatment to determine whether ECT would be appropriate. Surveys show that patients who have received ECT rate ECT as a highly effective treatment (Parker, Roy, Wilhelm, & Mitchell, 2001), and 85% of the patients who have received ECT would agree to a second course of ECT if needed (Bernstien, 1998). ECT-related relief of depression symptoms has also been associated with long-term improvements in health-related quality of life, an increasingly important outcome measure in medical research (McCall, Prudic, Olfson, & Sackeim, 2006).

Predictors of Response

Clinical predictors of response to ECT have not been consistent across studies. Potential positive predictors of response include increasing age (Dombrovski et al., 2005; O'Connor et al., 2001) and the presence of psychotic and catatonic symptoms (Birkenhager, van den Broek, Mulder, & de Lely, 2005; Buchan et al., 1992; Petrides et al., 2001). Several studies have reported that patients with longer current episodes of depression (Dombrovski et al., 2005; Prudic et al., 1996) or personality disorders (e.g. borderline personality disorder) (Feske et al., 2004; Parker et al., 2001) are less likely to respond to ECT. Patients with depression complicated by dysthymia (i.e., double depression) appear to respond to ECT to the same extent that patients without dysthymia do (Prudic, Sackeim, Devanand, & al., 1993). Attempts to link subtypes of depression (e.g. melancholic versus atypical, unipolar versus bipolar) to the likelihood of ECT response have generally failed to reveal differences. However, response by session 3 of ECT may predict long-term efficacy relieving depression (Tsuchiyama et al., 2005).

Medication resistance also has been consistently correlated with a failure to respond to ECT. Patients who had failed one or more antidepressant trials before ECT responded less favorably to ECT than did patients who had not failed a medication trial before ECT (Devanand, Sackeim, & Prudic, 1991; Dombrovski et al., 2005; Prudic, Sackeim, & Devanand, 1990; Sackeim et al., 1990). This finding held up for resistance to the heterocyclic antidepressants but not the selective serotonin reuptake inhibitors or monoamine oxidase inhibitors (MAOIs) (Prudic et al., 1996).

To date, the most consistent biological marker for ECT response has been increased frontal delta activity (i.e. postictal depression) on the electroencephalogram (EEG) post-ECT (Mayur, 2006; Sackeim et al., 1996) associated with decreased cerebral blood flow (CBF) in the immediate postictal period (Nobler et al. 1994). More sophisticated methods of EEG analysis (e.g. nonlinear analysis) may hold promise in helping to discern EEG predictors of antidepressant response to ECT (Mayur, 2006)

Coffey et al. (Coffey, Figiel, Djang, Saunders, & Weiner, 1989) described an increase in structural abnormalities observed on brain magnetic resonance imaging (MRI) scans (e.g., deep white matter, basal ganglia, and periventricular hyperintensities) in elderly depressed patients referred for ECT compared with age-matched control subjects. These preexisting structural brain changes may predispose elderly depressed patients to a less favorable response to ECT (Hickie et al., 1995; Steffens et al., 2001), although case reports indicate ECT may be helpful in the treatment of post-stroke depression (Currier, Murray, & Welch, 1992).

Mania

Early anecdotal reports as well as more recent case studies suggest that ECT is beneficial in the treatment of bipolar mania and delirious mania (Fink, 2001b; 2006). Recently, ECT also has been shown to be effective for treatment-resistant mixed mood disorders (Gruber, Dilsaver, Shoaib, & Swann, 2000). Given the benefit of anticonvulsant medications in mania and the evidence that ECT may exert its therapeutic effect by raising the seizure threshold (Sackeim, 1999), there is a theoretical basis to assume that ECT is effective in the treatment of mania. Since 1970, several retrospective studies have confirmed the efficacy of ECT in mania, with approximately two-thirds of patients showing marked clinical improvement (Mukherjee, Sackeim, & Schnur, 1994). In a prospective controlled trial, Small et al. (Small et al., 1988) compared the efficacy of ECT with that of lithium in the treatment of mania. Patients who received ECT improved more during the first 8 weeks of treatment than did patients who received lithium. Nevertheless, after 8 weeks of treatment, ECT and lithium were comparable in efficacy. In addition, patients with mixed symptoms of depression and mania responded particularly well to ECT. Catatonia may be particularly common in bipolar disorder and represents another scenario in which ECT may offer advantages in efficacy and rapidity of response versus pharmacotherapy (Taylor & Fink, 2003). Challenges specific to treating mania with ECT include the following: (1) concomitant use of anticonvulsants, which may interfere with seizure induction in ECT; (2) reports of prolonged seizures and delirium when ECT is given with lithium (Sartorius, Wolf, & Henn, 2005), though other authors have reported safe co-administration of ECT and lithium (Dolenc & Rasmussen, 2005); and (3) the decreased likelihood that manic (versus depressed) patients will voluntarily consent to ECT treatment.

Despite the rapid increase in studies evaluating alternative antimanic medications, including newer anticonvulsants and the atypical antipsychotics, there is a lack of research comparing the potential benefits of ECT in the acute and maintenance treatment of bipolar disorder (Fink, 2001b; Keck et al., 2000). This is regrettable given the advantages of ECT as a true mood stabilizer that can effectively treat both the manic and the depressed phases of the illness. ECT also has been given safely to

children with intractable mania (Hill, Courvoisier, Dawkins, Nofal, & Thomas, 1997) and to dementia patients with comorbid mania (McDonald, 2001). ECT also may have an important role in the treatment of mania during pregnancy, given the potential teratogenic effects of many anticonvulsants as well as the potential harm to both the mother and the fetus from a prolonged affective episode.

Controversy persists over whether unilateral ECT is as effective as bilateral ECT in the treatment of mania. Unfortunately, studies comparing unilateral and bilateral ECT in the treatment of mania have not reported either the amount of electrical charge used or the percentage by which the electrical stimulus exceeded the seizure threshold. Daly et al. (Daly et al., 2001) compared 228 patients with bipolar and unipolar depression who were randomized to ECT conditions that differed in electrode placement and stimulus intensity. They found that the bipolar patients had a rapid response and did not differ from the unipolar patients in either the rate of response or the response to unilateral or bilateral ECT. ECT also has been shown to be effective in the treatment of mixed mania (Ciapparelli et al., 2001). Future research is clearly needed to clarify the role of ECT in the treatment of mania, although clear evidence indicates that ECT is an effective treatment and should be included in any algorithm for treatment-resistant or severely disabling mania.

Schizophrenia

With the introduction of clozapine and the atypical antipsychotics, the use of ECT has become a third-line treatment in schizophrenia, although ECT continues to have an important role in the treatment of an acute psychotic break, catatonic schizophrenia, and neuroleptic malignant syndrome. Although the mechanism of action of ECT in treating psychosis has received much less attention than its antidepressant effects, one possible mechanism for ECT's antipsychotic effects has been inferred from the therapeutic action of ECT in patients with phencyclidine-induced psychosis (Dinwiddie, 1988). One of the major actions of phencyclidine and related drugs (e.g., ketamine) is open channel block of NMDA receptors. Phencyclidine block is voltage-dependent and long-lived, with the ion channel closing around the phencyclidine molecule (MacDonald et al., 1991). Relief of channel block requires NMDA ion channels to open at depolarized membrane potentials (Huettner & Bean, 1988). Thus, neuronal membrane depolarization and glutamate receptor binding are important for allowing phencyclidine to exit the channel. Although it is not certain that block of NMDA channels causes phencyclidine psychosis, it is interesting that ECT-induced seizures have the requisite effects to relieve the channel block. During a seizure, neurons depolarize (via synaptic excitation and action potential firing), and glutamate is released at synapses. These events together would be expected to relieve phencyclidine-induced block and could provide a rationale for the effectiveness of ECT. As a corollary, this mechanism would also lead to the prediction that use of ketamine for anesthesia during ECT should be associated with a low incidence of ketamine-induced psychosis.

Fink and Sackeim (Fink & Sackeim, 1996) reviewed the use of ECT in the treatment of schizophrenia and cautiously noted that most studies examining the efficacy of ECT in treating schizophrenia do not meet present standards for scientific methodology. Nonetheless, the authors concluded that ECT is a highly effective treatment for psychosis and that it should be considered particularly in patients with schizophrenia and an initial psychotic episode, symptoms of agitation, increased psychomotor activity, delirium, or delusions. The authors also concluded that ECT is effective in treating schizophrenia when catatonia, prominent affective symptoms, or positive symptoms of psychosis (e.g., hallucinations) are present. They speculated that the use of ECT early in the course of schizophrenia may decrease the progressive, debilitating effects of the illness.

ECT combined with neuroleptics has been shown to be more effective than ECT or neuroleptics alone in treating schizophrenia (Friedel, 1986; Gujavarty, 1987; Klapheke, 1993; Sajatovic, 1993). A recent meta-analysis of the four most methodologically sound studies of ECT augmentation to antipsychotics for schizophrenia concluded that ECT offered a modest but significant benefit (the equivalence of five points on the Brief Psychiatric Rating Scale) compared to neuroleptic therapy alone (Painuly & Chakrabarti, 2006). The effects are apparent in the first several weeks of treatment, but appear to diminish with more prolonged treatment. Interestingly, all of these studies were conducted in India, where ECT use for schizophrenia appears more common than in the US. Notably, open-label and case studies suggest ECT may be safe and helpful in combination with clozapine, another treatment also typically reserved for more refractory illness (Havaki-Kontaxaki, Ferentinos, Kontaxakis, Pappas, & Soldatos, 2006). ECT combined with neuroleptic therapy might also be effective in the management of aggressive behavior in patients with schizophrenia (Hirose, Ashby, & Mills, 2001) and maintenance treatment of schizophrenia (Chanpattana, 1999b).

The recommendations of the American Psychiatric Association Task Force on Electroconvulsive Therapy (Association,

2001) state that ECT is an effective treatment for schizophrenia in the following clinical conditions: 1) during acute onset of symptoms, 2) when the catatonic subtype of schizophrenia is present, and 3) when there is a history of a positive response to ECT. Not surprisingly, patients with an affective component (i.e., schizoaffective patients) also respond more favorably to ECT. ECT also represents a potentially life-saving intervention for neuroleptic malignant syndrome that does not respond to more conservative treatments (e.g. supportive care or pharmacotherapy). Clearly, there is a need for further research related to the role of ECT in treating schizophrenia.

Parkinson's Disease

ECT has been shown to be effective in the treatment of the motor symptoms of patients with Parkinson's disease (PD) (Faber & Trimble, 1991; Kellner, Beale, Pritchett, Bernstein, & Burns, 1994; Rasmussen & Abrams, 1991), and a recent meta-analysis of five studies confirmed that ECT acutely improves global motor functioning in PD (Fregni, Simon, Wu, & Pascual-Leone, 2005). These reports have included patients with and without psychiatric illnesses, and ECT improves the motor symptoms of Parkinson's disease independent of its effects on mood. Because antimuscarinic drugs are useful in treating parkinsonism, the effects of ECT on central muscarinic systems may be relevant (Fochtmann, 1988). However, ECT also alters central dopaminergic systems that are involved in the pathophysiology of Parkinson's disease (Fochtmann, 1994). Acutely, ECS increases dopamine levels in the frontal cortex and striatum and has variable effects on basal dopamine levels. Furthermore, dopamine autoreceptor sensitivity is diminished after ECS, an effect that would tend to augment dopamine release. There is also evidence that dopamine, subtype 1 (D_1), receptor agonists cause increased stimulation of adenylate cyclase after ECS. However, after ECS D_1 dopamine receptor binding is increased in the substantia nigra (Fochtmann, Cruciani, Aiso, & Potter, 1989), but not in the striatum (Nowak & Zak, 1989).

Favorable predictors of response include advanced age, severe disability ("on-off" syndromes), and painful dyskinesias. Reduction in the symptoms of Parkinson's disease tends to occur during the first several sessions of ECT. However, the effects from ECT are not permanent and usually last from several days to several months, although prolonged improvement has been reported in a few patients. Maintenance ECT also has been shown to be effective for up to 4 years in treating the motor symptoms of Parkinson's disease (Aarsland, Larsen, Waage, & Langeveld, 1997; Wengel, Burke, Pfeiffer, Roccaforte, & Paige, 1998).

Because of the increased risk for ECT-induced interictal delirium in patients with Parkinson's disease (or any neurological disease such as stroke or Alzheimer's disease), careful consideration must be given to the amount of electrical charge administered, the type of electrode placement used, and the frequency of treatments (Figiel et al., 1991). The delirium associated with ECT in Parkinson's disease patients can be significantly reduced without losing efficacy by 1) using right-unilateral ECT with an initial electrical stimulus approximately 3.5 times the seizure threshold, 2) administering ECT treatments every 3–4 days, 3) withholding the dose of levodopa on the morning of ECT, and 4) discontinuing ECT until the cognitive impairment completely resolves if any impairment in attention or orientation develops and then restarting ECT at a lower electrical charge.

