CHAPTER

92 Electroconvulsive Therapy

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> Although major depression can often be treated successfully, there is a great need for progress in developing treatments that can achieve and maintain recovery for patients with depressive disorders that do not respond readily to currently available treatments.
>
> *Glass 2001*

The profound advances in pharmacotherapy for mental disorders described in previous chapters are widely assumed to correlate with the demise of the older physical or somatic treatments. Indeed, both within and outside the field many assume that electroconvulsive therapy (ECT), as insulin shock treatment and crude forms of psychosurgery, has been confined to the dustbin of psychiatric history. In fact, following 6.5 decades of uneven use, modern ECT has found a narrow but crucial niche among contemporary treatments in psychiatry (US Department of Health and Human Services 1999, American Psychiatric Association 2001). A large body of controlled data supports the efficacy and safety of ECT in the treatment of major depression and other severe psychiatric disorders (American Psychiatric Association 2001).

History and Utilization

History

In contrast to the serendipitous discovery of most biological treatments of mental disorders, the introduction of induced generalized seizures for therapeutic purposes was based on a theoretical construct: the belief in a biological antagonism between schizophrenia and epilepsy. This hypothesis was later rejected. Nonetheless, the demonstration by Ladislas Meduna of the successful reversal of a 4-year catatonic stupor by a series of generalized convulsions induced by intramuscular camphor in oil led to research efforts that permanently altered the attitudes and approaches to treatment of the severely mentally ill. Using the more reliable convulsant agent, pentylenetetrazol (Metrazol), Meduna went on to treat more than 100 patients with schizophrenia during the mid-1930s, reporting a 50% response rate in those ill for less than 10 years (Fink 1984).

As word spread of the efficacy of convulsive therapy in dementia praecox, investigators sought to overcome its limitations, including difficulty in consistently inducing the desired generalized seizures. Having demonstrated the safety of electrically induced seizures in animals, in 1938 Ugo Cerletti and Lucio Bini applied this technique in the treatment of a delusional, incoherent man found wandering the streets of Rome. The patient showed improvement after a single treatment, recovered after a series of 11—proclaiming his enthusiasm about the new treatment at discharge—and was well and working at 1-year follow-up (Pallanti 1999). Thus "electro convulsive therapy," or ECT was born, along with the general principle, still debated today, that the "active ingredient" of convulsive therapy is the generalized seizure, and its means of production is unimportant (Cerletti 1956). Primed by a widely reported 1937 conference in Switzerland on convulsive and insulin coma therapies, clinicians around the world hastened to apply the new ECT to their schizophrenic patients.

The initial 2 decades of ECT use brought a continual stream of refinements in the treatment, as well as abuses, which continue to blemish its reputation and public image. Although an influential 1947 report by the Group for the Advancement of Psychiatry decried what many in the then predominant psychodynamic community felt to be overuse of ECT at the expense of more desirable psychotherapy, by then a wave of unprecedented therapeutic optimism was fueled by ECT, as its efficacy was demonstrated in the mood disorders and its adverse effects reduced by modifications in treatment technique. In the ensuing years, the introduction of general anesthesia, oxygenation, and muscle relaxing agents; and refinements in electrode placement, the seizure-inducing electrical waveform, and the informed consent process have helped to improve the benefit–risk ratio of convulsive therapy over the past half century (see Table 92–1).

Just as the more modern era of modified ECT was beginning, however, it was overtaken in many settings by the psychopharmacology revolution in the 1950s (Fink 1984, Rudorfer and Goodwin 1993). The introduction of effective medications that were easier to use and less expen-

Table 92–1 Central Events in the History of Electroconvulsive Therapy

1500s	The 16th century Swiss physician, Paracelsus, uses camphor by mouth to produce seizures to treat psychiatric conditions.
1764	Leopold von Auenbrugger treats "mania vivorum" with camphor every 2 h, producing seizures.
1785	Oliver reports in the *London Medical Journal* the therapeutic use of seizure induction to treat a case of mania, using camphor by mouth.
1934	Von Meduna introduces the modern use of convulsive therapy, unaware of the previous history. On January 23, 1934, Von Meduna begins treatment of a patient with schizophrenia who had been in catatonic stupor for 4 yr, using intramuscular injection of camphor in oil. He soon replaced this technique with intravenous infusion of pentylenetetrazol.
1937	The Swiss psychiatrist, Müller, organizes an international meeting on convulsive therapy in Münsingen. Meeting proceedings are published in the *American Journal of Psychiatry*, and use of convulsive therapy spreads worldwide.
1938	The Italian psychiatrist and neurophysiologist, Cerletti and Bini, introduce the use of electricity as a means of seizure induction. A mute, catatonic patient is first treated with ECT in mid-April 1938. The patient begins to talk after the first treatment.
1939	Lothar Kalinowsky, who observed the second treatment administered by Cerletti and Bini, introduces ECT in England.
1940	ECT is introduced to the US. Within a few weeks, two facilities in New York City and one in Cincinnati conduct the first treatments. Through the 1940s and 1950s use of ECT becomes widespread, and its particular efficacy in mood disorders is noted.
1940	The psychiatrist, A.E. Bennett, pioneers the extraction of curare from *Chondodendron tomentosum*. Curare is originally developed to serve as a muscle relaxant in ECT.
1951	Fatalities resulting from the use of synthetic forms of curare lead to the introduction of succinylcholine, which becomes the standard agent used for muscle relaxation. The routine use of general anesthesia ensues.
1958	The British psychiatrist, Lancaster, publishes the first controlled study of the use of unilateral ECT. From the outset, it is evident that cognitive side effects were lessened with unilateral relative to bilateral electrode placement. The controversy concerning the equivalency in efficacy continues to the present.
1960	The Swedish psychiatrist, Ottosson, reports a classic study demonstrating that interference with the seizure discharge by administration of an anticonvulsant medication reduces the efficacy of ECT. The view that the seizure activity provides the necessary and sufficient conditions for treatment efficacy is supported.
1962	Greenblatt in the US, and later, in 1965, the Medical Research Council in Great Britain, report large-scale, randomized clinical trials of the efficacy of ECT and medications in the treatment of depression. Antidepressant response rates are substantially higher with ECT than with pharmacotherapy.
1965	May and Tuma compare the use of neuroleptics, ECT, psychotherapy, and milieu treatment for "middle prognosis" schizophrenia. Neuroleptic medication shows superior short-term efficacy, although ECT is more effective than the other interventions on long-term follow-up.
1975	The popular movie, *One Flew Over the Cuckoo's Nest*, is released, portraying ECT as a form of punishment and behavioral control. In this era, use of pharmacological treatment increases and use of ECT in public sector facilities decreases markedly.
1976	The American psychiatrist, Blatchley, develops a constant current, brief pulse ECT device. This form of treatment ultimately replaces constant voltage, sine wave stimulation due to a substantial advantage with respect to cognitive side effects.
1978	The American Psychiatric Association releases its first Task Force Report on ECT. New standards are introduced regarding consent, and use of unilateral electrode placement is encouraged.
1984	A set of six double-blind, randomized trials, conducted in England in the late 1970s and early 1980s, compares the efficacy of ECT with administration of anesthesia alone. ECT is shown to be more effective than sham treatment in major depression.
1985	The National Institutes of Health/National Institute of Mental Health Consensus Conference on ECT confirms its role for special populations and calls for additional research and national standards of care.
1987	Sackeim and colleagues at Columbia University report that the combination of low dosage and right unilateral electrode placement is ineffective. By demonstrating that generalized seizures can be produced that lack efficacy, the long-standing view that the seizure provides the necessary and sufficient conditions for ECT response is contradicted.
1988	Following 50 yr of empirical use of ECT in the treatment of acute mania, Small and associates at Indiana University publish the first random-assignment controlled clinical trial. ECT and lithium are shown to be equally effective. This finding is soon replicated in medication-resistant manic patients in New York in a prospective trial that has to be aborted after several staff members are assaulted by the medication-free subjects.
1990	The American Psychiatric Association releases its second Task Force Report on ECT. Detailed recommendations for treatment delivery, education, and training are provided.
1993	A study reported in the *New England Journal of Medicine* provides the first demonstration that electrical dosage can influence the efficacy, speed of response, and cognitive side effects of ECT. An accompanying editorial offers evidence to the field of the contemporary role of ECT as "a modern medical procedure."
1995	Publication of the autobiographical book, *Undercurrents* by psychologist Martha Manning presents to a broad audience a compelling account of the life-saving potential of ECT by an initially reluctant recipient.
2000	Independent research groups confirm and extend the dose–response relationship in right unilateral ECT, demonstrating an equivalent clinical response between high-dose unilateral and bilateral ECT, but with a decided cognitive advantage to right unilateral electrode placement. Previous recommendation of unilateral stimulation at 150% above seizure threshold is found to be inadequate.
2001	The American Psychiatric Association publishes another ECT Task Force Report, this one constituting the 2nd edition of its highly successful ECT guidelines for practice, education, and training. Additional emphasis is placed on informed consent and avoiding narrow interpretations of potential ECT responders; position on combined medications plus ECT is softened.
2001	*Journal of the American Medical Association* publishes the largest modern trial of post-ECT continuation pharmacotherapy, demonstrating superiority of combined treatment with a tricyclic antidepressant (nortriptyline) plus lithium compared to nortriptyline alone or placebo in preventing relapse during the 6 mo following a successful course of ECT. An accompanying editorial (quoted at the beginning of this chapter) welcomes ECT to the medical mainstream.
2002	Ongoing research includes a multisite controlled trial of continuation ECT vs. optimal pharmacotherapy in relapse prevention, and further development of potentially alternative somatic treatments, including rTMS, magnetic stimulation therapy, and VNS.

sive than ECT led to the curtailment of convulsive therapy in many public institutions. This development was also driven by political factors, which, aided by outdated and, at times distorted media presentations, cast convulsive therapy as an oppressive, dangerous tool of the psychiatric establishment. The net effect was that during the 1960s and 1970s many training programs in psychiatry stopped the teaching of ECT and the treatment appeared to be dying.