Other Illnesses

ECT can be a lifesaving treatment in catatonia regardless of the etiology, including catatonia from a medical disorder (e.g., lupus erythematosus), neuroleptic malignant syndrome, schizophrenia, bipolar disorder, and unipolar depression (Fink, 1994; Fink, 1997).

Limited evidence suggests ECT may relieve symptoms associated with obsessive-compulsive disorder (OCD) (Maletzky, McFarland, & Burt, 1994; Thomas & Kellner, 2003) and schizophrenia complicated by OCD (Lavin & Halligan, 1996). Because it raises the seizure threshold, ECT can interrupt status epilepticus (Fink, Kellner, & Sackeim, 1999; Lisanby et al., 2001a) and treat intractable seizures (Griesemer, Kellner, Beale, & Smith, 1997; Regenold, Weintraub, & Taller, 1998). ECT also has been shown to be safe and effective in the treatment of comorbid mood disorders in patients with closed head injuries (Kant, Coffey, & Bogyi, 1999), dementia (McDonald, 2001), and mental retardation (Aziz, Maixner, DeQuardo, Aldridge, & Tandon, 2001; Fink, 2001a; Friedlander & Solomon, 2002; Gabriel, 1998; Waarde van JA, 2001). ECT may exert some analgesic effects independent of effects on mood, as evidenced in a recent positive trial of ECT for fibromyalgia (Usui et al., 2006).

During pregnancy, ECT may be an effective, safe treatment for bipolar disorder or major depression, and is recommended by the APA practice guidelines (Association, 1994) as a possible first-line treatment in for pregnant women

with mood disorders. ECT has been safely used in all three trimesters of pregnancy (Rabheru, 2001), although prospective, controlled studies of ECT in pregnancy are lacking. Miller's (Miller, 1994) review of more than 400 cases of ECT in pregnancy failed to identify a consistent pattern of complications; more recent case reports have associated ECT with premature labor (Bhatia, Baldwin, & Bhatia, 1999; Echevarria Moreno, Martin Munoz, Sanchez Valderrabanos, & Vazquez Gutierrez, 1998). The risks and risk management strategies for administering ECT during pregnancy have been reviewed by Rabheru (Rabheru, 2001).

The treatment of mania during pregnancy can be particularly difficult given the reported teratogenicity of several antimanic medications. Although the initial registry data suggested that lithium use in the first trimester was associated with an increased risk of cardiac anomalies, more recent prospective, case-controlled studies have shown only weak teratogenic effects (Cohen, Friedman, Jefferson, Johnson, & Weiner, 1994). Carbamazepine and valproic acid are both associated with neural tube defects (Oakshott and Hunt 1994). Many of the other medications, including atypical antipsychotics, benzodiazepines, and antidepressants, have less clear effects on the fetus. Yet the complications of untreated or partially treated bipolar disorder endanger both the mother and the fetus and include poor compliance with neonatal care, impaired judgment, substance abuse, poor nutrition and self-care, and depression with suicide attempts (Miller, 1993).

Stimulus Dosing in ECT for Treatment of Depression

Questions about the proper management of the electrical stimulus have been central to the science and practice of ECT since the inception of the treatment. Cerletti and Bini modeled ECT on the success of pharmacologically induced convulsive therapy and assumed that the stimulus should be convulsive. Interestingly, the first ECT session in 1938 involved two subconvulsive stimulations before Cerletti and Bini increased the stimulus intensity to produce a convulsion (Endler, 1988). Thus, the first ECT session was a "titrated" ECT session involving the serial application of increasing stimulus intensities passing from the subconvulsive range through the convulsive threshold. Issues in stimulus dosing that have been considered since that time have included 1) whether the stimulus should be subconvulsive or convulsive; 2) what the optimal stimulus waveform is; 3) if a convulsive stimulus is desired, to what degree the stimulus intensity should be in excess of the convulsive threshold; and 4) which physiological parameters, if any, provide useful feedback to continuously refine stimulus dosing throughout the ECT course.

Convulsive, Subconvulsive, and Sham Stimulation

The use of nonconvulsive electrical stimulation to treat psychiatric disorders preceded the introduction of ECT by decades. Most of the treatments involved administering static electricity to parts of the body not limited to the head (Grover, 1924). The availability of commercial ECT devices did not mean the immediate replacement of subconvulsive with convulsive stimulation. Instead, some practitioners used the devices to deliver lengthy (several minutes long) subconvulsive cranial stimulation. However, it became clear that subconvulsive stimulation was associated with a *poorer* outcome than conventional psychotherapy in psychoneurotic patients, and the practice of treating patients with subconvulsive stimuli decreased (Hargrove, 1953). Many years later, the use of rapid-rate transcranial magnetic stimulation (rTMS) has again raised the question of whether subconvulsive stimuli are an effective treatment for depression and this data will be reviewed in a later section.

The elements of modified ECT (including muscle relaxation and general anesthesia) were described early in the history of ECT. The wide-scale adoption of these modifications raised new questions as to whether the seizure was central to the antidepressant efficacy of ECT or whether anesthesia alone would be just as effective. The Northwick Park trial (Johnstone et al., 1980) and the Leicestershire trial (Brandon et al., 1984) are examples of two "sham" ECT studies in which anesthesia alone was compared with real ECT. It was convincingly demonstrated that real ECT was more effective, especially for the most severe forms of depression (Brandon et al., 1984; Group, ; Johnstone et al., 1980). The effectiveness of ECT was clearly linked to the production of a seizure. Neither anesthesia alone without the electrical stimulus nor the use of subconvulsive stimuli appears to have real merit in the treatment of depression.

Stimulus Waveform

Given that a convulsive stimulus is necessary for the antidepressant effects of ECT, a nearly infinite number of variations were available for formulating the stimulus waveform. The earliest ECT devices delivered a sinusoidal stimulus. Other waveforms available on early ECT devices included the "chopped" sine wave, the unidirectional pulse square wave, and the alternating brief-pulse square wave. Although some investigators had a suspicion that sine wave stimuli may have produced slightly better antidepressant effects than did brief-pulse stimuli, these suspicions were mitigated by a randomized

study showing that sine wave ECT produced more memory side effects than brief-pulse ECT, irrespective of the placement of the stimulating electrode (Weiner, 1986a). This finding was recently replicated in an effectiveness study using a prospective cohort study, this time showing that compared with brief pulse stimulation, sine wave stimulation was associated with a slowing of reaction time that persisted for at least 6 months after ECT (Sackeim et al., 2007). The more severe cognitive side effects produced by sinusoidal stimuli may be explained by the slower rise time for each sine wave cycle as compared with the brief-pulse cycle. Consequent to its slower rise time, much of the sine wave stimulus is subconvulsive and thus presumably adds nothing to the therapeutic effect of ECT, adding only to cognitive side effects. The steep rise in the brief-pulse waveform allows for the entire stimulus to be above the convulsive threshold (suprathreshold). Because much of the sine wave stimulus is "wasted" in the subconvulsive range, it would be predicted that brief-pulse stimuli would be more efficient, requiring a stimulus of smaller magnitude to produce a seizure. "Standard" brief pulse stimuli are defined by pulse duration of 1-2 milliseconds (ms), while 'ultrabrief' pulse stimuli are defined by pulse duration of 0.25-0.50 ms.

In 1980, Weiner showed that standard brief-pulse stimuli could provoke a seizure with only one-third of the energy required with sine wave stimuli (Weiner, 1980). In the last decade, standard brief-pulse ECT devices replaced sine wave devices in the United States (Farah, 1993). New devices using ultrabrief stimuli have the advantage of improving the efficiency of seizure induction. Abrams estimated that it takes only about 0.25 msec to initiate neuronal depolarization, and wider pulse widths are inefficient and waste electrical charge (Abrams, 2002). The total energy output of these ultrabrief pulse modalities is the same as the total energy output of the standard pulse widths; thus, as the stimulus pulse widths are shortened, the stimulus trains are lengthened. Ultrabrief pulse widths may have an advantage because shorter pulse widths and longer pulse trains have been shown to elicit seizures with smaller electrical charge and therefore may have fewer cognitive side effects (Sackeim et al., 2001b). Similarly, decreasing the frequency of pulses with a corresponding lengthening of the stimulus train will improve the efficiency of seizure induction (Kotresh, Girish, Janakiramaiah, Rao, & Gangadhar, 2004).

Magnitude of the Stimulus Dose

The consensus regarding the need for convulsive (as opposed to subconvulsive) stimuli and brief-pulse waveforms would seem to make stimulus dosing in ECT a straightforward process, except for the question of the degree to which the stimulus should exceed the convulsive threshold. For years, ECT practitioners were satisfied that the answer to this question was found in the work of Ottosson, who compared routine ECT with ECT modified by pretreatment intravenous lidocaine (Ottosson, 1962). He found that seizures induced by lidocaine-modified ECT were shorter than those induced by routine ECT, and an inverse relation was found between seizure duration and antidepressant effect. From this work, it was widely accepted that stimulus doses producing seizures longer than 25-30 seconds had an antidepressant effect (Therapy, 1978).

Initially, ECT was administered using bitemporal or bilateral placement. In 1949, Goldman introduced right-unilateral ECT and placed stimulating electrodes over the right hemisphere rather than the mesial temporal lobes in an attempt to decrease the direct stimulation of language areas and decrease cognitive side effects. Although right-unilateral ECT was associated with fewer cognitive side effects, most studies showed that bilateral ECT had a marked therapeutic advantage over unilateral ECT (d'Elia & Raotma, 1975).

The clinical wisdom that bilateral ECT was more efficacious than right-unilateral ECT came into question with the groundbreaking work of Sackeim's research group. Sackeim et al. (Sackeim et al., 1993) reported that if the magnitude of the electrical stimulus was just barely above the convulsive threshold, then ECT was ineffective with right-unilateral electrode placement, despite the production of electrographic seizures typically in excess of 25 seconds. In contrast, bilateral ECT was fully effective with stimuli minimally above or 2.5 times the seizure threshold, but excess memory side effects accrued at the higher stimulus dose.

The dose-response relationship of right-unilateral ECT is true to the extent that the stimulus exceeded the convulsive threshold for a given patient and was not related to the absolute magnitude of the stimulus dose. The efficiency of right-unilateral ECT follows a nearly linear relationship to the degree that the stimulus dose exceeds the seizure threshold, at least through 12 times the seizure threshold (McCall, Reboussin, Weiner, & Sackeim, 2000). This relationship is analogous to the pharmacological treatment of depression with tricyclic antidepressants: serum blood levels are more important than the absolute oral dose in determining both efficacy and side effects.

These findings led to the following conclusions: 1) with standard brief pulse stimulation delivered with right-unilateral electrode placement, the stimulus should be substantially above the convulsive threshold to ensure the efficacy of ECT, and 2) with standard brief pulse stimulation delivered with bilateral electrode placement, the stimulus should not be excessively above the convulsive threshold to avoid undue cognitive side effects. The convulsive threshold varies by a factor of at least 40-fold in large patient samples, thus making the mean threshold for a group of patients useless for individual cases (Sackeim, Devanand, & Prudic, 1991). It is clear that the convulsive threshold is related to age, sex, race, choice of stimulating electrode placement, and, perhaps, cranial dimensions (Chung, 2006; Colenda & McCall, 1996; McCall, Shelp, Weiner, Austin, & Norris, 1993b; Sackeim et al., 1991). Still, these factors predict only a small amount of the variance in

the convulsive threshold. Statistical models to predict the convulsive threshold fare poorly, including age-based dosing approaches (Colenda et al., 1996; Tiller & Ingram, 2006).

Seizure Morphology

The report of Sackeim et al. that threshold right-unilateral ECT produced seizures of 25 seconds or longer without antidepressant efficacy cast into doubt the clinical wisdom that the stimulus dose was therapeutic if the electrographic seizure lasted 25 seconds (Sackeim et al., 1993). Investigators have sought to find a physiological marker of treatment adequacy to replace seizure duration. The most promising candidate is seizure morphology. Ottosson (Ottosson, 1962) reported that lidocaine changed the shape of ECT seizures and affected duration, although the first finding is largely overlooked. Lidocaine-modified seizures, in addition to being less efficacious than standard ECT seizures, were characterized by loss of spike activity and poor postictal suppression.

This finding is now extended by evidence that seizure morphology varies with ECT techniques. That is, greater seizure intensity is correlated with ECT techniques that progress from lower (right-unilateral, low stimulus intensity) to higher (bilateral, high stimulus intensity) efficacy (Krystal et al., 1993). Electrode placement and stimulus intensity have independent and additive effects on seizure morphology. Seizures of greater intensity are characterized by higher peak ictal amplitudes, greater stereotypy of the ictal discharge, greater symmetry and coherence between the left and right cerebral hemispheres, and more profound postictal suppression. Preliminary evidence suggests that greater seizure intensity is predictive of greater likelihood of response and/or faster response (McCall, Farah, Raboussin, & Colenda, 1995; Nobler et al., 1993).

The natural extension of this reasoning leads to the hope that seizure morphology could guide decisions about stimulus intensity as the course of ECT progresses. For example, if seizure intensity is poor in the middle of the treatment course, then treatment technique should be changed (by switching electrode placement and/or increasing the stimulus intensity) in order to optimize clinical outcome. Manufacturers of ECT devices now incorporate automated measures of seizure intensity onto the ECT chart recorder, and the accompanying owner's manual instructs the practitioner to increase the stimulus intensity if the seizure morphology appears to be degraded. The unstated implication is that poor seizure morphology is a problem and that increasing the stimulus intensity will fix the problem. This instruction might have merit if stimulus intensity were the primary determinant of seizure morphology, but other factors, such as age, baseline convulsive threshold, and other intrinsic patient factors likely play an equal role in determining the seizure expression (McCall, Robinette, & Hardesty, 1996; McCall et al., 1998). For example, longer electrographic seizure durations coupled with greater EEG seizure regularity at the second ECT session are predictive of better antidepressant outcome at the conclusion of the ECT course, and this relationship is independent of choice of stimulus electrode placement (Rosenquist, Kimball, & McCall, 2007).

Poor seizure morphology (e.g., in older patients with high thresholds) is little influenced by increasing the stimulus intensity above 2.5 times the seizure threshold. Therefore, it is premature to recommend stimulus dosing on the basis of seizure morphology. The importance of seizure morphology in predicting clinical outcome is far from being understood, and more work is needed to make it a practical tool for governing ECT technique. Peak heart rate has been proposed as an alternative physiological measure of treatment adequacy, with higher heart rate perhaps indicating better clinical outcomes (Swartz, 2000). Again, this approach has yet to be widely accepted.

Integrating the Science of Stimulus Dosing with the Choice of Electrode Placement

The recent advances in knowledge pertaining to stimulus dosing leads to the conclusion that standard brief pulse right unilateral ECT should be initiated with a stimulus known to be ≥ 5 -times the seizure threshold, while standard brief pulse bilateral ECT should be initiated with a stimulus dosed about 50% above the seizure threshold. Choosing between these two strategies requires head-to-head comparisons made on the basis of both efficacy and side effects. An indirect test of this question was made by Stoppe et al. in a comparison of 17 older depressed patients randomized to a high fixed dose right unilateral condition contrasted with 22 older patients randomized to a high fixed dose bilateral group (Stoppe, Louza, Rosa, Gil, & Rigonatti, 2006). While the failure of this study to dose according to a known seizure threshold makes the cognitive findings difficult to evaluate, the similar remission rates for right unilateral (88%) and bilateral (68%) suggests that efficacy need not be compromised by choosing right unilateral placement. McCall et al. conducted the first randomized comparison of low dose (1.5-times seizure threshold) bilateral (N=37) versus high dose (8-times seizure threshold) right unilateral (N=40) (McCall et al., 2000). Again, antidepressant rates were not significantly different for right unilateral (60%) and bilateral (73%), and memory effects were likewise similar. This study can be criticized for insufficient power to detect small but meaningful effects. This concern was addressed by the subsequent study by Haskett et al. contrasting 339 patients randomized in a balanced design to either standard brief pulse right unilateral administered at 6-times seizure threshold or

bilateral at 1.5-times seizure threshold. While antidepressant effects were again indistinguishable, the extent of autobiographical memory loss was greater in the bilateral group (Haskett et al., 2007). This study solidifies the position of high dose right unilateral as the preferred initial strategy. Even if patients fail to respond to an initial approach using right unilateral, increasing the stimulus intensity with right unilateral is associated with a subsequent antidepressant response equal to switching to bilateral, and with fewer cognitive side effects (Tew et al., 2002).

The bulk of the evidence thus suggests that it is desirable to dose the stimulus as a proportion of the convulsive threshold and that the convulsive threshold of each patient should be known, preferably by measuring convulsive threshold early in the ECT course. The most accurate means of measuring the convulsive threshold for a given patient is empirical observation: giving intentionally subconvulsive stimuli at the first treatment and then, in the same session, administering successively larger stimuli until a seizure is produced. This stimulus "titration" technique defines the convulsive threshold for each patient. This conclusion pertains specifically to right unilateral and bilateral electrode placement. Although bifrontal electrode placement is a subject of interest, there is insufficient information regarding the stimulus dose-response relationships to make any dosing recommendations regarding bifrontal electrode placement at this time.

If ECT practitioners follow the above reasoning and the stimulus dosing technique, then most practitioners should titrate the convulsive threshold at the first ECT session. However, some ECT researchers have argued against titration of unilateral ECT and instead have encouraged practitioners to use fixed, high-dose unilateral ECT, (Abrams, 2002) or else a fixed, moderate dose bilateral (Kellner, 2001). In fact, a survey of ECT practitioners in 1993 showed that only a minority perform titration of the stimulus dose (Farah, 1993). The reasons for this are unclear, but possible explanations include concerns that 1) the subconvulsive stimulation inherent in stimulus titration might be medically dangerous, 2) subconvulsive stimulation might add to memory side effects, or 3) producing a barely suprathreshold seizure with right-unilateral placement is an ineffective treatment, thus "wasting" the first treatment.

It is true that subconvulsive stimulation transiently slows the heart rate, and if subconvulsive stimulation is given in the presence of β -blockers and no anticholinergic drug, there is risk of substantial asystole (McCall, Reid, & Ford, 1994). On the other hand, atropine pretreatment eliminates this risk. The possibility of excess acute cognitive side effects with subconvulsive stimuli has been examined and discounted (Prudic, Sackeim, Devanand, Krueger, & Settembrino, 1994). The possibility of a sluggish antidepressant response when a titrated, "moderately" suprathreshold approach is combined with right-unilateral placement, however, is a real concern. A prospective randomized trial of a titrated, moderately suprathreshold dosing strategy with right-unilateral electrode placement in older depressed subjects produced a slower antidepressant response than did a fixed, high-dose stimulus with right-unilateral electrode placement (McCall et al., 1995). Similar results were seen in a naturalistic comparison of young adults receiving titrated right unilateral placement at 2-3 times the seizure threshold as compared with right unilateral at a fixed high dose (Ward, Lush, Kelly, & Frost, 2006). Interpretation of these studies is made more difficult because of differences between treatment assignments (titrated vs. fixed dose; moderate vs. high dose). At the very least, however, it is clear that different dosing strategies affect the antidepressant outcome of right unilateral ECT, even when the doses being compared are substantially above the convulsive threshold.

Abrams (Abrams, 2002) recommended that the most efficient method of administering unilateral ECT is to use 100% of the maximum device capacity and a pulse width of 0.25–0.50 msec and change to bilateral ECT if the patient does not improve sufficiently. However, insufficient data support the routine use of ultrabrief pulse widths (Fink, 2002), and use of seizure titration to establish a dose relative to the seizure threshold would potentially decrease cognitive problems while ensuring an adequate seizure (Rasmussen, 2002). Alternatively, twice-weekly bilateral ECT could be started using the half-age method (Abrams, 2002). The half-age method takes the age of the patient divided by 2, and that number is the percentage of maximal output of the machine at which the patient is first treated (e.g., a 50-year-old would be treated at 25% maximal output). Kellner (Kellner, 2001) recommended an alternative fixed-dose strategy that involved starting with 75% maximal output for right-unilateral ECT and 30%–60% output for bilateral ECT.

Our recommendations for stimulus dosing are made with the following two caveats: 1) recommendations can be made only in regard to major depression, as it is unknown whether dosing strategies for other diagnoses should be the same as those for depression and 2) dosing recommendations can be made only in the context of the chosen electrode placement and the patient's clinical condition. It is clear that a supraconvulsive stimulus is necessary to obtain an antidepressant effect with right-unilateral ECT. It is unclear if any supraconvulsive stimulus will have equivalent antidepressant efficacy with bilateral electrode placement, but a stimulus at least 2.5 times the convulsive threshold is required for right-unilateral ECT in most patients.

Those patients with the most serious complications of major depression (i.e., active suicidal behavior in the hospital, catatonia, or food refusal) merit an approach most likely to yield quick antidepressant results. In such circumstances, bilateral ECT with a relatively high, fixed dose (e.g., 50% of maximal output) could be justified; stimulus dose titration would not be required because concern about cognitive side effects becomes a purely secondary issue, based on the severity of the

patient's clinical status. However, whether fixed, high-dose right-unilateral ECT could provide an equally fast and effective response needs to be examined.

In contrast, a depressed patient in whom medication has failed but who is otherwise not urgent may be an appropriate candidate for right-unilateral ECT at 5–6 times the seizure threshold, especially if cognitive side effects are a concern or the patient is being treated in an outpatient setting. The patient can start with right-unilateral ECT and after five or six treatments change to bilateral ECT if he or she has not had an adequate response. Other special situations favoring titrated right-unilateral ECT include depressed patients with comorbid dementia and other neurological conditions such as Parkinson's disease. The treatment of these patients should minimize even transient memory side effects and may include starting at a very conservative unilateral dose (i.e., 3.5 times the seizure threshold) and increasing the dose as tolerated.

Other dosing strategies, such as titrated bilateral or high, fixed-dose right-unilateral ECT, occupy the strategic middle ground between titrated right-unilateral and fixed-dose bilateral ECT for patients whose condition is of intermediate acuity. One promising area of research is the development of bifrontal ECT, which has the potential for providing the efficacy of bilateral ECT with a cognitive side-effect profile similar to that of right-unilateral ECT. In bifrontal ECT, the electrodes are placed 5 cm above the lateral angle of each orbit in a line parallel to the sagittal plane in order to directly stimulate the frontal lobes, which have been implicated in the pathology of major depression (Nobler et al., 2000) and response to ECT (Nobler et al., 1993). Compared with bilateral and right-unilateral ECT, bifrontal ECT would potentially spare the temporal lobes and decrease cognitive side effects. Preliminary research has shown that bifrontal ECT is comparable in efficacy to bilateral ECT, and preliminary evidence indicates that bifrontal ECT (at or 1.5 times the seizure threshold) has fewer cognitive side effects than bilateral ECT (Bailine et al., 2000; Lawson et al., 1990; Letemendia et al., 1993; Ranjkesh, Berekatani, & Akuchakian, 2005). A retrospective chart review of 76 patients found that bitemporal ECT was more effective than bifrontal ECT with modestly increased side effects (Bakewell, Russo, Tanner, Avery, & Neumaier, 2004).

In a study comparing right-unilateral and bifrontal ECT, Heikman et al. (Heikman et al., 2002) randomized 24 depressed patients to high-dose right-unilateral (5 times the seizure threshold), moderate-dose right-unilateral (2.5 times the seizure threshold), or low-dose bifrontal (just above the seizure threshold) ECT. It was found that seven of eight patients (88%) treated with high-dose right-unilateral ECT had their depression remit compared with just 43% (three of seven) of the patients in the low-dose right-unilateral and bifrontal groups (the difference was not statistically different). All three groups were similar in cognitive changes measured by the Mini-Mental State Exam (MMSE; (Folstein, Folstein, & McHugh, 1975)). Presently it is difficult to know exactly when bifrontal ECT should be used in a clinical ECT service as the research is lagging clinical practice (Loo, Schweitzer, & Pratt, 2006). A multisite study funded by the NIMH is presently underway using more sophisticated cognitive testing and outcome measures to determine whether bifrontal ECT is a viable alternative to high-dose right-unilateral or bilateral ECT.

ECT Techniques

Pretreatment Medical Evaluation

Although there are no medical conditions that are absolute contraindications for ECT, several clinical conditions may increase the risk of complications from ECT:

- Recent myocardial infarction or unstable cardiac conditions
- Any illness that increases intracranial pressure (e.g. brain tumor)
- Recent cerebral infarction, particularly hemorrhagic infarction
- Aneurysm or vascular malformation
- American Society of Anesthesiology (ASA) physical status classification of level 4 or 5
- Severe pulmonary disease

When treating high-risk patients with ECT, clinicians must evaluate the effects of ECT on cerebral and cardiac physiology and data from the extant ECT literature to help develop individual risk-benefit ratios (Applegate, 1997; Association, 2001; Bader, Silk, Dequardo, & Tandon, 1995; Krystal & Coffey, 1997; Weisberg, Elliott, & Mielke, 1991; Zwiil, 1992). All patients should undergo a thorough medical and neuropsychiatric review of systems before beginning ECT. Particular emphasis should be placed on diseases affecting the CNS and the cardiovascular system. The pre-ECT evaluation should include a

physical examination, detailed neurological examination, mental status examination, medical history, and review of systems. The patient's mental status should be evaluated before initiation of ECT and monitored closely before administration of ECT at every session thereafter.