The subsequent reemergence of ECT and its role today as a valued member of the treatment armamentarium can be accounted for by several factors. First, critical limitations of psychopharmacology and other treatment approaches have been recognized, including a significant rate of treatment resistance in the major psychiatric disorders and medication toxicities. Second, a series of critical reexaminations of ECT by professional organizations around the world, including Britain (Pippard and Ellam 1981, Royal College of Psychiatrists 1995), Scandinavia (Heshe and Roeder 1976, Frederiksen and d'Elia 1979), Canada (Clark 1985), and, in the US, a National Institutes of Health (NIH)/ National Institute of Mental Health (NIMH) consensus conference (1985), three sets of recommendations by American Psychiatric Association (APA) Task Forces (1978, 1990, 2001), and the first-ever Surgeon General's report on mental health (US Department of Health and Human Services 1999), have supported the important role of convulsive therapy in modern medicine (Potter and Rudorfer 1993). Finally, coincident with advances in the clinical science of ECT and with the personal testimonies to the benefits of convulsive therapy by a number of public and private figures (Manning 1995, Hartmann 2002), media accounts of this treatment have become notably more balanced over the past decade.

Utilization

Throughout its long history, the actual usage of ECT has been determined not only by the results of clinical trials and experience, but by the status of alternative treatments, cost, rates of institutionalization, diagnostic shifts, and, more than any other extant psychiatric treatment, public and professional attitudes about the procedure. A consistent feature of the utilization of ECT over the past several decades has been its unevenness—regionally (Hermann et al. 1995, Olfson et al. 1998) and even locally (Westphal et al. 1997, Glen and Scott 2000, Prudic et al. 2001). Current use of ECT is influenced most by treatment setting, demographic features of patients (including psychiatric and medical diagnoses, age, and ethnicity), and, in several instances, local legal restrictions. In addition, there remain wide variations in the rate of utilization or recommendation of ECT within the mental health professions, on both sides of the Atlantic (Glen and Scott 2000, Prudic et al. 2001). Hermann and associates (1998) have described some of the characteristics of the relatively few (<8%) American psychiatrists who perform ECT, including a greater likelihood of being a male international medical graduate not having performed residency during the ECT "training deficit" in the 1970s, and practicing in private care settings in the southeast or mid-Atlantic sections of the country. Despite the low rate of ECT utilization in Texas, state hospital psychiatrists there profess a favorable attitude toward the use of ECT in generally accepted circumstances (Finch et al. 1990).

Rates of ECT Use

Several surveys in this country and abroad between the 1970s and early 1990s documented the extent of ECT use over time. Representative psychiatric inpatient data collected by NIMH demonstrated a 46% decline in ECT use in the American hospitals between 1975 and 1980 (Thompson and Blaine 1987) totaling only 2.4% of psychiatric admissions in 1980. However, ECT use during the 1980s remained constant or actually increased, reaching 36,558 US inpatients in 1986 (Thompson et al. 1994), some 5,000 more individuals than had been counted at the start of the decade. Among Medicare beneficiaries, the number of patients treated with ECT continued to rise into the next decade, from 12,000 in 1987 to 15,560 in 1992 (Rosenbach et al. 1997); during that 5-year period, the rate of ECT use increased from 4.2 to 5.1 individuals for every 10,000 Medicare beneficiaries. More recently, a large-scale national survey of representative acute-care hospital records sponsored by the US government yielded a wealth of information on more than 2,000 inpatients who received ECT in 1993, representing 9.4% of sampled individuals discharged with a diagnosis of recurrent major depression (Olfson et al. 1998). By the mid-1990s, legislative restrictions on the use of ECT in some states, for example, Texas, were associated with relatively low rates of use of this modality (Finch et al. 1990).

ECT Setting

Even more striking was the shift in the type of institutional setting where ECT is used. In contrast to its origins in the public mental health sector, in the US ECT now is primarily a treatment offered in private general and psychiatric hospitals (Thompson and Blaine 1987, Kramer 1990, Thompson et al. 1994, Olfson et al. 1998). Approximately 10% of admissions to academic and private psychiatric facilities receive ECT (Asnis et al. 1978, Fink 1992). In contrast, relatively few public institutions provide ECT (Asnis et al. 1978, Kramer 1990, Malsch et al. 1991, Fink 1992, Rosenbach et al. 1997, Olfson et al. 1998, Reid et al. 1998, Sylvester et al. 2000). For example, in a recent survey, only 164 of the more than 10,000 inpatients, that is <2%, in the New York state hospital system received ECT over a 2-year period. Data from other countries conform in general to the American experience, including a reduced use of ECT in the 1970s in countries like Great Britain (Lambourn and Gill 1978) followed by an increase in usage the next decade, as shown in Denmark (Stromgren 1991). In England, where most ECT is performed in National Health System hospitals, the decline in the prescription of convulsive therapy continued throughout the 1980s, but in an uneven fashion, such that Pippard (1992) found 12-fold differences in ECT use across health districts. Similarly, 22-fold differences in ECT use were seen among hospitals in the Republic of Ireland, where more ECT is performed per capita than in England (Latey and Fahy 1985). Across the entire UK, current estimates of ECT use are approximately 150 per 100,000 population annually.

It should be noted that most of the large surveys of ECT use to date have not accounted for the outpatient

administration of convulsive therapy (Thompson et al. 1994, Fink et al. 1996), a growing but still less-common practice with considerable cost-effectiveness potential (Komrad 1988, Rosenbach et al. 1997, Prudic et al. 2001). Indeed, the cost implications for ECT in general constitute the proverbial two-edged sword. On the one hand, a course of ECT per se, even without the additional charge for hospitalization, costs thousands of dollars, putting it out of reach for many poorly insured patients (Olfson et al. 1998). On the other hand, the appropriate use of ECT may save money over the long haul, especially if its timely application prevents weeks or months of fruitless medication trials and hospitalization (Markowitz et al. 1987). Thus, among patients hospitalized for recurrent depression in the early 1990s, those who received ECT beginning in the first 5 days in hospital, compared to those whose ECT started later in their hospital stay, experienced (controlling for several demographic and other variables) a hospital stay that was on average 6 days shorter and nearly $6,000 less expensive (Olfson et al. 1998). The savings in time and money were even greater for the subgroup of inpatients with psychotic depression. However, it must be borne in mind that even with prompt institution of ECT, these patients' total hospital charges were more than $5,000 greater than those of similar inpatients who did not receive ECT at all (Olfson et al. 1998). Similarly, the use of ECT in very old (at least 75 years) depressed patients (Manly et al. 2000) and in patients with Parkinson's disease (Moellentine et al. 1998) has been associated with increased hospitalization length of stay, compared to similar cohorts treated pharmacologically.

Demographic Factors

Patient characteristics associated with the use of ECT were identified in several large surveys (Thompson and Blaine 1987, Thompson et al. 1994, Olfson et al. 1998). These include the following:

Gender

As depression is diagnosed more commonly in women than in men, it is not surprising that most individuals who receive ECT are female. For example, 71% of ECT recipients in 1986 were women, a figure that was virtually unchanged in the 1993 nationwide survey (Olfson et al. 1998), a British survey of ECT in geriatric patients (Gormley et al. 1998), and a contemporary review of ECT use in a Pennsylvania state hospital (Sylvester et al. 2000). Olfson and associates (1998) did find that a slightly greater proportion of women with a diagnosis of recurrent depression were treated with ECT compared to their male counterparts (10.1 versus 8.0%). Consistent with that finding, men did not share in the increase in ECT use among Medicare beneficiaries in the 1987 to 1992 survey (Rosenbach et al. 1997).

Age

More than one-third of ECT patients in 1986 were at least 65 years old, a fourfold greater representation than among the psychiatric inpatient population. Among adult inpatients with recurrent depression in 1993, the rate of ECT use approximately doubled with every 15-year age increment, rising from 10.6% of patients between age 50 and 64 years to 21.2% of those older than 65 years (Olfson et al. 1998). Similar results were obtained in Norway, where 22% of 239 patients consecutively admitted to a geriatric psychiatry unit received ECT (Kujala et al. 2002). A retrospective survey of ECT use at 59 of the New York City metropolitan area facilities in 1996 found that >50% of ECT recipients were older than age 60 years (Prudic et al. 2001). Similar findings have been reported in other surveys in the US (Westphal et al. 1997, Reid et al. 1998, Sylvester et al. 2000) and abroad (Jorm and Henderson 1989, Glen and Scott 2000) consistent with the well-recognized advantages of ECT in the elderly, such as safety in the face of concomitant medical illness (NIH/NIMH 1985, Sackeim 1993, American Psychiatric Association 2001). However, the increased utilization of ECT seen in the Medicare population in the late 1980s to early 1990s was actually driven by individuals younger than age 65 years (Rosenbach et al. 1997).

While ECT can be safely and effectively administered to children and adolescents, such use remains rare (Duffett et al. 1999), for example only 0.17% of inpatients younger than age 18 years with recurrent major depression received ECT in 1993 (Olfson et al. 1998). None of the ECT patients in the 1996 New York City area survey were younger than age 13 years, and few were between age 13 and 18 years (Prudic et al. 2001). Only 20 patients younger than age 19 years received ECT for mood disorder over a decade, according to a Paris survey of five centers, three of which specialized in adolescent psychiatry (Taieb et al. 2001). Prospectively collected data for the city of Edinburgh, Scotland, during the 1990s documented an extremely low annual rate of ECT use in young people of 0.5 patients per 100,000 total population (or 2.5 patients per 100,000 population < age 18 years; no one younger than age 17 years actually received this treatment) (Scott and Glen 2000). During the same time period, ECT was administered to Edinburgh adults between age 18 and 64 years at a rate of 26.3 patients per 100,000 population. In some US locales the administration of ECT to young people is restricted by law; for example, between 1974 and 1993, legislation in the states of California, Tennessee, Colorado, and Texas prohibited the use of ECT in anyone younger than a cutoff age that ranged from 12 to 18 years (Reid et al. 1998, Taieb et al. 2001).