In addition to the physical examination, some basic laboratory tests (blood count and electrolytes) and an electrocardiogram should be done as a part of the baseline screening. Clinicians should obtain a chest X ray in patients with pulmonary disease. Finally, spine films should be considered in patients with a history of back pain, positive findings on physical examination, or medical conditions that may affect the skeletal system. Practically, even patients who are recovering from surgery to repair a broken hip can be safely treated with ECT if appropriate doses of succinylcholine are used to ensure adequate relaxation. The greatest risk for fractures is in the recovery room if the patient has significant postictal confusion and agitation or during the acute ECT course when patients, particularly the elderly and those with Parkinson's disease, are at increased risk for falling.

Information obtained from the patient's neuropsychiatric history should include the following:

- Complications from anesthesia (including a family or personal history of malignant hyperthermia)
- Dementia or other neurological disease
- Any symptoms on neurological examination suggestive of increased intracranial pressure (e.g., severe headaches, new-onset incontinence, or gait ataxia) or primary neurological disease (e.g., lateralizing neurological deficits)

Based on the patient's examination, brain imaging may be ordered before ECT. Some (Kellner, 1996) have called for a reevaluation of the common practice of obtaining brain imaging on all patients prior to ECT. Kellner argues that with proper screening, the number of patients with significant CNS findings on imaging who have normal neurological examination findings is very low, and the expense of routine screening is high.

The clinician also must assess the patient's cardiovascular status, including evidence for dyspnea on exertion, angina, orthopnea, or conditions that might increase the risk of coronary artery disease (e.g., hyperlipidemia, hypercholesterolemia, poorly controlled hypertension, obesity, diabetes). ECT in some ways represents a cardiac stress test, with an abrupt rise in the heart rate and blood pressure occurring after the stimulus. Therefore, one of the most important screens to determine whether a patient can tolerate ECT is accurately assessing exercise tolerance. This can be accomplished by asking questions such as the number of stairs a patient can climb without becoming short of breath. Patients with evidence of coronary artery disease can be screened with a relatively inexpensive treadmill test establishing a peak heart rate of approximately 120. However, ECT patients with severe depression are typically sedentary, elderly, and often unable to tolerate even minimal physical activity. Many would be unable to complete a treadmill test, and more expensive tests, such as a persantine thallium stress test, can be substituted when appropriate.

Establishing a working relationship with a cardiologist is an essential part of developing an ECT service. Often the consulting cardiologist is asked to "clear a patient for ECT" without an understanding of exactly what effects ECT would have on the cardiovascular system. A significant acute risk to the patient undergoing ECT is the potential for a cardiovascular event, and optimizing the management of cardiovascular disease before and during ECT can decrease this risk. Inviting the consulting cardiologist to observe the ECT procedure and including the cardiologist in discussions with both the patient and the family help ensure that all the involved parties make informed decisions regarding the relative risk-benefit ratio of the procedure.

Finally, informed consent should be obtained from all patients before ECT. Patients deemed to be incompetent may require the appointment of a legal guardian for consent (Sackeim, 1995). States vary in the legal regulations of involuntary ECT.

Medications Used During ECT

Patients should have nothing by mouth the night before their treatment and should limit the number of medications (and water needed to swallow the medications) on the morning of ECT to cardiac (except lidocaine), pulmonary (except theophylline), and glaucoma (except cholinesterase inhibitors, e.g., echothiophate) medications. Since the patient is NPO, consideration should also be given as to whether to hold any diuretics until after the treatment depending on the patient's cardiac status. As a result, it is recommended that theophylline be discontinued and inhalers substituted and brought to the ECT suite to be given immediately prior to the treatment. Theophylline has been associated with status epilepticus during ECT

(Devanand, Decina, Sackeim, & Prudic, 1988). A case review of ECT use in patients with asthma was recently published, noting overall good safety (Mueller, Schak, Barnes, & Rasmussen, 2006). Patients with glaucoma who are receiving echothiophate should be switched to another medication because echothiophate can potentially interact with succinylcholine and prolong the apneic period. The same is potentially true for the cholinesterase inhibitors used to treat Alzheimer's disease—tacrine, donepezil, rivastigmine, and galantamine—although there are no data to determine whether this interaction is clinically significant. In fact, a preliminary study reported successful and safe use of donepezil to mitigate cognitive side effects associated with ECT (Prakash, Kotwal, & Prabhu, 2006). In diabetic patients, hypoglycemic medications are usually withheld on the morning of treatment to minimize the risk of hypoglycemia in a patient who is taking nothing by mouth. A blood sugar should be obtained before ECT and hyper or hypoglycemia treated appropriately. An ECT treatment will result in a modest short term increase in the patient's blood sugar. In general, patients with epilepsy or mania should continue taking their anticonvulsants during ECT. If difficulty arises in eliciting seizures, a decrease in the dose of the anticonvulsant can be considered. Lunde et al. (Lunde, Lee, & Rasmussen, 2006) recently summarized reports of ECT in persons with epilepsy and recommendations for its safe use in this population.

In the past, it was recommended that all psychotropic medications be stopped prior to beginning ECT. In other countries, it is common practice to continue antidepressants during ECT (Royal College of Psychiatrist, 1995). Available data are mixed regarding the use of antidepressants concurrently with ECT. Previous studies in the 1950s and 1960s suggested possible improved response to ECT when combined with tricyclic antidepressants (Dunlop, 1960; Kay DW, 1970; Sargent W, 1961). Later studies also suggested an improved response to ECT when combined with tricyclic antidepressants but not with selective serotonin reuptake inhibitors (Lauritzen, 1996; Nelson JP, 1989). Further research is needed to clarify this issue. When neuroleptics are necessary to control agitation or psychotic symptoms, a high-potency neuroleptic or an atypical antipsychotic is preferable to minimize any hypotension that may develop during ECT. Antipsychotics are generally continued during ECT treatment of persons with primary psychotic disorder (e.g. schizophrenia or schizoaffective disorder).

Concerns have been raised over whether MAOIs can be used safely with anesthesia. Although some clinicians still recommend caution and a 7- to 14-day washout period before proceeding with ECT, extensive reported experience with MAOIs and ECT documented few significant problems (Association, 2001; Dolenc, Habl, Barnes, & Rasmussen, 2004).

Lithium usually is discontinued at least 48 hours before ECT because of a potentially increased risk of delirium and cognitive impairment during ECT (Ahmed & Stein, 1987; Small, 1990; Small, Kellams, Milstein, & Small, 1980). More recent studies have shown that lithium was not associated with increased confusion in acute (Jha, Stein, & Fenwick, 1996; Mukherjee, 1993) and maintenance (Stewart, 2000) ECT. This is discussed further in the section on Mania.

Benzodiazepines can interfere with the induction of a seizure during ECT, thereby resulting in a decreased efficacy from the treatments (Jha & Stein, 1996). As a result, benzodiazepines should be reduced to the lowest possible dose or stopped before ECT. Patients taking benzodiazepines should be receiving a stable dose for 24–48 hours before ECT to reduce the risk of prolonged seizures or status epilepticus during ECT. Flumazenil, a competitive benzodiazepine antagonist, in a dose of 0.4–0.5 mg, has been effective in maintaining seizures without decreasing efficacy in patients who could not be withdrawn from benzodiazepines prior to ECT (Krystal, Coffey, Weiner, & Holsinger, 1998).

ECT Administration

ECT sessions usually are scheduled for the morning. The patient's bladder should be emptied before treatment. Patients should not eat or drink for at least 6–8 hours before receiving a treatment. Famotidine or ranitidine is given the night before and the morning of ECT to neutralize the gastric contents. Alternatively, sodium citrate can be given the morning of the treatment and will have an effect within 5–10 minutes. The ECT treatment team consists of a psychiatrist, an anesthesiologist (or nurse anesthetist), and a nursing team that is specially trained in ECT. The ECT treatment area should have resuscitative equipment available in case a medical emergency arises.

The historically standard anesthetic agent is methohexital, a short-acting barbiturate with minimal anticonvulsant effects, but its availability has been limited in recent years, prompting searches for suitable substitutes. Methohexital is given in a dose of approximately 0.75–1.0 mg/kg, but propofol (in a dose of approximately 0.75–1.50 mg/kg) also can be used. Methohexital has been used more commonly because of its effectiveness and safety record. The concerns regarding the use of propofol include its effect of shortening seizure length compared to methohexital and the increased number of missed seizures (Swaim, Mansour, Wydo, & Moore, 2006). However, the seizure duration has not been correlated with clinical

efficacy, and trials comparing methohexital and propofol have not shown significant differences in antidepressant efficacy (Avramov, Husain, & White, 1995) based on anesthetic agent. Substituting propofol may result in a decrease in the motor seizure such that some patients will not achieve a seizure duration of >20 seconds. Etomidate (0.15–0.3 mg/kg) can be used instead of propofol and is associated with a significant increase in the seizure duration (Bergsholm, Swartz, & Conrad, 1996; Stadtland, Erfurth, Ruta, & Michael, 2002) and significantly shortened treatment course in one retrospective naturalistic study (Swaim et al., 2006). Another strategy that is suggested by the results of one small randomized trial is to add remifentanyl, an ultrarapid-acting opioid that is used to induce and maintain anesthesia, to propofol. This study found that the addition of remifentanyl had no adverse anesthesia or cardiovascular effects and patients on the combination had significantly longer seizure duration than those on propofol alone (Vishne, Aronov, Amiaz, Etchin, & Grunhaus, 2005).

Immediately after the patient is anesthetized, a muscle relaxant is administered intravenously. Succinylcholine, in doses of 0.75–1.50 mg/kg, is a widely used depolarizing blocking agent. In patients with musculoskeletal disease, a nondepolarizing agent can be considered. Anticholinergic agents, such as atropine or glycopyrrolate, are used to prevent ECT-induced bradycardia and to minimize airway secretions. Glycopyrrolate does not cross the blood-brain barrier and therefore may be associated with decreased postictal confusion in the elderly. An anticholinergic agent always should be used in conjunction with a β -blocker to control the ECT-induced rise in blood pressure and heart rate. Atropine (0.4–1.0 mg) or glycopyrrolate (0.2–0.4 mg) can be given either intramuscularly 30 minutes before the treatment or intravenously at the time of the treatment.

Regardless of the electrode placement selected, meticulous care should ensure that the electrodes are properly applied. The scalp should be cleansed and prepared with a saline or conductive gel. The electrodes should be adequately spaced to prevent excess shunting of the electrical stimulus and to prevent skin burns. In bilateral ECT, electrodes are placed frontotemporally, with the center of each electrode approximately 1 inch (2.54 cm) above the center of an imaginary line whose endpoints are the tragus of the ear and the external canthus of the eye. With unilateral ECT, d'Elia electrode placement is the safest and most effective placement (Weiner, 1986b). In this technique, one electrode is placed over the nondominant frontotemporal area, and the other electrode is placed high on the nondominant centroparietal scalp, just lateral to the midline vertex. The treating physician may choose to either titrate the first seizure or use a fixed dose of ECT.

The patient is oxygenated by positive-pressure ventilation from the onset of anesthesia until spontaneous respiration is resumed. In addition, the patient is monitored with a pulse oximeter and should have blood pressure and heart rate continuously monitored. Before the electrical stimulus is administered, a rubber bite block is inserted into the patient's mouth.

Titration or the method of limits approach uses a table with incremental increases in the electrical energy to determine the minimal amount of energy necessary to produce a seizure of at least 25 seconds by EEG criteria. Typically, a seizure lasting 30–90 seconds occurs during treatment if the seizure is monitored by electroencephalography. Seizures lasting longer than 3 minutes should be terminated by administering a second dose of methohexital. Inflating a blood pressure cuff on the right ankle before the muscle relaxant is administered allows the clinician to monitor the motor manifestations of the seizure. The patients usually are alert and oriented 20–45 minutes after receiving a treatment.

If a stimulus is given and no seizure is elicited, a detailed reevaluation should be performed. Often, immediately re-treating with a higher stimulus charge is effective in producing a seizure. Medications should be reviewed, and anticonvulsants and benzodiazepines should be reduced or discontinued, before subsequent ECT treatments. In situations that do not allow the reduction of benzodiazepines, flumazenil, a benzodiazepine antagonist, can be used to help produce seizures¹. Reducing the methohexital to the lowest effective dose and vigorous hyperventilation are other relatively easy methods that can be used to aid in producing a seizure. Some patients who are sensitive to the pain at the IV site (particularly when an IV is inserted in a small peripheral vein) may be given IV lidocaine as a local anesthetic just prior to administering the methohexital and, if possible, the lidocaine should be omitted as it can shorten the seizure length. If these methods are not effective, switching to etomidate, which should have less effect on the seizure threshold, may be considered (Bergsholm et al., 1996; Folk, Kellner, Beale, Conroy, & Duc, 2000; Stadtland et al., 2002).