Race/Ethnicity

In the US, ECT is predominantly used for the treatment of the white individuals. For example, in 1986 the African-American patients (23% of the total inpatient sample) were grossly under represented among ECT subjects (1.5%) (Thompson et al. 1994). Seven years later the black and Hispanic inpatients with recurrent major depression remained less likely than their white counterparts to receive ECT (Olfson et al. 1998). During that time span, the increased use of ECT among Medicare recipients did not include a proportionate number of minority individuals (Rosenbach et al. 1997).

Indications for ECT

General Considerations

In contrast to its origins as a treatment of schizophrenia, ECT today is generally utilized more frequently in patients with depression (NIH/NIMH 1985, Thompson et al. 1994, Olfson et al. 1998, US Department of Health and Human Services 1999, American Psychiatric Association 2001).

Mania and schizophrenia account for most of the remainder of convulsive therapy use, across the life span (Rey and Walter 1997, Van Gerpen et al. 1999, Kramer 1999). The decision about when to use ECT is based on signs and symptoms of severe mental disorders that cut across diagnostic lines (Fink 1994). These have been most clearly spelled out by the American Psychiatric Association Task Force (now Committee) on ECT (American Psychiatric Association 1990, 2001), which identified "primary" and "secondary" use of convulsive therapy. Primary indications are those for which ECT may appropriately be used as a first-line treatment. These include situations where the patient's medical or psychiatric condition requires rapid clinical response, where the risk of alternative treatments is excessive, or where, based on past history, response to ECT or nonresponse to medications is anticipated. In line with these findings, Prudic and associates (2001) reported that the New York area clinicians cited as the immediate indication for ECT previous successful use of the treatment almost 30% of the time and psychiatric urgency in nearly 20% of patients. If these conditions are not met, medication or other alternative treatment is recommended first, with ECT reserved for cases of nonresponse to adequate trial(s), unacceptable adverse effects of the alternative treatment, or deterioration of the patient's condition, increasing the urgency of the need for response (American Psychiatric Association 2001). These general principles in turn require individualized interpretation in the presence of specific psychiatric and medical disorders. Even where ECT is not used as treatment of first choice, its introduction sooner in the decision tree rather than being reserved as a "last resort" may spare the patient multiple unsuccessful medication trials, thereby avoiding months of suffering and possibly reducing the likelihood of treatment resistance (Potter and Rudorfer 1993, American Psychiatric Association 2001, Glass 2001). Modern diagnostic and clinical considerations in the recommendation of ECT are summarized in Table 92–2.

Contemporary use of ECT overwhelmingly conforms to evidence-based indications. Hermann and associates (1999) surveyed nearly 1,000 ECT recipients in one New England health plan and found 86.5% to conform to evidence-based indications, with most of the remainder suffering from disorders with substantial depressive components; no indiscriminant use of ECT was identified.

Table 92–2 Indications for Electroconvulsive Therapy

I. Diagnostic Considerations

A. Major depression: unipolar, especially primary *psychotic* (but other subtypes may respond); bipolar
B. Mania
C. Schizophrenia: acute
D. Schizoaffective disorder
E. Neurologic disorders: Parkinson's disease
catatonia
neuroleptic malignant syndrome

II. Clinical Considerations

A. Need for rapid response on medical or psychiatric grounds (e.g. suicidality, inanition)
B. History of treatment-resistance or excessive risk of alternative treatments
C. Severity of illness
D. History of previous positive response to ECT
E. Patient preference
F. Informed consent required

Depression

More than 30,000 individuals hospitalized with mood disorders in the US in 1986 (about 1 in 20 with those diagnoses) received ECT, accounting for 84% of the use of this treatment (Thompson et al. 1994). Of these, the vast majority suffered from severe major depression. Similar data were obtained in the more recent survey of the New York City area facilities (Prudic et al. 2001). It is well established that major depression is a heterogeneous disorder, encompassing mildly ill, functioning outpatients, as well as profoundly disturbed, dysfunctional, or often psychotic inpatients. Along this spectrum, ECT appears higher in the treatment hierarchy for the more severe presenting depression, usually defined by the presence of neurovegetative signs, psychosis, or suicidality (Abrams 1982, American Psychiatric Association 2000, 2001). Contemporary use of ECT reflects this severity spectrum, with rates of inpatient ECT administration falling from 9.4% in patients with recurrent major depression to 3.2% of those with a single episode of major depression and only 0.5% of patients with a discharge diagnosis of dysthymia (Olfson et al. 1998).

This severity of depression also partly determines whether alternative treatments will be attempted prior to a trial of convulsive therapy. While there are no absolute rules, severely melancholic or psychotic patients are often appropriate candidates for ECT as treatment of first choice, whereas more moderately ill individuals might not be considered for ECT until adequate medication trials have failed. In the presence of primary, melancholic depression, a case can be made that a single adequate unsuccessful trial of appropriate antidepressant medication is a sufficient prerequisite for ECT (Potter and Rudorfer 1993). On the other hand, a patient with mood shifts secondary to a personality disorder may not be a candidate for ECT even after multiple medication failures (Kramer 1982).

Clinical Trials

The evidence supporting the efficacy of ECT in depression is overwhelming. Three main types of data have appeared, to a large part sequentially, over the past half century: uncontrolled case series in the early years, followed in the 1950s and 1960s by controlled comparisons of ECT and psychotropic medications, and finally, in the 1970s and 1980s, the use of sham ECT-treated patient samples to control for the nonspecific effects of the procedure and its associated anesthesia and other medications. Janicak and associates (1985) conducted a meta-analysis of ECT comparison studies in depression. Their results were clear-cut: ECT was found to have superior efficacy to all comparison groups, being 41% more effective than placebo, 32% more effective than sham ECT, 20% more effective than generally adequate doses of tricyclic antidepressants (TCAs), and 45% better than monoamine oxidase inhibitors (MAOIs). Although this sweeping conclusion has been challenged (Rifkin 1988), due to the shortcomings of some studies by

today's methodological standards, the extraordinary efficacy of ECT is now well accepted (NIH/NIMH 1985, Potter and Rudorfer 1993), with no controlled study ever showing any other treatment to have superior efficacy to ECT in the treatment of depression.

Controlled comparisons of ECT with the modern generation of antidepressants are sparse, in large part due to the difficulty in recruiting patients for such a random assignment study. A notable exception is a German clinical trial that entailed randomization of 39 patients with major depression resistant to at least two previous medication trials to either a course of brief-pulse right unilateral ECT or a trial of the standard selective serotonin reuptake inhibitor (SSRI), paroxetine (Folkerts et al. 1997). The ECT group (mean of 7.2 treatments) showed superiority to the paroxetine subjects (mean daily dose of 44 mg), both in magnitude of clinical improvement (71 versus 28% response rate) and speed of antidepressant effect (Folkerts et al. 1997). As a useful, if uncontrolled reference point, the recent New York survey of ECT practice in the community (Prudic et al. 2001) found an acute clinical benefit for >84% of patients, the vast majority of whom were suffering from depression. Although published reports describe a 63% ECT response rate in depressed children and adolescents, there have been no controlled trials in this population (Rey and Walter 1997).

Predictors of Response

The literature describes an overall response rate to ECT of 75 to 85% in depression (Crowe 1984, O'Connor et al. 2001). Efforts to delineate subtypes of depression particularly responsive to ECT have yielded inconsistent results. ECT is most likely to be helpful in an acute episode of severe depression of relatively brief duration (Rich et al. 1984). Combined data from two simulated ECT-controlled trials (Brandon et al. 1984, Buchan et al. 1992) identified the presence of delusions and psychomotor retardation as predictive of preferential response. A later open British study (Hickie et al. 1990) replicated the finding of psychomotor retardation as a positive predictor.

Psychotic depression, increasingly recognized as a distinct subtype of mood disorder that responds poorly to antidepressants alone, has emerged as a powerful indication for ECT (Potter et al. 1991, Petrides et al. 2001). In this subgroup, ECT is at least as effective as a combination trial of antidepressant and antipsychotic medications. On balance, the evidence supports the early use of ECT in psychotic depression, particularly in lieu of prolonged, complicated medication trials that may be poorly tolerated in the elderly (Khan et al. 1987, Potter et al. 1991, Sackeim 1993). Indeed, in one modern study in three academic medical centers, only 4% of psychotically depressed patients referred for ECT had received adequate pharmacotherapy trials (Mulsant et al. 1997). By the 1990s, these findings were incorporated into routine clinical practice, as evidenced by the relatively high rates of ECT used with patients hospitalized with major depression with psychotic features, both recurrent (11.8%) and single episode (5.5%) (Olfson et al. 1998). Nearly half of the geriatric patients receiving ECT at three UK hospitals in the mid-1990s exhibited psychotic features associated with unipolar or bipolar depression (Gormley et al. 1998), twice the rate seen in a smaller US retrospective survey of very old patients (Casey and Davis 1996). The most definitive contemporary data comparing ECT effectiveness in psychotic versus nonpsychotic depression emerge from the acute treatment phase of an ongoing NIMH-supported four-site Consortium for Research in ECT (CORE) trial of continuation treatments (Petrides et al. 2001). Among 253 patients with unipolar major depression who underwent an acute course of bilateral ECT were 77 individuals, of similar age and gender distribution to the group as a whole, with psychotic features. More than a third of the old–old patients in this group had psychotic features, compared to less than a quarter of those aged 45 years and younger (O'Connor et al. 2001). The remission rate among treatment completers was significantly greater for the psychotic patients (95%) than the still impressively high 83% remission rate for the nonpsychotic completers; there was no difference in the number of treatments between the groups. Time to remission was also shorter in the psychotically depressed patients (Petrides et al. 2001).

Data from the acute phase of another NIMH-supported three-site trial (Sackeim et al. 2001) have shown a history of antidepressant medication resistance to predict nonresponse to a subsequent course of ECT (Prudic et al. 1996). The predictive power of medication resistance applied only to heterocyclic antidepressants, not SSRIs or MAOIs. It is also relevant that the 100 patients analyzed for this relationship were all nonpsychotic; psychotically depressed patients typically fail to respond to antidepressant medication alone, yet, as noted, consistently demonstrate high response rates to ECT (Petrides et al. 2001). Recent advances in optimizing right unilateral ECT, to be reviewed later, may help overcome the reported resistance to convulsive therapy (Prudic et al. 1996).