Caffeine sodium benzoate (usual dose=120–140 mg) may be administered intravenously during ECT to maintain

¹ When flumazenil is administered it should be given immediately after induction as the patient may experience a sudden withdrawal from the benzodiazepine. After the seizure has terminated, IV midazolam should be given as the flumazenil has a longer half life than methohexital and the patient may experience withdrawal on emergence from the anesthesia.

adequate seizure duration (Coffey et al., 1987). Caffeine appears to lengthen seizure duration during ECT without lowering the seizure threshold (McCall et al., 1993a). At present, it is not known whether caffeine augments antidepressant effects of ECT or increases the speed of response during a course of ECT. Theoretically, caffeine would have little therapeutic effect on unilateral ECT because the length of the seizure is less important than the degree to which the seizure stimulus is above the seizure threshold. Caffeine during ECT should be reserved for patients who are having short seizures during ECT and who cannot tolerate higher stimulus doses.

Conversely, if the seizure is too long (over 180 seconds), then the seizure can be terminated using additional IV methohexital, propofol or midazolam. Seizure length is inversely correlated with age and increased particularly in young women. Propofol can be used as the anesthetic agent to shorten the seizure length (Bailine, Petrides, Doft, & Lui, 2003).

Frequency and Number of Treatments

The American Psychiatric Association Task Force on Electroconvulsive Therapy (Association, 2001) recommends that an ECT course should be completed when a plateau in response occurs. No convincing data support that additional treatments beyond this point reduce the rate of relapse after ECT (Barton, Mehta, & Snaith, 1973). In addition, these recommendations imply that, rather than predetermining the number of ECT sessions, the patient's clinical status during the course of ECT should dictate the number of treatments given.

Shapira et al. (Shapira, Tubi, & Lerer, 2000) have shown that ECT administered twice weekly is as effective as treatments administered three times a week. One advantage of a more frequent treatment schedule is a faster rate of response. On the other hand, a disadvantage is the potential development of cognitive side effects. Given these observations, it is recommended that the frequency of ECT treatments be tailored to the individual patient's needs. For example, a patient with a life-threatening illness will benefit from a faster rate of response and should be given more frequent treatments. In patients for whom the risk of cognitive side effects from ECT is a concern (i.e., those with Alzheimer's disease, Parkinson's disease, or severe frontal lobe and caudate hyperintensities on brain MRI scan, as well as those receiving outpatient or bilateral ECT), a less frequent ECT treatment schedule is certainly a reasonable choice.

Management of ECT-Related Side Effects

Post Ictal Agitation

Post ictal agitation or PIA can be a significant practical problem in ECT with the potential for causing injury to both the patient and the nursing staff caring for the patient (Augoustides, Greenblatt, Abbas, O'Reardon, & Datto, 2002). PIA is difficult to predict in an individual patient but is more likely to reoccur if it occurred on the initial treatment. PIA must be differentiated from *status epilepticus* and is clearly distinguished by the random flailing movements of the patient rather than the rhythmic convulsions of a seizure and the fact that the patient does not lose consciousness or demonstrate the fixed gaze noted in a patient experiencing a grand mal seizure.

There are several strategies to treating PIA and most involve IV access. Midazolam or additional methohexital will often sedate the patient and can be very effective. Additionally propofol can be used to manage PIA (O'Reardon, Takieddine, Datto, & Augoustides, 2006). IV haldol has been associated with ventricular ectopy (Greene, McDonald, Duggan, & Cooper, 2000) and should only be used in patients with cardiac monitors. The intramuscular atypical antipsychotics can be just as effective with a more benign cardiac profile.

There are also preventative measures that can be taken including additional preoperative medication and changing the way ECT is administered to reduce the chance of PIA in future treatments. First, the use of a dissolvable atypical antipsychotic such as olanzapine or risperidol formulations 5- 10 minutes prior to ECT can be very effective and does not require any additional liquids. Lithium has been associated with PIA (el-Mallakh, 1988) and should be discontinued during the ECT course or held the night and morning of ECT treatments. Carbidopa has also been associated with postictal delirium and should be held the morning of ECT treatment (Nymeyer & Grossberg, 1997). PIA may also be associated with increasing serum lactate levels and some have argued that increasing the succinylcholine dose to decrease ictal muscle activity and subsequent rises in serum lactate levels can decrease PIA (Auriacombe et al., 2000). One strategy may therefore be to increase the succinylcholine dose if any muscle movement is present during the seizure. However care

should be taken as another potential cause of post ictal agitation occurs if the patient awakens from the anesthesia with latent paralysis of their respiratory muscles. Patients describe this as a frightening feeling and may question continuing in ECT.

The data on the effect of switching from bilateral to unilateral to decrease PIA is unclear (Augoustides et al., 2002) and is probably dependent on a number of factors including ECT dosage and age.

Interictal Delirium

Interictal ECT-induced delirium develops during a course of ECT and persists on days when the patient does not receive a treatment. This side effect is primarily observed in elderly patients who are receiving ECT and increases in incidence with advancing age (Figiel, Coffey, Djang, Hoffman, & Doraiswamy, 1990). ECT-induced interictal delirium is associated with prolonged hospitalizations and an increased risk of falls. Among the elderly, additional risk factors for interictal delirium are 1) Parkinson's disease, 2) Alzheimer's disease, 3) one or more cardiovascular risk factors, and 4) preexisting structural changes in the caudate nucleus observed on brain scans. Patients who develop postictal confusion are more likely to have greater retrograde amnesia in the weeks and months after ECT (Sobin et al., 1995).

The incidence of delirium during ECT can vary dramatically depending on the ECT technique used. As a rule, ECT-induced interictal delirium is a short-lived, reversible side effect if identified early. Once it has been identified, treatments should be held until the delirium resolves. Subsequent treatments should be administered less frequently and/or at a lower electrical charge.

Cardiovascular Side Effects

ECT is associated with an increased risk of cardiovascular complications in elderly patients who have, or who are at risk for, cardiovascular disease. Prior studies have found different rates of cardiac complications in the elderly receiving ECT. The retrospective design of these studies, the lack of continuous cardiovascular monitoring, and the different definitions of what constitutes a cardiac complication probably accounts for the wide discrepancy in these results. Despite the inconsistencies among these findings, most studies have found a correlation between cardiac complications and age. ECT often produces transient systemic hypertension and abrupt transitions in cardiac rate, which can result in myocardial ischemia or arrhythmias. The increased incidence of cardiac complications among elderly patients is probably associated with the increased rate of preexisting cardiac illnesses such as hypertension, coronary artery disease, and arrhythmias. On the basis of these observations, several authors have recommended the use of prophylactic cardiac medications to dampen cardiovascular responses during ECT in elderly patients with cardiovascular disease.

Research has now documented that labetalol (a medication with both α - and β -adrenergic blocking activity), esmolol (a shorter-acting β -blocker), and nifedipine (a calcium channel-blocking agent with vasodilating effects) can be safely used to attenuate the cardiac response during ECT (Cattan et al., 1990; Figiel, McDonald, & LaPlante, 1994; Figiel, 1994; McCall WV, 1991; Stoudemire A, 1990; Zielinski, Roose, Devanand, Woodring, & Sackeim, 1993). Nicardipine (a shorter-acting calcium channel blocker) is routinely substituted for nifedipine because it can be given intravenously and has a shorter half-life.

It is recommended that adequate doses of an anticholinergic medication (intravenous atropine or glycopyrrolate) be used to prevent bradycardias whenever β -blockers are used during ECT. To help prevent ECT-induced hypotension, it is additionally recommended that all patients be adequately hydrated before undergoing ECT. If patients experience significant orthostatic hypotension in the recovery room, labetalol can be switched to the shorter-acting pure β -blocker esmolol.

The anesthetic agent propofol has also been shown to have decreased cardiovascular effects compared to methohexital and can be used in patients with preexisting cardiac conditions requiring attenuated hemodynamic response during treatment (Bailline et al., 2003). As noted above the trade off is a shortening of the seizure length with the use of propofol.

Cognitive Side Effects

The greatest area of concern with the lay public, patients, and their families is the potential development of adverse cerebral and cognitive changes with ECT. The medical community's concerns about cognitive side effects and the negative images of

ECT in the media also are important factors in determining the availability of ECT in certain areas. The technique by which ECT is administered determines the incidence and severity of cognitive side effects that may develop during a course of ECT. Specifically, electrode placement, the type of electrical waveform, the intensity of the electrical stimulus, and the frequency of ECT sessions determine the type and severity of cognitive side effects from ECT. Preexisting structural brain changes and medical illness, advancing age, and concomitant administration of certain psychotropic medications also may be involved. It is important to recognize that depression itself (especially late-life depression) often causes cognitive deficits, such that successful treatment of depression with ECT may actually improve some aspects of cognition in certain patients. Hihn et al. (Hihn et al., 2006) showed that prefrontally-mediated aspects of cognition, such as attention and immediate encoding, were improved during ECT treatment of depression, whereas long-term memory functions remained impaired.

The memory loss attributed to ECT is typically anterograde and retrograde and has a temporal gradient, being more profound around the time of the treatments and extending back months before the treatment and several weeks after the ECT course (Association, 2001; Sackeim, 2000). In most patients, the anterograde memory loss clears quickly after ECT, but in some patients, the retrograde memory loss can be permanent and may extend back years before ECT. Clearly, the degree of amnesia incurred during a course of ECT is greater with bilateral ECT than with unilateral ECT (Lisanby, Maddox, Prudic, Devanand, & Sackeim, 2000) and is increased with the number of treatments administered and the higher stimulus intensity (Sackeim et al., 2000). Although unilateral ECT is associated with fewer memory problems, the cognitive deficits show a dose relationship and increase as the stimulus dose is increased to 8–12 times the threshold (McCall et al., 2000). Research comparing bilateral and unilateral ECT has not addressed the important question of whether right-unilateral ECT given at a dose 10–12 times the seizure threshold would cause more cognitive side effects than bilateral ECT that was minimally above or 1.5 times the seizure threshold.

Sine wave stimulus produces greater amnesic deficits than does a brief or ultrabrief stimulus pulse. In addition, Sackeim et al. (Sackeim et al., 1991; Sackeim et al., 1993) reported that within a specific waveform, the magnitude by which an electrical dose exceeds the seizure threshold (rather than the absolute electrical dose) is related to the severity of cognitive defects that develop during ECT. In a prospective, naturalistic, longitudinal study of cognitive outcomes in depressed patients treated with ECT at seven facilities in the New York City metropolitan area (Sackeim et al., 2007), sine wave stimulation resulted in pronounced slowing of reaction time, both immediately and 6 months following ECT. As expected, bilateral ECT resulted in more severe and persisting retrograde amnesia than right unilateral ECT. They found that several clinical variables also were associated with post ECT memory problems including older age, lower premorbid intellectual function, and female gender. Finally, Shapira et al. (Shapira et al., 2000) reported that twice-weekly treatments produced less cognitive impairment than did treatments administered three times a week.

The causes of the memory disturbance are therefore multifactorial and likely include the effects of anesthetic drugs, electrode placement, stimulus waveform, generalized seizures and electrical dose (Sackeim et al., 2007). Progress in understanding the neural mechanisms underlying memory makes it possible to consider how neurotransmitter changes might contribute to ECT-induced memory dysfunction. Muscarinic cholinergic receptors participate in some forms of memory, and antimuscarinic drugs are associated with memory impairment in humans (Krueger, Sackeim, & Gamzu, 1992). In animals, the effects of ECS on central muscarinic systems have been variable (Fochtmann, 1994). However, some studies suggest that ECT diminishes muscarinic binding in cortex and hippocampus. Twenty-four hours following a series of ECS, there are also decreases in mRNA for m1 and m3 muscarinic receptors in the hippocampus, although mRNA levels are significantly increased twenty-eight days after the last seizure (Mingo et al., 1998). Other studies indicate that following ECS behavioral responses to muscarinic agonists are diminished, and brain choline acetyltransferase and acetylcholine levels are decreased (Nutt, 1993). These findings suggest that alterations in muscarinic neurotransmission may contribute to memory impairment.

Long-term, use-dependent plasticity of glutamatergic synapses appears to play a major role in memory processing in the CNS and disruption of this plasticity could contribute to anterograde amnesia. The term *long-term potentiation* (LTP) typically refers to a persistent enhancement of glutamate-mediated transmission that follows repeated high frequency synaptic use, and LTP is a potential synaptic memory mechanism. Repeated ECS disrupts the induction of LTP and produces memory impairment in animals (Anwyl, Walshe, & Rowan, 1987; Stewart & Reid, 1993), suggesting a possible tie to anterograde memory problems.