In general, beyond psychosis, individual clinical features, even melancholia, the predictor of long-standing conventional wisdom (Rush and Weissenburger 1994), and psychomotor retardation (Sobin et al. 1996) have not proven to be reliable indicators of response to ECT in modern studies (Zimmerman et al. 1986, American Psychiatric Association 2001). Indeed, recent data have shown ECT effectiveness even in so-called "atypical depression" (McClintock et al. 2002). While bipolar (discussed later) and unipolar depressions are equally responsive to ECT (Zorumski et al. 1986a, Zornberg and Pope, 1993, American Psychiatric Association 2002), response may be less likely with secondary than primary depression, in both adults (Kramer 1982, Zorumski et al. 1986b, Zimmerman et al. 1986a)—including the elderly (Zorumski et al. 1988)—and adolescents (Schneekloth et al. 1993). This may be especially true when depression is secondary to another psychiatric disorder, rather than to a medical illness (Winokur et al. 1988, Zorumski et al. 1988). A family history of nonaffective psychiatric disorder, specifically alcohol dependence or sociopathy, may also lessen responsivity to ECT among primary depressives (Coryell and Zimmerman 1984).

Suicidal ideation is of special relevance in evaluating the potential role of ECT in the treatment of an individual with major depression. While commonly regarded as an indication for the prescription of ECT, suicidal ideation has not been shown by itself to predict responsivity (Tanney 1986, Prudic and Sackeim 1999). While historically, the introduction of ECT was regarded as associated with a

reduction in completed suicides, careful review of the literature (Prudic and Sackeim 1999) revealed considerable methodological limitations in most relevant surveys; a more accurate interpretation of the data may be that ECT is associated with a reduction in mortality from all causes, not necessarily specifically suicide. Indeed, retrospective reports continue to appear claiming a failure of ECT to prevent suicide, based on similar rates of utilization of the treatment in depressed patients who did or did not go on to commit suicide (Sharma 1999).

However, recent data have indicated a significant acute antisuicidality effect of ECT. Prudic and Sackeim (1999) found a significant reduction in the suicide item score on the Hamilton depression rating scale following a course of ECT, both in responders ($N = 72$) and, to a lesser but still significant extent, in nonresponders ($N = 76$). Similar results are being observed in the acute phase of the ongoing CORE trial. Among the first 235 patients rated as suicidal at baseline, two-thirds had a suicidality item rating of zero after three bilateral ECT treatments, and 90% were free of suicidal ideation after completion of seven treatments (Kellner et al. 2002). As with its general antidepressant effect, this apparent antisuicidal action of ECT should be regarded as acute and not long-term without the introduction of appropriate continuation and maintenance treatment, as will be discussed further.

Biological measures have proven unhelpful as predictors of ECT response, including the initially promising dexamethasone suppression test (DST) (Coryell and Zimmerman 1984, Scott 1989, Devanand et al. 1991). Similarly, although the pretreatment blunting of the thyroid-stimulating hormone (TSH) response to thyrotrophin-releasing hormone (TRH) challenge has been reported to return to normal following successful ECT (Kirkegaard and Faber 1986, 1998), the state versus trait nature of this challenge paradigm remains under investigation, making its clinical application at this time premature (Golden and Potter 1986). While assurance of an adequate seizure induction at each treatment session is necessary for a successful outcome (Sackeim et al. 1993, Abrams 2000), efforts at constructing a ''dose–response'' relationship based on total seizure duration over an ECT course, likewise have proven disappointing (Zorumski et al. 1986a). A number of physiological responses to ECT, including release of posterior pituitary peptides (Scott 1989, Scott et al. 1991) and changes in sensitivity to the barbiturate anesthesia (Barry et al. 1991) remain under investigation as possible predictors of outcome. Others, such as the typical rise in seizure threshold over a course of ECT (Scott 1989, Sackeim et al. 1993), have proven unrelated to clinical response (Scott et al. 2000).

Finally, a previous history of antidepressant medication failure is emerging as a potent predictor of ECT nonresponse and early relapse (Prudic et al. 1990, Sackeim et al. 1990a, 1990b). This concept challenges decades of generally retrospective case series claiming considerable (often >70%) success rates with ECT in pharmacotherapy-resistant depressed patients (Avery and Lubrano 1979, Paul et al. 1981, Magni et al. 1988). These earlier findings have been questioned based on methodological limitations of these uncontrolled treatment trials, most notably inadequacies in the definition of treatment response and resistance (Prudic et al. 1990). In one prospective trial of bilateral ECT administered to 53 patients with major depression (Prudic et al. 1990, Sackeim et al. 1990a), only a 50% clinical response rate was obtained in the 24 patients who previously had failed to respond to adequate pharmacotherapy. In contrast, 86% of patients lacking a history of medication resistance responded to ECT. A range of clinical factors potentially might account for these results and requires further prospective study. Nonetheless, in community surveys, medication resistance is the cited precipitating factor leading to a course of ECT in about two-thirds of cases (Prudic et al. 2000).

Bipolar Disorder

ECT is an extremely effective and rapidly acting treatment for both acute mania and bipolar depression (American Psychiatric Association 2002). However, it is infrequently used for mania, because of the availability of pharmacological strategies (Goodwin and Jamison 1990). Nonetheless, ECT has been repeatedly endorsed as an accepted second- or third-line treatment of acute manic episodes, particularly in cases of medication resistance, in patients of all ages (NIH/NIMH 1985, Goodwin and Jamison 1990, Mukherjee et al. 1994, Van Gerpen et al. 1999, American Psychiatric Association 2002). Although 20 to 30% of bipolar patients are refractory to lithium and other medications, mania accounts for only approximately 3% of ECT use in this country. Under certain circumstances, such as manic delirium, ECT can be life-saving (Fink 2002), a reminder that prior to the development of somatic treatments, mania had a mortality rate of at least 10%. Thus, in medical emergencies associated with mania, ECT should be regarded as a treatment of first choice (American Psychiatric Association 2002). The same is true for medical conditions accompanying acute mania (including pregnancy, discussed later) that contraindicate or render intolerable the use of psychotropic medications.

Clinical Trials

The methodological problems that hamper research in ECT generally (Rudorfer 1994, Potter 1994) are starkly illustrated in the case of mania. The imperatives of securing informed consent and withdrawing confounding psychotropic drugs are difficult to reconcile with the clinical realities of dealing with a severely ill, often irritable and aggressive, patient population. Indeed, hospital staff were injured and hospitalized in one prospective trial (Mukherjee 1989). Another pilot study that sought to avoid use of neuroleptics in manic patients scheduled for an ECT versus lithium trial (Small et al. 1988) was aborted when all four subjects dropped out within 10 days. Adjunctive antipsychotic medications had to be permitted to allow the study to go forward.

Half a century's worth of uncontrolled case series on the use of ECT in mania has only recently been supplemented by a trio of prospective clinical trials (totaling 69 patients) and several large and small retrospective chart reviews (Mukherjee et al. 1994). In a comprehensive review of the literature, Mukherjee and associates (1994) tabulated a total of nearly 600 manic patients, of whom 80% showed marked clinical improvement or remission following convulsive therapy. Most compelling were two controlled

retrospective studies from the 1970s and early 1980s (McCabe 1976, McCabe and Norris 1977, Thomas and Reddy 1982), a large but uncontrolled naturalistic survey (Black et al. 1987), and the three controlled prospective trials (Small et al. 1988, Mukherjee 1989, Sikdar et al. 1994).

Related record reviews at the University of Iowa demonstrated the superiority of ECT in acute mania over no active treatment (in historical controls from the 1930s) (McCabe 1976) or chlorpromazine (McCabe and Norris 1977). In the latter study, all 10 of 28 chlorpromazine-treated patients who failed to improve subsequently responded to ECT, joining the 18 of 28 initial ECT responders. A later retrospective study (Thomas and Reddy 1982) found very high (100% in the case of ECT), and not significantly different, antimanic response rate to convulsive therapy, lithium, or chlorpromazine. Naturalistic surveys have found higher response rates when ECT was used as a first-line treatment of mania (100%) (Mukherjee and Debsikdar 1992) than when it was reserved for medication-resistant manic patients (Alexander et al. 1988, Stromgren 1988). Black and colleagues (1986, 1987) found a 78% response rate to ECT, superior to the approximately 60% response rate with lithium. In contrast to recent experience with depressed patients discussed above, subsequent ECT in manic lithium nonresponders yielded an impressive response rate of 69%.

The first prospective and randomized comparison of ECT and lithium was obtained in 34 manic inpatients (Small et al. 1988). ECT resulted in greater improvement during the 8-week trial than lithium. However, at the end of the acute treatment period, the two groups did not differ in clinical improvement, and went on to similar rates of relapse and recurrence during a subsequent 2-year trial of lithium maintenance. As noted, the primary confound in the Indiana study (Small et al. 1988) was the use of concurrent neuroleptic medication. Different methodology was applied in the other American prospective trial of ECT in mania, where patients were preselected for nonresponse to lithium or a neuroleptic in the index episode (Mukherjee 1989, Mukherjee et al. 1994). In this New York study, amobarbital, but no antipsychotics, was permitted as prn medication. Either unilateral or bilateral ECT was associated with clinical improvement in most (59%) of 22 patients, compared to no responders among five patients assigned to an intensive lithium plus haloperidol combination. The efficacy of ECT in acute mania was also demonstrated in the only non-US prospective trial (Sikdar et al. 1994), in which bilateral ECT was compared to sham ECT. Both groups received concurrent chlorpromazine 600 mg/day, but no patients received lithium. Twelve of 15 patients who received real ECT, compared to only one manic patient treated with sham ECT, showed complete recovery, with improvement in all manic symptoms. Follow-up neuroleptic requirements were accordingly lower in the real ECT group. Looking at another way, the addition of ECT to the antipsychotic medication regimen cut the duration of the index manic episode in half (Sikdar et al. 1994).