Several ECS-induced changes, including effects on muscarinic and adrenergic neurotransmission, could contribute to the disruption of LTP. Furthermore, the enhanced inhibition that may contribute to the anticonvulsant effects of ECT could also play a role because these inhibitory systems modulate efficacy at glutamatergic synapses. Finally, the release of glutamate during a seizure may contribute to memory impairment. In many CNS regions, the induction of LTP depends on NMDA receptors. However, untimely activation of NMDA receptors before delivery of a stimulus that usually induces LTP

results in LTP inhibition, a process broadly referred to as "metaplasticity." This metaplasticity may result from activation of certain intercellular messengers, such as nitric oxide, or from the activation of phosphatases that alter the phosphorylation of key synaptic proteins (Zorumski & Izumi, 1993). Longer-term effects of ECS on basal synaptic transmission or NMDA receptor function could also contribute to memory impairment (Petrie et al., 2000; Stewart, 2002). To date, there is little clinical evidence favoring any of these mechanisms in ECT-induced memory impairment, although several avenues are worth pursuing. Interestingly, there is some evidence that use of an anesthetic that blocks NMDA receptors, ketamine, results in improved verbal memory following ECT compared to etomidate, a GABAergic anesthetic (Krystal et al., 2003; McDaniel et al., 2006). Propofol, an agent that enhances GABAergic transmission but also inhibits NMDA receptors partially at anesthetic concentrations, may also have beneficial effects on memory following ECT compared to thiopental (Butterfield, Graf, Macleod, Ries, & Zis, 2004).

Effects on Cerebral Physiology

Immediately after an ECT treatment, the EEG shows generalized slowing. This slowing tends to increase and persist longer after successive treatments. After a course of ECT is completed, slow-wave activity gradually decreases, and the EEG reverts to baseline activity within 3 months (Weiner, 1986a). Rarely, EEG abnormalities may persist for more than 3 months. Prior EEG abnormalities may increase the risk for developing prolonged abnormalities after ECT, but the clinical significance of these abnormalities is unknown.

Electrically induced seizures in animals and humans have been shown to produce transient increases in permeability of the blood-brain barrier (Laursen, 1991). These findings are consistent with a brain MRI study in which increased T1 relaxation times were observed after ECT (Scott, Douglas, Whitfield, & Kendell, 1990). Laursen et al. (Laursen, 1991) reported that the ECT-induced increase in blood-brain barrier permeability is associated with increased stimulus intensity and an increased number of ECT treatments. In addition, Bolwig et al. (Bolwig, Hertz, & Westergaard, 1977) were able to decrease changes in blood-brain barrier permeability during ECT by blocking ECT-induced hypertensive response with high-spinal anesthesia. Because a disturbed blood-brain barrier may predispose some patients to ECT-induced neurological complications, research is needed to examine the ways that ECT-induced changes in blood-brain barrier permeability can be minimized, such as by attenuating the ECT-induced cardiovascular response or by reducing the amount of the stimulus charge.

The combination of increased carbon dioxide production, decreased pH, and systemic hypertension can cause the CBF to increase to 300% of baseline and the cerebral metabolic rate (CMR) to increase by 200% (Ingvar, 1986). The transient increase in CBF results in a sharp rise in both intracranial and intraocular pressure (Maltbie et al., 1980). Both the CBF (Saito et al., 1995) and the CMR (Ackermann, Engel, & Bäxter, 1986) return to baseline during the postictal period. Methods that limit the accumulation of carbon dioxide, such as forced hyperventilation, or that attenuate the increase in blood pressure tend to diminish the rise in intracranial pressure associated with ECT.

Does ECT Cause Brain Damage?

Human autopsy studies of patients who have received ECT have shown no convincing evidence of irreversible brain damage when ECT was administered with current techniques (Devanand et al., 1994; Weiner, 1984). These findings are supported by a brain MRI study, in which no significant structural brain changes were found immediately and 6 months after the completion of ECT (Coffey et al., 1991). In a study of six depressed patients, CSF markers of neuronal/glial degeneration (tau protein, neurofilament, and S-100 β protein) were measured before and after a successful course of ECT and showed no biochemical evidence of neuronal/glial damage of blood-brain barrier dysfunction (Zachrisson et al., 2000).

Minor Complications

Patients often report nausea and headaches after ECT, and these complaints usually are easily treated and do not appear to be related to different electrode placement or stimulus dose (Devanand et al., 1995). The exact incidence of nausea is not known; estimates indicate that approximately one-quarter of patients complain of some nausea (Gomez 1975). Treatment of nausea includes prochlorperazine, metoclopramide, and ondansetron. If effective, they can be given pre-ECT on subsequent treatments. The anesthetic propofol can also be substituted for etomidate or methohexital to reduce post ECT nausea and vomiting (Bailine et al., 2003).

The incidence of ECT-induced headaches is also unknown; however, some estimates show that up to 45% of patients

had headaches post-ECT (Devanand, Fitzsimons, Prudic, & Sackeim, 1995; Weiner, 1994). Acetaminophen or nonsteroidal anti-inflammatory agents (NSAIDs), including intravenous ketorolac, usually are effective. The etiology of the ECT headache is unclear, but a vascular process (Weiner, 1994) has been suggested, and sumatriptan can be effective (Fantz, Markowitz, & Kellner, 1998). Patients who have a history of migraine headaches should be given their medication before ECT. Prophylactic treatment with these agents immediately prior to the ECT treatment usually is effective in reducing future headaches.

Prophylactic Somatic Treatment of Patients with Acute Response to ECT

Although the short-term therapeutic benefits of ECT are clearly established, the 6-month relapse rate after ECT during antidepressant therapy remains high (Bourgon & Kellner, 2000; Sackeim, 1995). The debate over appropriate prophylactic treatment for patients with an acute response to ECT has focused on the clinical decision to continue either antidepressant therapy or maintenance ECT. Confusion in this area persists because of the lack of controlled studies comparing the efficacy of antidepressants with that of maintenance ECT.

Most study designs have been naturalistic. O'Leary and Lee (O'Leary & Lee, 1996) evaluated the 7-year mortality and readmission rates in the Nottingham ECT cohort and found that the risk of death was doubled over the general population, and the probability of not being readmitted was 0.79 at 16 weeks and only 0.27 over the 7-year follow-up. Delusions were the most important clinical characteristic predicting relapse. Two studies (Aronson, Shukla, & Hoff, 1987; Spiker, Stein, & Rich, 1985) evaluated adult patients after an acute course of ECT for psychotic depression and found a combined relapse rate of 68% ($n=53$ patients) at 1 year. Spiker et al. (Spiker et al., 1985) found a 1-year relapse rate of 50% in patients with delusional depression who initially responded to an acute course of ECT. Aronson et al. (Aronson et al., 1987) followed up patients with delusional depression who responded to either medication or ECT and found that 80% of the medication-responsive group and 95% of the ECT-responsive patients relapsed in the first year after hospitalization. These studies did not compare the adequacy of either the initial (pre-ECT) or the continuation medication trial.

In a prospective, naturalistic study of 347 patients at seven hospitals, Prudic et al. (Prudic, Olfson, Marcus, Fuller, & Sackeim, 2004) found that between 30-47% of patients met criteria for remission at the end of their acute course of ECT. In the 24-week follow-up period, 64% of remitters relapsed. Among those patients who did not achieve remission during the acute course, only 23% had sustained remission during the 6 month follow-up period.

Sackeim et al. (Sackeim et al., 1990) followed 58 patients for 1 year after ECT and found a differential relapse rate of 64% in those with major depression (with and without psychotic features) in whom an adequate pre-ECT medication trial had failed. In contrast, the relapse rate in patients who did not receive an adequate pre-ECT antidepressant trial was only 32%. Other clinical and demographic factors, including the presence of delusions, were not significant in predicting relapse. The adequacy of the post-ECT maintenance medication was not correlated with relapse. However, as in the studies cited above, the maintenance medications post-ECT were not standardized, and the evaluation of the pre-ECT medication trial was retrospective. The conclusion of this study is intuitively appealing. Patients whose symptoms do not respond to antidepressant medication before ECT are those most likely to relapse during maintenance medication. As is true of depressed patients with psychotic features, the rate of relapse within 1 year (with relapse occurring in almost two-thirds of patients) remains alarmingly high.

In a prospective, randomized, double-blind trial, Sackeim et al. (Sackeim et al., 2001a) compared three maintenance strategies: placebo, nortriptyline (target steady-state level = 75–125 ng/mL), and nortriptyline plus lithium (target steady-state level = 0.5–0.9 mEq/L). Over the 24-week trial, the relapse rate was 84% for placebo, 60% for nortriptyline, and 39% for nortriptyline plus lithium, indicating a statistically significant advantage for combination therapy. In another prospective study, Shapira et al. (Shapira, Gorfine, & Lerer, 1995) found that patients who responded to an acute course of ECT and subsequently received maintenance lithium for 6 months had a relapse rate of only 36%. Of the 22 patients, the 8 who relapsed did so in the first 13 weeks. Several clinical factors were associated with relapse; these included shorter duration of index depressive episode, additional depressive episode in the previous 12 months, and, again, failure of an adequate trial of antidepressant therapy before the ECT course.

Lauritzen et al. (Lauritzen, 1996) randomized patients who were receiving ECT to either paroxetine 30 mg, imipramine 150 mg, or placebo and continued the medication treatment after they had responded to ECT. In the continuation phase, paroxetine was superior to both imipramine and placebo in preventing relapse: 65% of the placebo-treated patients relapsed, compared with 30% of the imipramine-treated patients and 10% of the patients treated with paroxetine.

The elderly are particularly prone to increased disability from depression and form a substantial proportion of patients in an acute ECT program. Data from naturalistic studies confirm that the relapse rates for elderly patients treated with ECT are high. These rates have varied from 21% within 6 months (Karlinsky & Shulman, 1984) to 50% (10 of 20) within 1 year (Murphy, 1983); the rehospitalization rate was 44% within 3 years (Stoudemire, Hill, Dalton, & Marquardt, 1994). Of the 10 patients in the Murphy study who did not relapse within 1 year, 1 developed dementia and 4 died; thus, only 5 of the 20 elderly patients were well at 1 year. The elderly are therefore at increased risk for relapse after acute ECT. However, two small studies in adolescent populations showed that younger patients also have high relapse rates: 40% within 1 year (Cohen, Paillere-Martinot, & Basquin, 1997) and 38% within 3 years (Moise & Petrides, 1996).

Studies primarily in the 1980s focused on finding a biological marker that would predict relapse after ECT; these markers included nonsuppression of cortisol to a challenge dose of dexamethasone (i.e., dexamethasone suppression test, or DST), blunted thyrotropin to thyrotropin-releasing hormone (TRH) (i.e., TRH stimulation test), and shortened rapid eye movement (REM) latency on a sleep EEG. These studies had many methodological problems, including the fact that most of the studies were retrospective reviews, had nonblinded raters and a small number of subjects, and used nonstandardized follow-up treatment after ECT. Given these limitations, preliminary evidence suggests that patients who continued to show a biological marker consistent with depression after responding to ECT (e.g., positive DST result) were at increased risk for relapse. In Bourgon and Kellner's (Bourgon et al., 2000) review, six of the nine studies in which the DST was used, two of the four studies in which the TRH test was used, and the one sleep EEG study showed that persistent abnormalities in these biological markers after ECT are predictive of relapse.

Continuation/Maintenance ECT in Major Depression

The high relapse rates of depressed patients receiving antidepressants after ECT have led clinicians to use alternative therapies, such as continuation/maintenance ECT, in patients who are at high risk for recurrence of their mood disorder. *Continuation ECT* is defined as ECT for up to 6 months after the acute ECT course (i.e. aimed at *relapse* prevention). Continuation ECT is differentiated from *maintenance ECT*, which is defined as ECT that continues for more than 6 months after the index course (i.e. aimed at *recurrence* prevention). In this chapter, the term *prophylactic ECT* is used to refer to any ECT treatments given as continuation or maintenance. Many of the studies reviewed here do not differentiate patients receiving continuation ECT from those receiving maintenance ECT, although treatment indications, side effects, and outcomes may be different for these two types of prophylactic ECT.

According to clinical guidelines, candidates for prophylactic ECT include patients who have recurring affective episodes that are responsive to ECT and/or who are resistant or intolerant to, or noncompliant with, antidepressant medications (Association, 2001). Prophylactic ECT strategies are increasingly being used to treat major depression and bipolar disorder in patients thought to be at high risk for relapse. In a 1985 survey of private hospitals, 64% of the hospitals that provided ECT also provided prophylactic ECT (Levy & Albrecht, 1985). Kramer (Kramer, 1987) found a similar use pattern, with 59% of the respondents using continuation/maintenance ECT primarily for recurrent depression.

Several theories have been advanced to explain the potential therapeutic efficacy of prophylactic ECT over medication. First, Bourne and Long (Bourne & Long, 1954) suggested that patients with psychotic depression may become "convulsion dependent" such that they need to be tapered from ECT to prevent relapse. Second, prophylactic ECT has a different mechanism of action than antidepressants, and patients who are medication resistant respond to an acute course of ECT. The corollary is that patients who respond preferentially to ECT may have lower relapse rates with prophylactic ECT than with medication. Third, prophylactic ECT may not provide an increased therapeutic benefit over medication at all. Rather, the benefit may be the result of better treatment compliance in the groups receiving ECT than in those receiving maintenance medication. Most reports of relapse rates in patients receiving prophylactic ECT include only those patients who were compliant and presented for their treatments. As Clarke et al. (Clarke, Coffey, Hoffman, & Weiner, 1989) pointed out, when patients receiving continuation ECT do not complete 6 months of treatment, then relapse rates approach the 50% seen in patients receiving maintenance medication. Thus, future studies of ECT need to include both compliant and noncompliant patients in their outcome measures.