Predictors of Response

There is little information on which manic patients benefit most from ECT or on optimal ECT treatment in mania. The Indiana group (Small et al. 1986, Milstein et al. 1987) suggested that bilateral electrode placement was superior to unilateral ECT in treating manic symptoms. However, the naturalistic Iowa study (Black et al. 1987) and the prospective New York trial (Mukherjee 1989) failed to find significant differences in the response rates of manic patients treated with bilateral, unilateral, or mixed electrode placements. In terms of clinical features associated with response, Small and associates (1988) found baseline depression rating most highly related to 8-week outcome. Extreme manic behavior and mixed symptoms of mania and depression were also associated with a superior response to ECT over lithium. However, in contrast to the situation in psychotic depression, discussed earlier, the presence or absence of psychosis has not been found to affect the high response rate of mania to ECT (Black et al. 1987). Schnur and colleagues (1992) reported that response to ECT was reduced among manic patients with prominent symptoms of anger, irritability, and aggression, consistent with findings regarding lithium.

Bipolar depression responds as well as unipolar depression to ECT, in both adult and geriatric patients (Gormley et al. 1998, American Psychiatric Association 2002). In the early years of psychopharmacology, several controlled trials in bipolar depression found ECT superior to first-generation antidepressant (MAO inhibitor or tricyclic) medications (American Psychiatric Association 2002). Hypomania or mania is a risk of using ECT for depression in bipolar patients, but this is not different from the experience with any antidepressant treatment in this disorder (Gormley et al. 1998, American Psychiatric Association 2001, American Psychiatric Association 2002). A number of small trials over the years have described a beneficial role of maintenance ECT for some patients with bipolar disorder, an approach endorsed by the American Psychiatric Association (2002) for those patients who fail to respond or cannot tolerate maintenance medication. In one recent study by Gagné and colleagues (2000), discussed in detail later, the 12 depressed patients with bipolar disorder had long-term outcomes with maintenance medications, alone or in combination with maintenance ECT, that were similar to those of the 46 unipolar depressed patients studied.

While Small and colleagues (1988) identified mixed mood states as predictors of ECT response in bipolar disorder, little systematic research has addressed that issue in the intervening decade and a half. A chart review by Devanand and associates (2000) confirmed the responsiveness of mixed bipolar disorder to ECT, but these patients seemed more difficult to treat, tending toward longer hospital stays and more ECT sessions, compared to matched samples of pure bipolar depressed and manic inpatients; however, multiple potentially confounding variables, including presence of psychosis, ECT treatment parameters, and concurrent medications were not controlled. A prospective but also uncontrolled Italian study was more encouraging about the role of ECT in medication-resistant mixed mood states. Ciapparelli and colleagues (2001) found a higher response rate (56 versus 26%) and a greater reduction in suicidality in consecutive ECT patients with mixed mania ($N = 41$) compared with those with bipolar depression ($N = 23$). While additional definitive controlled trials are required, the existing database strongly supports a role for ECT in the treatment of all phases of bipolar disorder in the face of

clinical urgency or refractoriness or excessive risk associated with psychotropic medications (American Psychiatric Association 2001, 2002).

Schizophrenia

Among the changes undergone by convulsive therapy over its 60-year history, few are as striking as those associated with its use in chronic psychotic illness. ECT has evolved from a treatment of first choice for 1930s dementia praecox to often a treatment of last resort for DSM-IV schizophrenia. Advances in diagnostic assessment and classification, shifting some of the former overabundance of would-be schizophrenics to more appropriate, often mood disorder categories, partly accounted for this change. Perhaps more critical were the general factors noted earlier, that is the psychopharmacology revolution, deinstitutionalization, disappointment with ECT effects in chronically psychotic patients, and the limited availability of ECT in public care settings. More recently, the development of clozapine and other atypical antipsychotic medications provides another treatment option for the refractory patient with schizophrenia, further rendering ECT more likely to be unnecessary. Thus, throughout the 1980s the use of ECT for schizophrenia fell in this country, representing 16.5% of inpatient ECT in 1980, but only 6.5% of the increased 1986 pool of ECT recipients (Thompson et al. 1994). In another modern survey, only 1% of hospitalized schizophrenic patients received ECT (Thompson et al. 1994). However, the efficacy of ECT for depressive symptoms associated with psychotic illness is reflected in recent nationwide data showing the use of convulsive therapy in almost 12% of patients with recurrent major depression comorbid with schizophrenia (Olfson et al. 1998), a utilization rate higher than that seen in uncomplicated recurrent depressive disorder.

Clinical Trials

Much of the early literature on ECT in schizophrenia is methodologically unacceptable by modern standards. Diagnoses were assigned by clinical judgment, treatment and assessment paradigms were rarely standardized, and control groups often were absent (Ridell 1963, Salzman 1980, Kreuger and Sackeim 1995). From Meduna's time on, however, it was observed that ECT efficacy in schizophrenia appeared inversely related to length of illness, such that the more acutely ill patients responded best. Some evidence for the need for a large number of treatments (20 treatments were common), sometimes given intensely, also emerged in the early work. However, until the 1960s, little controlled data supported the efficacy of ECT in true "Schneiderian" chronic schizophrenia (Turek and Hanlon 1977). Controlled studies in the 1960s and 1970s positioned ECT between the more-effective neuroleptics and the less-useful milieu or psychotherapy (May 1968, Greenblatt 1977). May and associates (1976), in a conclusion that still stands, observed that pharmacotherapy is generally superior to ECT alone in chronic schizophrenia, but that convulsive therapy may be helpful in some patients who fail to respond to medication. Long-term follow-up 2 to 5 years after acute treatment showed no significant differences between neuroleptic and ECT groups, but on a variety of quality-of-life and symptom measures the outcome in chronic schizophrenia was "grim" (May et al. 1981). The potential value of ECT in combination with antipsychotic medications also began to be appreciated once appropriate studies were performed (Krueger and Sackeim 1995).

These preliminary observations have been solidified over the past 2 decades in a new generation of controlled studies of ECT in schizophrenia (Crowe 1984). Small (1985) reviewed the prospective trials conducted between 1953 and 1985, including five studies of real versus sham ECT and six trials comparing ECT with neuroleptics. She concluded that ECT alone is effective over the short-term in acutely ill schizophrenic patients, but that the majority of "middle prognosis" patients fared better on medication. In such individuals, ECT should be reserved for cases of drug resistance or intolerance.

The latest update of the Cochrane Review of the still inadequate research data (Tharyan and Adams 2002), based on 24 controlled trials in schizophrenia, found a higher rate of improvement with active versus sham ECT or placebo. Other advantages of ECT over inactive control conditions included trends toward increased likelihood of hospital discharge and fewer relapses on short-term follow-up. Another eight randomized clinical trials, however, favored antipsychotic medications over ECT, although, as noted, the addition of continuation ECT to antipsychotic drugs was superior to medications alone (Tharyan and Adams 2002). The potential value of ECT for acute and maintenance treatment in older patients with medication-resistant schizophrenic spectrum disorders—mainly schizoaffective disorder—also has been described in open case series (Kramer 1999).

Additionally, three studies were noted to support a more rapid and complete short-term response to the combination of ECT and neuroleptics than to medication alone. Subsequently, the apparent potentiation of antipsychotic drugs by ECT in medication-refractory schizophrenic patients has been reported in additional clinical samples (Friedel 1986, Gujavarty et al. 1987, Sajatovic and Meltzer 1993), but the presence of affective symptoms and relatively short duration of illness in some patients again raised the question of diagnostic heterogeneity (Christison et al. 1991, Meltzer 1992). A limited controlled database finds continuation treatment in schizophrenia with combined ECT and antipsychotic medications superior to either modality alone (Tharyan and Adams 2002).

With the development of clozapine and other atypical antipsychotic drugs, ECT has been pushed further back in the treatment algorithm for medication-resistant schizophrenia. Case reports and series, often with positive outcomes (Frankenburg et al. 1993, Hirose et al. 2001) are now appearing on the next logical step: clozapine or other atypical antipsychotics combined with ECT. The mechanisms of action of combined ECT–antipsychotic drug treatment remain undefined (Kellner et al. 1991, Klapheke 1993).

The net effect of this body of not particularly well-controlled data is that the American Psychiatric Association Task Force on ECT (American Psychiatric Association 2001) and the Canadian Psychiatric Association (Enns and Reiss 1992) identified a role for ECT as a second-line treatment for selected patients with schizophrenia, particularly when associated with a brief duration of illness and/or affective symptoms. Both groups found chronic schizophrenia to respond no better to real ECT than to sham

treatment. Accenting these views is the speculation by Wyatt (1991) that the long-term presence of psychosis per se may be biologically "toxic" to the brain—in addition to the clear debilitating psychological and social costs of chronic mental illness—suggesting that no treatment option, including ECT, be overlooked in the service of inducing a prompt remission in newly ill, "first-break" patients (Sakar et al. 1994, Fink and Sackeim 1996). Indeed, a substantial proportion of such patients prove on follow-up to be suffering from a mood disorder, for which ECT would be expected to help, but which might be worsened by a neuroleptic (Van Valkenburg and Clayton 1985). Additionally, should ECT enable the delay or reduction in lifetime exposure to neuroleptic drugs, the risk of tardive dyskinesia or other adverse effects of medications might be decreased. Reports of even occasional response to ECT in the more chronically ill schizophrenic individual indicate that convulsive therapy should not be abandoned altogether in this poor-prognosis patient population (Van Valkenburg and Clayton 1985, Hertzman 1992, Fink and Sackeim 1996, Tang and Ungvari 2001b).

Predictors of Response

Despite the considerable variability in methodology across the studies over the past 50 years, several trends have emerged regarding ECT use in schizophrenia. It has been consistently found that the schizophrenic patients most likely to respond to ECT are those with good prognosis signs: mood disturbances, short duration of illness, predominance of positive rather than negative symptoms, and overexcitement (Fink and Sackeim 1996). The potential responsiveness of acute psychotic symptoms in schizophrenia to ECT is more emphatically stated in the 2001 revision of the American Psychiatric Association Task Force Report compared to the previous edition, based on research conducted and compiled in the intervening decade (Fink and Sackeim 1996). Diagnostic subtypes of schizophrenia associated with a positive response to ECT include acute, schizophreniform, schizoaffective, catatonic, and paranoid (Milstein et al. 1990, Rudorfer and Harris in press). Two prospective studies addressing the issue of predictors of outcome in schizophrenic and schizoaffective patients treated with ECT and concurrent neuroleptics found positive treatment response to be associated with recent onset of illness, shorter duration of current episode, dearth of premorbid schizoid personality traits, the presence of perplexity, mood-congruent delusions or hallucinations, and a lesser family history of schizophrenia (Dodwell and Goldberg 1989, Chanpattana and Chakrabhand 2001). Successful ECT in schizophrenia may require a greater number of treatments than is typical in the treatment of mood disorders. No evidence has emerged favoring either bilateral or unilateral electrode placement in the treatment of schizophrenia (Small 1985). A recent report from Hong Kong notes that the benefits of ECT in chronic schizophrenia may extend beyond symptomatic change (Tang and Ungvari 2001b). Although only modest improvement in positive and negative symptoms was observed in six long-term hospitalized patients completing at least eight ECT treatments, four of these individuals experienced clinically significant enhancement of occupational and social functioning (Tang and Ungvari 2001b). This enabled patients with schizophrenia to benefit further from rehabilitative psychosocial interventions. These factors of social and occupational functioning are probably important in determining subjective feelings of improvement following ECT for all chronically ill patients (Rohland 2000), and are especially important as data emerge showing that even where ECT (plus neuroleptics) benefits positive symptoms of schizophrenia, negative symptoms are not improved (Chanpattana and Chakrabhand 2001); the impact of newer atypical antipsychotics on these effects awaits further study.

Other Axis I Disorders

As reiterated in the recent Surgeon General's report on mental health (US Department of Health and Human Services 1999), ECT has no demonstrated efficacy in dysthymia, substance abuse, or anxiety disorder. Nonetheless, ECT may play a role when the severity of a secondary major depression is severe and/or treatment refractory (Olfson et al. 1998, American Psychiatric Association 2001). In such circumstances, ECT can be expected to improve the comorbid mood component, leaving the underlying primary disorder untreated; in some circumstances, removal of the burden of overlying depression may indirectly benefit the underlying disorder. A case in point is obsessive–compulsive disorder (OCD). Despite half a century of literature describing the use of ECT in this anxiety disorder, there is no convincing evidence for the efficacy of convulsive therapy in combating the core symptoms of OCD. Rather, what efficacy has been described can more parsimoniously be traced to a therapeutic action of ECT against the comorbid depression that commonly accompanies OCD (Rudorfer 2000). On the other hand, in the face of a potentially ECT-responsive major depressive episode, the presence of a nonmood Axis I disorder, even substance abuse, should not constitute a contraindication to the use of convulsive therapy (Olfson et al. 1998, American Psychiatric Association 2001).

Axis II Disorders

There are no evidence-based biological treatments for DSM-IV Axis II personality disorders, including ECT. Given the high incidence of comorbid, often treatment-refractory depression that accompanies Axis II pathology, ECT has been used in personality disordered patients, with inconsistent—but generally negative—reports of success, for many years. Most of the literature has focused on what today falls under DSM-IV cluster B personality disorders, especially borderline personality disorder (BPD). In the absence of controlled clinical trials, the perceived clinical wisdom has been along the lines of one recent Canadian retrospective survey (Sareen et al. 2000), which found that compared to ECT candidates with major depression and no Axis II diagnosis, those with comorbid personality disorders had a poorer acute response to ECT and a higher rate of depressive relapse during 1-year follow-up after completion of the treatment course. Even in that methodologically challenged chart review, most patients with comorbid depression and personality disorder did respond acutely to ECT, and more than a quarter of that cohort successfully completed 1-year follow-up without relapse into depression (Sareen et al. 2000).

Even in prospective trials with standardized diagnostic criteria, totaling some 75 patients with major depression plus personality disorder, the role of ECT is not well

defined. This is true of all treatment studies with personality disorder patients, who commonly endorse symptoms on depression rating scales that may reflect Axis II rather than I pathology, confounding the measurement of antidepressant treatment response. In a comprehensive review of the literature, DeBattista and Mueller (2001) summed up current understanding of this dilemma by observing that "the depressed, borderline patient appears to have two distinct disorders, one which is responsive to ECT and the other which is not." Definitive, randomized studies are necessary to determine whether the mixed and often disappointing effects of ECT in patients with comorbid Axis I and II disorders reflect a reduced efficacy of the intervention or is consistent with the treatment-resistant nature of depression in these individuals. However, based on present knowledge, in an individual case, the presence of a major depressive episode that is clearly separate and distinct from the underlying personality disorder should determine the appropriateness and likelihood of response to ECT (DeBattista and Mueller 2001).

Neurologic Disorders

Only 1% of patients admitted with a primary diagnosis other than a mood disorder or schizophrenia are treated with ECT in this country (Thompson et al. 1994). Nonetheless, individuals with neurologic or other medical problems often suffer from primary or secondary mood or motor disorders that are ECT-responsive.

Catatonia

From the inception of convulsive therapy, its efficacy in the syndrome of catatonia, which is dominated by motor signs, has been consistent and often dramatic (Fink and Sackeim 1996). Nearly always successful in this situation, ECT typically induces remission in catatonia in less than a week with only two to four closely spaced, for example daily, treatments (Fink 2002). The use of ECT in this behavioral disorder marked by extremes in activity has been extremely selective, due in large part to the confluence of mostly practical factors. Thus, until recent years the official classification system relegated catatonia exclusively to a subtype of schizophrenia which, according to prevailing wisdom, was not a primary indication for ECT. Moreover, immobile and unresponsive catatonic patients as a rule are unable to give informed consent, and ECT is not typically available in general medical settings, complicating the use of a nonpharmacological somatic treatment (Fink 2002). In recent years, as catatonia has been identified as a component of mood disorders, especially mania (Taylor and Abrams 1977) and "depressive stupor," as well as systemic medical disorders, such as lupus, DSM-IV-TR has broadened its classification beyond schizophrenia.

The case report literature describes the generally prompt and complete response to ECT of catatonic syndromes associated with both primary psychiatric (Pataki et al. 1992, Fink and Sackeim 1996) and systemic disorders (Fricchione et al. 1990). ECT may justifiably be described as life-saving where catatonia leads to inanition and in the often fatal, malignant form of catatonia (Mann et al. 1990b, Philbrick and Rummans 1994). However, controlled trials are lacking and, in the absence of sham ECT comparisons, questions have been raised as to the potential efficacy of the barbiturate anesthesia per se without seizure induction in the catatonic syndrome (Rosebush et al. 1992). A review of the literature over the past 3 decades, however, found all three uncontrolled trials of ECT in catatonia to be efficacious (Hermann et al. 1999); 40 of 43 catatonic patients described in published case reports also responded to ECT. Three quarters of 24 children and adolescents with catatonia associated with mood disorders, schizophrenia, or physical illness are described in an uncontrolled literature as showing marked improvement with ECT (Rey and Walter 1997).

Over the past decade, benzodiazepines have emerged as the pharmacological treatment of choice for catatonia (Rosebush et al. 1992, Ungavari et al. 1994). However, in medication-unresponsive patients, prolonged drug trials with continuing clinical deterioration should be avoided in favor of a course of ECT (Ungavari et al. 1994). Reflecting current understanding of the syndrome and its treatment, Fricchione (1989) recommended that "given the significant morbidity and mortality associated with catatonia, ECT should be considered if an expeditious 48- to 72-hour benzodiazepine trial is unsuccessful." As a practical point, given the now-common initial use of benzodiazepines in this condition, the catatonic patient may come to ECT with an initially elevated seizure threshold, and treatment parameters should be adjusted accordingly (Fink 2002).

Neuroleptic Malignant Syndrome

This clinical syndrome of fever, muscle rigidity with elevated serum creatine phosphokinase, autonomic instability, and mental status changes occurring in patients treated with neuroleptics, may be a form of malignant catatonia (Philbrick and Rummans 1994). Thus, ECT would be expected to be useful. Nevertheless, in the absence of controlled trials, the efficacy of ECT in this syndrome was questioned as recently as the mid-1980s (Levenson 1985).

A subsequent comprehensive review (Davis et al. 1991) refuted this uncertainty and established ECT as a safe and effective treatment of neuroleptic malignant syndrome (NMS). Tabulating 665 detailed cases of NMS, Davis and colleagues (1991) identified 48 who had received ECT, 29 of them during the acute phase of the syndrome. The mortality rate for the ECT-treated patients (10.3%) was comparable to that (9.7%) with accepted dopaminergic pharmacotherapy (bromocriptine, amantadine, levodopa, dantrolene) and half that associated with supportive care alone (21%). Critically, failure to respond or death in ECT-treated patients was associated with continued use of high-potency neuroleptics. Careful physiological monitoring of patients undergoing ECT in the face of ongoing NMS is essential (Hughes 1986, Devanand et al. 1987). Although formal controlled trials will probably never be feasible, the use of ECT is indicated in NMS patients unresponsive to supportive care or use of one of the dopaminergic or benzodiazepine medication options (Lazarus 1986, Fink 2000). Moreover, ECT may be a feasible alternative treatment for the underlying mental disorder in the NMS patient for whom continuation or reintroduction of an antipsychotic is inadvisable (Pelonero et al. 1998).

A theoretical concern was raised regarding the use of ECT in NMS: that exposure to succinylcholine as an ECT premedication might precipitate malignant hyperthermia—possibly related pathophysiologically to NMS—in these

vulnerable individuals. This fear has not been borne out (Addonizio and Susman 1987, Davis et al. 1991).

Although the incidence of NMS can be expected to drop with the decreasing use of conventional neuroleptics in favor of atypical antipsychotics, ECT retains a place in the treatment algorithm for delirium of any cause, including metabolic, infectious, and toxic brain and systemic disorders, particularly where ongoing symptoms interfere with the necessary correction of an underlying systemic etiology (Fink 2000).