A recent study in an elderly woman with recurrent psychotic depression receiving maintenance ECT showed a correlation between resolution of cerebral hypoperfusion and a treatment response to her depressive symptoms (Suzuki 2006). At baseline, the patient demonstrated anterior cerebral hypoperfusion on single photon emission computerized

tomography (SPECT) which did not change 12 days after the acute course. After the acute course she continued to have residual depressive symptoms. Two weeks later she relapsed and then improved again after a second course of acute ECT. The hypoperfusion improved after the second course of ECT and resolved completely after two years of maintenance ECT. This case report is interesting particularly given the data by Prudic et al. (Prudic et al., 2004) demonstrating the relationship between residual depressive symptoms and relapse. A second study of two patients found that cerebral blood flow and metabolic rates were no different than controls pre-ECT and that at the end of a successful continuation course of ECT, there was decreased cerebral blood flow and metabolic activity in the prefrontal cortex (Conca, Prapotnik, Peschina, & Konig, 2003) consistent with similar findings of cerebral activity and response to an acute course of ECT (e.g., Nobler et al., 2001).

Most of the studies examining maintenance ECT are case reports and retrospective case series. The more recent reports follow a naturalistic design with relatively few subjects but generally describe a marked decrease in the number of hospitalizations, hospital days, and depressive symptoms; increased functional status; and stable cognitive functioning for the period of continuation ECT (Clarke et al., 1989; Decina, Guthrie, Sackeim, Kahn, & Malitz, 1987; Fox, 2001; Gagne, Furman, Carpenter, & Price, 2000; Kramer, 1999; Russell et al., 2003; Thienhaus, Margletta, & Bennet, 1990; Thornton, Mulsant, Dealy, & Reynolds, 1990). These positive results have been extended to elderly depressed patients (Dubin et al., 1992; Loo, Galinowski, De Carvalho, Bourdel, & Poirier, 1991), bipolar patients (Nascimento, Appolinario, Segenreich, Cavalcanti, & Brasil, 2006; Sienaert & Peuskens, 2006; Tsao, Jain, Gibson, Guedet, & Lehrmann, 2004) (Husain, Meyer, Muttakin, & Weiner, 1993; Vanelle et al., 1994), schizophrenia (Suzuki 2006) (Shimizu et al., 2007) and patients with Parkinson's disease (Shulman, 2003) (Faber and Trimble 1991). A moderately sized study of treatment-resistant schizophrenia cases responsive to combined ECT-antipsychotic found that these individuals fared better with the combination of continuation ECT and antipsychotic than either treatment alone (Chanpattana, 1999b).

In a prospective study, Clarke et al. (Clarke et al., 1989) used continuation ECT in 27 patients who received an acute course of ECT because of a history of medication intolerance or resistance. The rate of rehospitalization was six times lower (8%) in patients who completed a 5-month course of continuation ECT than in patients who did not complete the protocol (47%). Swoboda et al. (Swoboda, Conca, Konig, Waanders, & Hansen, 2001) prospectively followed 13 patients diagnosed with major depression and 8 patients who had schizoaffective disorder who were administered M-ECT and compared them with controls who received maintenance pharmacotherapy alone. The M-ECT group had a significantly decreased rate of rehospitalization in one year, although overall the schizoaffective patients has a poorer outcome overall compared to patients with major depression. The largest prospective study of to date included 184 patients who were randomized to either maintenance pharmacotherapy with a combination of lithium and nortriptyline or continuation ECT, found that both had treatments had limited efficacy, with more than half of patients in each group either relapsing or dropping out of the study (Kellner et al., 2006). Although these results were disappointing, the efficacy of continuation ECT was being compared to the "gold standard" of nortriptyline and lithium and both treatments were better than the historical placebo controls or follow-up with monotherapy. There are few other prospective studies and/or controlled trials of continuation/maintenance ECT.

There are limited studies which have evaluated memory side effects from M-ECT. In a retrospective study of 18 patients receiving M-ECT for 3- 10 months, there were minimal memory side effects and an excellent clinical response (Abraham, Milev, Delva, & Zaheer, 2006). Three patients (17%) had slight memory impairment which improved to normal and one patient experienced severe memory problems in the third month of treatment and discontinued treatment. A second study found that after an acute course of ECT there was no difference in the neuropsychological functioning of 13 patients receiving maintenance pharmacotherapy and 11 patients administered maintenance ECT (Vothknecht et al., 2003). A telephone screen for evaluating cognitive side effects post M-ECT has been proposed and successfully identified a patient with significant deficits the day after ECT (Datto, Levy, Miller, & Katz, 2001). This type of testing would be practical for evaluating both clinical and research patients in M-ECT.

Guidelines for the use of prophylactic ECT unfortunately remain vague primarily because of the paucity of data on which to base these guidelines. Monroe (Monroe, 1991) delineated the contradiction of the increasing use of continuation/maintenance ECT and the lack of research defining the parameters of administering the treatments and potential side effects and contraindications. More recently the use of continuation and maintenance was questioned in the National Institute for Clinical Excellence (NICE) Technology Appraisal, "Guidance on the Use of Electroconvulsive Therapy" (Excellence, 2003) has questioned the use of maintenance and continuation because of the lack of empirical evidence. From their examination of the data, they concluded ECT is "not recommended as a maintenance therapy in

depressive illness". Yet other researchers have questioned this conclusion pointing out that the typical patient in continuation or maintenance ECT has chronic relapsing depression and has failed multiple medication trials (Frederikse, Petrides, & Kellner, 2006). In fairness, the NICE report was published before the above cited studies by Prudic et al. (Prudic et al., 2004) and Kellner et al. (Kellner et al., 2006) which provided prospective studies supporting the use of continuation ECT.

Treatment Recommendations for Continuation ECT

Patients who receive an acute course of ECT usually fall into three categories: 1) patients who have failed previous trials of medication and are therefore relatively medication resistant; 2) patients who are severely ill (e.g., psychotic or suicidal); and 3) patients who cannot tolerate the side effects of antidepressant medication because of either concomitant medical illness or a personal sensitivity to antidepressant side effects or patients who are noncompliant with their medication trial. These three groups overlap and include a number of patients who, because of their own experience or the experiences of acquaintances or relatives, prefer ECT to the traditional somatic treatments.

Patients Who Have Failed Previous Trials of Medication and Are Therefore Relatively Medication-Resistant

A significant minority of patients with major depression are relatively medication resistant despite adequate medication trials. Sackeim et al. (Sackeim et al., 1990) found that the most important factor in relapse after an acute course of ECT is whether the patient received an adequate pretreatment medication trial. In patients who had undergone an adequate pretreatment medication trial, the relapse rate after ECT was found to be twofold higher (Sackeim et al., 1990). Shapira et al. (Shapira et al., 1995) also found that patients who had received an adequate pretreatment pharmacotherapy trial relapsed at a significantly higher rate when they received lithium maintenance therapy. Interestingly, Grunhaus et al. (Grunhaus, Pande, & Haskett, 1990) reported a relapse rate of only 17% in patients in whom a previous medication trial had failed and who received up to 12 weeks of maintenance ECT.

Patients in whom an adequate medication trial failed before ECT should be informed of the risk of relapse and given the option of continuation ECT for 6 months, followed by maintenance medication. The clinical decision of whether to continue ECT beyond 6 months should be made on an individual basis, weighing the risks (primarily cognitive effects of continuing ECT vs. the risk of suicide or recurrent psychosis if the patient relapses while taking medication) and benefits (long-term effects of a period of mood stability).

Patients Who Are Severely Ill

Some researchers have found that the 1-year relapse rate in patients with psychotic depression treated with medication alone may be as high as 95% (Aronson et al. 1987; Spiker et al. 1985). Petrides et al. (1994) retrospectively examined the records of patients with delusional depression treated with prophylactic ECT and found the relapse rate at 1 year to be only 42%. They compared their findings with those from the study by Aronson et al. (1987). Both patient groups were drawn from the same institution, although prophylactic ECT was not available at the time that Aronson et al. (1987) reported relapse rates of 95% in patients with delusional depression who were taking antidepressants. Vanelle et al. (1994) prospectively administered maintenance ECT, often with concomitant antipsychotic medication, approximately once a month for 1 year to a group of patients with psychotic depression and found full or partial remission in 80% of the patients. Grunhaus et al. (1990) also found an excellent clinical response in patients with psychotic depression who were administered prophylactic ECT. Prophylactic ECT may therefore be a viable option in patients with delusional depression and should be discussed with these patients and their families.

Patients Who Cannot Tolerate the Side Effects of Antidepressant Medication or Who Are Noncompliant With Their Medication Trial

Most of the patients who cannot tolerate the side effects of antidepressant medication because of either concomitant medical illness or a personal sensitivity to antidepressant side effects can be tried on maintenance medication after a successful course of ECT. Many patients who are acutely ill may be extremely sensitive to the side effects of medications but may tolerate the same medication once they have responded to acute treatment. Conditions associated with depression, such as malnutrition

and dehydration, may worsen the orthostatic hypotension from tricyclic antidepressants. In a patient with agitated depression, minimal activation from the selective serotonin reuptake inhibitors may be experienced as extreme agitation. Once the depressive episode has remitted, patients usually can tolerate an additional medication trial. Patients who are noncompliant with their antidepressant medication should be evaluated on an individual basis, and, after discussions with the patient and the family, the risks and benefits of prophylactic ECT should be weighed against an additional medication trial.

Procedural Guidelines for Continuation ECT

Treatment Parameters

The electrode placement and dose parameters used in the index course are maintained during continuation ECT. Retrospective reviews have not found stimulus placement to affect outcome (Petrides et al. 1994), although no systematic studies have compared unilateral and bilateral placement in prophylactic ECT. Since seizure threshold can increase during acute treatment because of the frequency of treatments, the threshold would also be expected to decrease during prophylactic ECT. In one small study the threshold was shown to decrease significantly when the treatments were separated by 60 days or more (Wild, Eschweiler, & Bartels, 2004).

Treatment Intervals, Frequency, and Duration

There are few guidelines on the frequency of continuation ECT that is optimal to maintain mood stability. The intervals between courses of prophylactic continuation ECT in the studies reviewed vary from 3–5 weeks (Loo et al. 1991) to 4–8 weeks (Thienhaus et al. 1990). Other clinicians argue that treatments should be gradually tapered from once a week to once a month, depending on clinical response (Aronson et al. 1987; Clarke et al. 1989; Matzen et al. 1988). Kramer (1987) surveyed 51 clinicians in 24 states and found the frequency and duration of maintenance ECT to vary from two treatments per week, extending to once every 3–4 weeks over 30 months, to one treatment every 6 months over 60 months, to as long as 48 years. In Kramer's survey, clinicians described continuing ECT until the patient was asymptomatic for a predetermined period ranging from 1 month to 2 years.

Grunhaus et al. (1990) assessed individual patients' clinical histories and assigned them to either abbreviated continuation ECT (i.e., once or twice a week for 4–12 weeks) or full continuation ECT (i.e., gradually tapering ECT to once a month over 3 months and continuing once a month for 6 months). Abbreviated continuation ECT was used when symptoms were unresponsive to medication after the index episode and lasted more than 12 months or when the patient relapsed after a successful course of ECT or had difficulties tolerating continuation pharmacotherapy. Full continuation ECT was used in patients who relapsed after a successful course of ECT despite adequate pharmacotherapy. Among 10 patients, these researchers found an excellent response in 6 (5 of 6 receiving abbreviated continuation; 1 of 4 receiving full continuation), particularly in those with delusional depression.

In a prospective study, Vanelle and associates (1994) administered maintenance ECT with an average frequency of once every 3.5–3.9 weeks for 1 year and found that 64% of the patients needed shorter intervals to prevent a recurrence of their depressive disorders. The patients who required a shorter interval were older and had a longer duration of illness. Vanelle et al. (1994) posited that the older patients may have had a shorter time to relapse, a suggestion that is consistent with data showing that older patients tend to have accelerated mood cycles (Zis et al. 1980). Others have suggested tapering the ECT treatments from once a week for 1 month to every 2 weeks for 4 weeks and then monthly for 4–6 months (Fox 2001).

Recommendations for Treatment

The greatest risk of relapse after ECT is within the first few months after acute treatment (Clarke et al. 1989; Sackeim et al. 1990; Shapira et al. 1995). During this crucial period, many patients and their families describe a recurrence of symptoms of depression when treatment intervals are extended by even a few days. This pattern of response has resulted in the development of a continuation ECT protocol in which treatment intervals between continuation ECT are extended in increments—from once a week for the first four treatments, to every 10 days for the next three treatments, and then every 2 weeks for the final 4 months. During the initial 6 months of continuation ECT, treatments are not extended beyond every 2 weeks. If a patient becomes symptomatic, the treatment interval is again shortened for additional treatments until the patient

is clinically stable. Usually this requires an additional 3–4 treatments and not a full acute course of 6–10 treatments. The patient is then returned to the longest ECT treatment interval during which he or she remained healthy.

Patients are encouraged to continue ECT for at least 6 months. In the final month of continuation ECT, treatment with an antidepressant is initiated. However, which antidepressant drug can be safely and effectively used during continuation ECT requires further study. Patients who relapse quickly after discontinuation of continuation ECT should be considered for maintenance ECT.

Informed Consent

Individual hospital policies and state laws dictate the procedure for obtaining informed consent. Patients in outpatient and prophylactic ECT are subject to the same guidelines as are applicable to the ambulatory surgery service in the treating hospital. In general, the same policies governing consent for the index ECT course apply to the prophylactic course of ECT. The consent procedures have been reviewed extensively elsewhere (Abrams 1997; American Psychiatric Association Task Force on Electroconvulsive Therapy 2001). A new consent should be obtained before each course of prophylactic ECT, when a patient changes from inpatient and outpatient status, and at least every 6 months. The physician also should document at the beginning of each ECT course (i.e., at the time of the consent) the justification for the prophylactic ECT.

Cognitive Complications

There are few data on the cognitive changes of patients receiving repeated ECT over a period of months to years. Most of the available reports in which prophylactic ECT has been used describe only minor subjective complaints (e.g., Fox 2001). Grnhan et al. (1990) reported that the patients in their study experienced minor memory difficulties (recent recall and names) that returned to normal with 6–8 months. Patients in a study by Vanelle et al. (1994) (mean age = 70 ± 13 years) described either no subjective memory problems ($n=8$) or minor subjective cognitive complaints ($n=14$). Petrides and associates (1994) noted only minor subjective memory problems in 30 patients (mean age = 52 ± 15 years) who received an average of seven continuation ECT treatments over 2 months. Thienhaus et al. (1990) found stable cognitive function (as measured on the MMSE) in six elderly patients (mean age = 71 ± 5 years) over 1–5 years of prophylactic ECT. A naturalistic 1-year study of 20 persons receiving maintenance ECT found no global cognitive decline over this time period (Rami et al., 2004).

Transcranial Magnetic Stimulation and Subconvulsive Stimuli

To date there are a number of subconvulsive treatments for depression including transcranial magnetic stimulation (TMS), vagal nerve stimulation (VNS) and deep brain stimulation (DBS) which all hold promise both in the treatment of depression and in elucidating the underlying biology of depression.

All of these treatments are subconvulsive and bring into question the axiom that subconvulsive stimuli cannot be therapeutic. Prototypes of the modern subconvulsive brain stimulation devices were first developed by Pollack and Beer in 1903. These colleagues of Sigmund Freud used electromagnetic currents to stimulate cortical neurons, but it was not until 80 years later that Barker developed modern TMS equipment (Barker, Jalinous, & Freeston, 1985) and research began to focus on the effects of TMS on psychiatric disorders. TMS equipment is relatively simple and uses capacitors to store an electrical charge. The charge is then discharged through a coil and produces a magnetic field that lasts from 100 to 200 msec. When placed over the skull, the magnetic field passes unimpeded into the brain, stimulating the underlying brain regions, and can be used to understand both motor function (Homberg, Stephan, & Netz, 1991) and other complex brain functions such as speech (Epstein et al., 1996) and visual information processing (Beckers & Zeki, 1995). Early preclinical studies of TMS in rats showed that TMS had similar effects as ECS in behavioral models of depression including enhancement of apomorphine-induced stereotypy, reduction of immobility in the Porsolt swim test and increases in seizure threshold for subsequent stimulation (Fleischmann, Prolov, Abarbanel, & Belmaker, 1995; Lisanby & Belmaker, 2000).

Within a decade, TMS was being used to treat depression and schizophrenia (Grisaru, Yaroslavsky, Abarbanel, Lamberg, & Belmaker, 1994; Hoflich, Kasper, Hufnagel, Ruhrmann, & Moller, 1993; Kolbinger, Hoflich, Hufnagel, Moller, & Kasper, 1995). These studies used TMS coils that were nonfocal, and the antidepressant effects were limited.

Additional work by George et al. (George et al., 1995) provided the impetus for a renewal in TMS research in mood disorders. These studies used repetitive or rapid-rate TMS (rTMS) to apply multiple stimuli in one session and target treatment to the prefrontal cortex, an area that also has shown to be important in the response to ECT (Nobler et al., 2001). Imaging studies have demonstrated a response to TMS based on changing metabolic patterns in the frontal cortex (Kimbrell et al., 1999).

Yet the magnitude of the response to rTMS is rarely more than a 50% decline in the depression rating scales (e.g., clinical criteria for response), and few patients meet the criteria for clinical remission (or an absolute value for a scale that indicates no evidence of depression). A metaanalysis noted that although TMS was clearly superior to sham and the effect size was moderate (effect size = 0.81 (95% CI: 0.42-1.20, $P < .001$)) the clinical significance of TMS was modest (Holtzheimer, Russo, & Avery, 2001).

Studies comparing rTMS with ECT have shown that rTMS is equivalent to ECT in the treatment of major depression (Grunhaus et al., 2000; Janicak et al., 2002). A combination of ECT and rTMS was equivalent to ECT alone (Pridmore, 2000) and would potentially produce fewer side effects. Some researchers have pointed out that studies comparing ECT and rTMS had unusually low response rates in the ECT treatment arms, suggesting possible underdosing of ECT (Euba, 2005; Kellner, Husain, Petrides, Fink, & Rummans, 2002). Another recent study found rTMS less effective than "a standard ECT course" for relieving acute symptoms of depression, without appreciable differences in cognitive side effects (Eranti et al., 2007).

Recent data from an industry sponsored trial demonstrated a modest effect for rTMS in the treatment of depression. In this study, 301 medication free patients participated in a double blind sham controlled multisite study (O'Reardon et al., in press). The response rate at week 4 was significant indicating a 50% decline in depression scores for approximately 18% of patients in the active group and 11% for those in the sham control (24% vs. 12% at week 6). The remission rates at week 6, but not week 4, were also significant (14% vs. 5%). The FDA is reviewing this data to determine if rTMS should be approved as a clinical treatment for depression.

rTMS clearly has several advantages over ECT. rTMS requires no anesthesia, is easy to administer, and has only transient, mild cognitive side effects. Additionally, rTMS does not have the negative stigma associated with ECT. Yet some question whether the subconvulsive stimuli of rTMS can have an antidepressant effect comparable to that of ECT (Swartz, 1997). Magnetic seizure therapy recently has been developed as an alternative to ECT and combines the therapeutic effect of a seizure with the more focused stimulation of rTMS (Lisanby, Luber, Sackeim, Finck, & Schroeder, 2001b; Lisanby, Schlaepfer, Fisch, & Sackeim, 2001c). Magnetic seizure therapy initiates a tonic-clonic seizure using a magnetic stimulator that focuses on a specific area of the brain and delivers a peak electrical charge that is comparable to that of an ECT treatment. The potential advantage of magnetic seizure therapy is that the maximum voltage (and area associated with the greatest side effects) can be focused on an area associated with a therapeutic benefit (e.g., prefrontal cortex) and spare areas associated with debilitating side effects (e.g., hippocampus). Magnetic seizure therapy offers the opportunity to target areas for stimulation and has some advantages over ECT, which affects multiple cortical and subcortical areas. Work in this area is ongoing and still in the preliminary stages.

Vagal nerve stimulation (VNS) is approved for treatment resistant epilepsy and exerts this effect by applying intermittent subconvulsive electrical stimulation to the left vagal nerve. The left vagal nerve has autonomic connections to limbic and cortical areas known to be involved in mood regulation (George et al., 2000; Nemeroff et al., 2006) and as previously discussed a putative effect of ECT is to act as an anticonvulsant (Sackeim, 1999). Studies of the effect of VNS on mood regulation in patients with epilepsy demonstrated a trend in a small sample (Elger, Hoppe, Falkai, Rush, & Elger, 2000) or showed a positive effect that was no different from a group of epilepsy patients using anticonvulsants alone (Harden, Pulver, Nikolov, Halper, & Labar, 1999). However a ten week open pilot study of 60 depressed nonepileptic patients showed a response rate of 31% and remission rate of 15% (Rush et al., 2000; Sackeim et al., 2001c) with a continuation of the initial treatment response over the following two years (Nahas et al., 2005). This pilot data served as the basis for a larger multicenter trial with 222 patients (Rush et al., 2005a). The study design included a two-week, single-blind recovery period (no stimulation) and then 10 weeks of masked active or sham VNS following implantation. At 10-weeks, response rates were 15% for the active ($n = 112$) and 10.0% for the sham ($n = 110$) groups ($p = .251$). And although this study did not yield definitive evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression, patients were followed for an additional year in a naturalistic study in which they had stimulator adjustments and could have medication changes or other treatments for their underlying depression (Rush et al., 2005b). With these caveats in mind, the response rate was 27% (55/202) and remission rate was 16% (32/202). These patients showed significant improvement

when compared to a matched medication only control group of patients with similar treatment resistant depression (George et al., 2005). The FDA considered this data and approved VNS therapy for treatment resistant depression, although they required the patients receiving VNS to be followed over time to determine the long term treatment response.

The promise of these new treatments is that they will provide relief for the significant number of patients who suffer from major depression, yet have minimal or no response to psychotherapy, pharmacotherapy and/or ECT. The response to ECT is remarkable given the data that more than 80% of patients may remit despite multiple medication failures. However ECT is expensive, stigmatized and has a number of significant side effects including long term memory loss. Even when patients respond to ECT, they face a relapse rate of up to 60% in six months on antidepressant medication. Maintenance ECT is a viable and cost effective option (McDonald et al. 1998 but can be difficult to do given the time and potential side effects. Clearly the field needs new, innovative treatments.

Although TMS and VNS provide therapeutic alternatives, neither provides the efficacy of ECT. Practically TMS may be difficult to administer as the patient is required to come in five days a week for up to six weeks. VNS is expensive and requires surgery and adjustments of the stimulator. Like ECT, pharmacotherapy and psychotherapy, both these treatments are relatively nonspecific with the treatment effects targeted to areas of the brain and circuits involved in depression, rather than specific nuclei and nodes. This lack of specificity may be an advantage in that major depression is a relatively nonspecific disease that includes diagnoses as disparate as post partum depression and depression secondary to stroke. This lack of specificity may also account for the suboptimal treatment response for major depression treated with antidepressant medication. This point was recently highlighted by the STAR-D trial which found a 37% remission rate for patients treated with an SSRI (Rush et al., 2006).

Deep brain stimulation is the most targeted treatment for depression and has shown promise as a subconvulsive stimulus. DBS has been used for the treatment of refractory Parkinson's disease and was the direct result of preclinical research that outlined the neural circuits and underlying positive and negative feedback loops integral to the disease process. Understanding this circuitry enabled surgeons to place a small electrical stimulator in specific subcortical nuclei including the subthalamic nucleus and internal globus pallidus to redirect neural stimuli and treat the disease with remarkable success (Rodriguez-Oroz et al., 2005). With advances in neuroimaging, the neural networks underlying depression have been further defined and targets for DBS have been identified. In an open study, Mayberg and her colleagues demonstrated that bilateral high-frequency stimulation of white matter tracts adjacent to the subgenual cingulate cortex produced a treatment response in four of six highly treatment resistant patients (Mayberg et al., 2005). In fact five of the six patients had failed ECT and at 6 months, half of the patients were in remission. The treatment was well tolerated and was correlated with regional blood flow changes in areas of the dorsolateral prefrontal cortex, subgenual cingulate and anterior cingulate hypothesized to be integral to the development of depression.

The further development of targeted research tools such as genomics and neuroradiology may help develop an understanding of the neural targets in depression treatment (Holtzheimer & Nemeroff, 2006). If successful these treatments may replace ECT, particularly for patient who need long term maintenance ECT or the minority of patients who fail to respond to ECT.

Conclusion

More than 70 years have passed since ECT was first used in the treatment of psychiatric disorders. The lack of rigorous scientific studies during the early use of ECT in part allowed controversy to develop over the use of ECT. A significant stigma associated with ECT remains. This stigma is related more to the past perceptions of ECT and portrayals of ECT in the media than to the current use of ECT. No medical treatment is as effective in treating a debilitating, life-threatening illness, yet associated with such a negative public perception. Despite this ongoing controversy, ECT continues to be an extremely important tool in the treatment of several psychiatric disorders. The increased use of ECT in outpatient settings and as a prophylactic treatment for depression has been shown to be both effective and cost-efficient compared with medication. Alternative strategies such as rTMS have recently gained interest as possible replacements for ECT, but clearly these treatments are still in the investigational phase. In the treatment of severe, resistant depression, ECT remains the gold standard.

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