Parkinson's Disease

A great deal of interest currently attends the use of ECT for this disabling, progressive neurodegenerative disease. Kellner and Bernstein (1993) compiled 22 reports from the literature between 1959 and 1991, totaling 77 Parkinson's disease patients, who had received ECT, most often for a concomitant mood disorder. Most showed a positive response of both motor signs (often improving first) and mood disturbance, but occasional patients showed a dissociation, whereby one or the other syndrome improved with no change in the other (Young et al. 1985). Tallying the literature through 1998, Hermann and associates (1999) described antidepressant efficacy in patients with Parkinson's disease in both published controlled trials (one of which was randomized), in three of the four uncontrolled trials, and in 24 of 30 case reports. In the largest case series, investigators at the Mayo Clinic (Moellentine et al. 1998) retrospectively compared 25 patients with Parkinson's disease with an equal number of neurologically healthy psychiatric patients, all of whom received ECT, typically for major depression and generally utilizing unilateral electrode placement. Ratings of depression and anxiety, by nonblind raters, fell significantly in both groups; 14 of the 25 Parkinson's disease patients also demonstrated improvement in motor function at hospital discharge, although further follow-up was not available (Moellentine et al. 1998).

The presence of psychosis may predict lack of an antidepressant effect in patients with Parkinson's disease (Price and McAllister 1989). Clinical response of parkinsonian signs to ECT in general occurs early in the treatment course but often is transient, lasting for hours to months. Right unilateral electrode placement has been reported effective, for example in the Mayo Clinic series (Moellentine et al. 1998), with a switch to bilateral electrode placement recommended if early response to ECT is not observed (Rasmussen and Abrams 1991).

Most of the work in Parkinson's disease uncomplicated by psychiatric illness has been performed in Sweden and consisted of two parts. In an open case series of nine patients, five responded to bilateral ECT with significant reductions in rigidity and bradykinesia ("off time"), lasting from 1 to 10 months (Balldin et al. 1981). A later double-blind trial by Andersen and colleagues (1987) found bilateral or unilateral ECT effective in all nine patients receiving active convulsive therapy, with improvement in motor signs continuing for 2 to 6 weeks. In contrast, neither patient assigned to sham ECT responded. Similar positive findings have been reported for refractory Parkinson's disease patients openly treated with ECT in the US (Douyon et al. 1989, Zervas and Fink 1991). Older patients have done especially well on ECT for parkinsonian signs (Balldin et al. 1981, Andersen et al. 1987, Douyon et al. 1989).

Taking the treatment paradigm the next step, two reports (Zervas and Fink 1991, Wengel et al. 1998) have described the use of maintenance ECT in nondepressed Parkinson's disease patients, an intervention that has been recommended, given the frequent finding of relapse within weeks of completion of ECT in these individuals (Rasmussen and Abrams 1991, Kellner and Bernstein 1993, Kellner et al. 1994). Positive results were seen in five of six patients completing maintenance ECT, typically every 3 to 4 weeks, up to 12 months (Zervas and Fink 1991, Wengel et al. 1998). Motor improvement was most evident in reductions in off time, with little effect on other parkinsonian signs, such as tremor (Wengel et al. 1998).

In general, the baseline cognitive impairment commonly associated with Parkinson's disease is not worsened by ECT and may actually improve (Moellentine et al. 1998, Wengel et al. 1998). The effects of ECT on dopamine systems are consistent with its antiparkinsonian properties (Rudorfer et al. in press), and may also account for its toxicity in this clinical context. Moellentine and others (1998) reported transient interictal delirium in 13 (of 25) Parkinson's disease patients during a course of ECT, 10 of whom were on levodopa at the time of ECT initiation. Indeed, the commonly observed dyskinesias or delirium late in the course of ECT in these patients responds to reductions in dose of levodopa and carbidopa (Douyon et al. 1989, Rasmussen and Abrams 1991, Oh et al. 1992, Kellner and Bernstein 1993, Kellner et al. 1994), perhaps reflecting the increased dopamine receptor sensitivity (Balldin et al. 1982, Rudorfer et al. 1992) or number (Fochtmann et al. 1989) that accompanies a course of ECT.

Other Neurologic Illness

The remaining neurological indications for ECT can be considered to fall into two major categories: (1) those for which, as with any medical illness (see later), ECT is considered for treatment of a secondary depression when benefit–risk analysis favors ECT over antidepressant medications and (2) those for which ECT may play a special role by virtue of its unique actions compared to alternative treatment options.

In the first category are such conditions as poststroke depression (Murray et al. 1986, Currier et al. 1992) and mood disturbance in the context of brain trauma, tumor, or dementia (Hsiao et al. 1987, Liang et al. 1988, Kohler and Burock 2001). Medication may be difficult to tolerate by these neurologically ill patients, tilting the potential benefit–risk ratio in favor of ECT (Price and McAllister 1989). The case report literature is encouraging in that ECT can successfully treat a secondary depression in, for example, patients with primary dementia (Liang et al. 1988, Mulsant et al. 1991) or poststroke (Currier et al. 1992), while the underlying cognitive and neurological deficits are most often unaffected. Although the outcomes are not presented, the 1993 national survey of ECT use in the community (Olfson et al. 1998) found that one in six patients with recurrent major depression with underlying dementia was treated with ECT, making dementia the most common comorbidity associated with depression among ECT recipients.

Despite a high rate of mental disorders in people with mental retardation, there are no controlled trials of ECT in these individuals. In a comprehensive review of the field, Dutch investigators (Van Waarde et al. 2001) culled published reports of 44 mentally retarded patients, most of whom suffered from psychotic depression, who had received ECT. With an 84% response rate and no unusual adverse effects reported, Van Waarde and associates (2001) concluded that the apparent underuse of ECT in patients with mental retardation and severe mental disorders results more from diagnostic, legal, and ethical challenges in this population rather than an inherent lessened efficacy or increased risk.

Potential contraindications to ECT are very few and rarely are absolute (American Psychiatric Association 2001). Although ECT generally should not be performed in the presence of raised intracranial pressure, it has been given safely even in the face of brain tumors and other mass lesions (Hsiao et al. 1987, Fried and Mann 1988, Abrams 1991, 1992, Kohler and Burock 2001) with special steps taken to protect against the ECT-associated hemodynamic changes; intracranial pressure may be reduced with the use of oral or parenteral steroids (Beale et al. 1997). Postsurgical patients may require individualized ECT electrode placement to avoid skull defects (Lisanby et al. 2001a). Patients with Down syndrome require careful pre-ECT assessment for atlantoaxial instability, found in 1 to 2% of these individuals, which would render neck hyperextension during ventilation contraindicated (Van Waarde et al. 2001). However, although structural brain abnormalities are not induced or worsened by ECT (Currier et al. 1992, Devanand et al. 1994) their presence at pretreatment may increase the likelihood of ECT-associated transient cognitive deficits or interictal delirium (Botteron et al. 1991). In younger neurologically impaired patients, the literature describes 15 individuals with multiple sclerosis who received ECT for treatment of depression (Mattingly et al. 1992); the high rate of antidepressant response (80%) must be tempered by a disproportionate (20%) incidence of delirium or other neurologic deficit these patients developed during the course of treatment. On the other hand, despite the neurotropic properties of the human immunodeficiency virus (HIV), nondemented depressed patients with HIV seropositivity or acquired immune deficiency syndrome (AIDS) have responded to ECT without cognitive decline (Schaerf et al. 1989). Similarly, ECT has been used successfully, without reported cognitive deterioration, in individuals suffering from depression or delirium following closed head injury (Kant et al. 1999).

The second group of neurologic indications for ECT, of which Parkinson's disease is the prototype, include intractable epilepsy or status epilepticus (Price and McAllister 1989, Kellner and Bernstein 1993, Lisanby et al. 2001a). In this condition, should anticonvulsant medications prove insufficient to adequately control seizures, a trial of ECT would seek to take advantage of its anticonvulsant properties (Sackeim et al. 1983, 1987a). Achievement of an adequate seizure during ECT in such circumstances may require tapering of what is often a complex anticonvulsant medication regimen and/or use of a benzodiazepine antagonist to temporarily reduce seizure threshold at the time of treatment (Lisanby et al. 2001a). Maintenance ECT or anticonvulsant medication would be required to sustain these otherwise-transient effects beyond the acute ECT trial. Although case reports have been published for decades (Caplan 1946, Sackeim et al. 1983, Regenold et al. 1998, Lisanby et al. 2001); no controlled ECT studies have been conducted for this potential indication.

Other Considerations in the Use of ECT

It can be appreciated that while accurate psychiatric diagnosis is essential to prioritize treatment options, it is far from the only consideration for the clinician weighing the advantages and potential problems of prescribing ECT (American Psychiatric Association 2001). Two often-related variables are the patient's state of physical health and age. A disproportionate number of individuals receiving ECT in this country are elderly, many of whom are physically compromised. Fortunately, advances in the understanding and practice of ECT, according to Abrams (1991), "now enable its routine and successful application in a population of patients previously believed to be too old or too physically ill to undergo the stress of induced convulsions."

Advanced Age

More vulnerable than younger individuals to both the symptoms of depression, particularly psychosis, decreased nutritional intake, and suicidal ideation, and the adverse effects of antidepressant medications, the elderly represent a growing segment of the patient base for ECT (Benbow 1989, Blazer 1989, Sackeim 1993, Olfson et al. 1998). A substantial proportion of geriatric depressed patients referred for ECT suffer from significant concurrent medical illness, which often preclude adequate trials of pharmacotherapy (Tew et al. 1999). Indeed, interpretation of case–control studies of geriatric depression treatment is fraught with difficulty, as elderly patients able to successfully undergo medication trials often have less severe physical illness than those undergoing ECT (Kroessler and Fogel 1993). With the introduction of SSRIs and other newer and potentially less toxic medications, that factor may be changing. However, the benefit–risk ratio, influenced by speed of response, tolerability, and adherence factors, still often favors ECT over pharmacotherapy in the older person with severe depression.

Even with a dearth of controlled studies, the efficacy of ECT in geriatric depression is well established (Sackeim 1993) and is often perceived as even superior to that in younger age groups (Benbow 1989). In addition to the usual clinical criteria for recommending ECT, as discussed earlier, some have suggested that anxiety or agitation, commonly regarded as a negative prognostic sign in younger individuals, may be predictive of a good response to ECT in the older depressed patients (Salzman 1982, Benbow 1989). More than 1,000 elderly depressed patients (some with dementia) were treated with ECT in 14 mostly retrospective reports published in the 1980s (Mulsant et al. 1991). Most patients responded to treatment, with significant medical complications noted in 6% and confusion or delirium in 11%. Similar findings emerged in one of the few prospective, albeit naturalistic, studies of ECT in 40 patients with late-life depression (Mulsant et al. 1991).

Systematic retrospective surveys on both sides of the Atlantic have focused on those at greatest physical risk from all invasive procedures: the ''old–old,'' commonly defined as individuals over age 75 years. In 22 courses of mostly bilateral, brief pulse ECT, investigators at Louisville (Casey and Davis 1996) found a very high (86.3%) response rate. Although the adverse effect rate of 22.7% was notable, only two patients experienced cardiovascular complications, and most adverse effects, including one case of prolonged confusion, were transient and did not interfere with completion of the ECT course. No pretreatment patient characteristics or treatment parameters were associated with adverse effects of ECT in this sample (Casey and Davis 1996). Similarly impressive efficacy (85% moderate or marked response) was observed in 93 courses of ECT administered to patients over age 75 years at three British and Irish hospitals in the last decade (Gormley et al. 1998). The observed 10% rate of complications consisted mainly of confusion and hypomania, which resolved within two weeks following completion of ECT; one case each of hypertension and headache was also transient. It is noteworthy that in addition to the use of brief pulse (albeit mainly bilateral) stimulation, in accord with usual British and European practice this study utilized a twice-weekly ECT schedule, rather than the usual American three times per week approach (Gormley et al. 1998). Employing a matched control group treated only with medication, Manly and associates (2000) demonstrated better antidepressant outcome, with fewer cardiovascular and gastrointestinal adverse effects, in old–old inpatients treated with ECT. The convulsive therapy patients, however, had significantly longer hospital stays.

These retrospective findings have been confirmed and extended by recent prospective data emerging from the acute phase of a pair of NIMH-sponsored continuation treatment studies. In a three-site trial, old–old patients actually showed greater antidepressant efficacy to ECT (67%) than the 54% response rate seen in adults up to age 59 years (Tew et al. 1999). The greatest ECT response (73%) occurred, however, in an intermediate ''young–old'' cohort aged 60 to 74 years, despite the fact that they as well as the old–old group aged 75 years and above presented for treatment with a greater burden of physical illness and global cognitive impairment than did the younger adults (Tew et al. 1999). The four-site CORE trial described above (Petrides et al. 2001, O'Connor et al. 2001) similarly found a higher rate of remission and response in geriatric patients, without a significant difference between ''old–old'' and ''young–old'' patients. Following a brief-pulse bilateral acute ECT course in CORE, those patients under age 45 years had a 75% remission rate (57% if all the dropouts are counted as nonresponders), compared to 93% of the middle age group (age 46–64 years; 86% including dropouts) and 90% for those over age 65 years (80% for complete group). Similar findings were seen for the less stringent outcome of response, obtained for the complete sample in 68% for the young adults, 91% for the middle group, and 90% for the old–old. Considering age as a continuous variable, there was a highly significant positive correlation between age and degree of change in the Hamilton depression score with ECT. Beyond the effect of age per se, in this study the geriatric patients also exhibited a higher incidence of psychotic features (Petrides et al. 2001), an older age of onset of depression, and a lower number of previous episodes than the younger age groups, which may have contributed to the superior ECT response in older individuals (O'Connor et al. 2001).

Two general points should be made about the use of ECT in the elderly: (1) the physiological changes associated with ECT—cardiovascular (elevated blood pressure, arrhythmias), cognitive (confusion, memory loss), risk of traumatic injury to bones and teeth—that are benign and easily tolerated in young and middle-aged patients are prominent sources of potential ECT-associated morbidity in geriatric patients and (2) the safety of ECT is appreciably enhanced if the foregoing effects on the older body, whether healthy or diseased, are anticipated and controlled. For example, Casey and Davis (1996) noted that a ''rigorous falls prevention protocol'' helped protect their elderly ECT patients from a potentially dangerous complication seen in earlier studies.

Younger Age

The very limited use of ECT in children and adolescents at present has been noted above. Only a generation ago, it was not unusual for the American textbooks of child psychiatry to omit any mention of convulsive therapy. As with adults, early use of ECT in young patients focused on childhood schizophrenia, which is no longer considered an appropriate primary indication for this intervention. Rather, modern practice guidelines direct that the use of ECT in children and adolescents with schizophrenia ''be reserved for those cases where several trials of medication therapy (including a trial of clozapine) have failed. ECT may also be considered for catatonic states'' (American Academy of Child and Adolescent Psychiatry 2001). When intractable psychotic illnesses in adolescents, including schizophrenia and schizoaffective disorder, are in fact treated with ECT, clinical response typically is less complete than that seen in mood disorders (Cohen et al. 2000a). The limited use of modern ECT in young people is generally reserved for cases of depression or mania complicated by medication resistance or the need for an urgent clinical response. However, even today, the literature in this area consists of case reports and series, with no controlled trials (Baldwin and Oxlad 1996, Cohen et al. 2000b, Rabheru 2001). Nonetheless, where ECT is utilized in younger patients, its efficacy and safety appear comparable to those in adults (Rey and Walter 1997, Cohen et al. 2000b), although additional controlled research is needed (Rabheru 2001).

In using ECT with children and adolescents, attention must be paid to the lower seizure threshold in young people, with appropriately low initial stimulus parameters and careful dose titration during an ECT course (American Psychiatric Association 2001). Although young patients may be at greater risk for prolonged seizures, other adverse effects are no more likely, aided by the more common lack of comorbid physical illness in younger patients (Rey and Walter 1997).

Physical Health

Recent national survey data across all age groups found the presence of physical illness comorbid with recurrent major depression to be associated with a >25% higher utilization rate of ECT compared with uncomplicated depressive dis-

order alone (Olfson et al. 1998). As the common occurrence of underdiagnosis and undertreatment of depression associated with serious medical illnesses, such as cancer, is increasingly recognized and rectified, the demonstrated efficacy and safety of ECT in such clinical circumstances should not be overlooked (Beale et al. 1997). Preliminary data suggesting improvement in chronic pain and associated affective symptoms suggest areas for further research (Bloomstein et al. 1996). Thus, careful pretreatment evaluation of the patient's medical and neurological status, as well as review of concurrent medications and their potential impact on ECT are crucial (Salzman 1982, Rasmussen and Zorumski 1993).

A special physical health challenge to the treatment of mental disorders is presented by pregnancy. According to clinical lore, the efficacy and safety of ECT in this circumstance were discovered accidentally in the early 1940s when, following successful treatment, a patient's ''abdominal mass'' was determined to be a fetus. More systematic, if uncontrolled, experience over the ensuing decades, totaling >300 published cases (Miller 1994)—combined with the introduction of effective, but potentially teratogenic psychotropic medications—has confirmed this initial favorable impression. When used with appropriate care and modifications, ECT is relatively safe and effective during all trimesters of pregnancy and in the postpartum period (Miller 1994, American Psychiatric Association 2001, Rabheru 2001). These are times of high risk for mood disorders, certainly detrimental to the well-being of the pregnant patient and her baby, yet the very circumstance in which many women and their physicians wish to avoid medications which could be harmful to the developing fetus. Hence, the niche for nonpharmacological somatic interventions, particularly ECT, has persisted throughout the last half century of medication development, especially for severe depression or mania during pregnancy (American Psychiatric Association 2002). Advantages of ECT that operate in favor of persons with medical illness are especially pertinent for the pregnant woman: the times of highest risk are the times of treatment sessions, at which close monitoring of the patient and the fetus can take place, with the obstetrician in attendance, and brief and transient exposure to anesthesia and ECT premedications that cross the placenta. Fewer than 10% of published cases of ECT in pregnancy have described adverse effects, the majority of these described as benign and self-limited (Miller 1994, Bhatia et al. 1999). Guidelines for the administration of ECT in the pregnant patient, incorporating measures such as intravenous hydration, avoidance of hyperventilation and nonessential anticholinergic medication, measures against gastric reflux, proper positioning of the patient during treatment, and uterine and fetal cardiac monitoring, have been developed and incorporated into modern practice (Miller 1994, Walker and Swartz 1994, American Psychiatric Association 2001).

Appropriate precautions and monitoring during and following ECT can minimize complications and permit safe and effective convulsive therapy even in the medically compromised patient of any age (Rasmussen et al. 2002a).

Pretreatment Evaluation

Once the decision has been made to proceed with a course of ECT, specific steps are taken by the treatment team to maximize the benefits and minimize the risks. In some instances these procedures are part of the initial workup, and the results may influence treatment decisions, as when certain psychiatric or physical disorders are ruled in or out.

The psychiatrist will want to make liberal use of appropriate consultants, especially representing the fields of anesthesiology and, when indicated, internal medicine (often cardiology) or obstetrics. However, the careful and complete history and physical examination will often abrogate the need for unnecessary tests in the interest of ''defensive medicine.'' Given the current regulatory climate, the physician needs to be aware of local requirements regarding the need for second opinions or other pretreatment procedures in certain circumstances, or to arrange for guardianship or court proceedings where the patient's capacity to consent to ECT is in question, to assure that the initiation of treatment is not unduly delayed.

Psychiatric Considerations

The pre-ECT evaluation is a good time to confirm psychiatric diagnosis, including Axis II and III, which often must be given short shrift in the course of the admission process. In many settings, a specific ECT consultation may be helpful in evaluating the patient for a potentially ECT-responsive disorder and weighing the various treatment options (Klapheke 1997). Input from nursing and other professional staff that have been working with the patient should be factored in. Should the indications for ECT remain present, baseline assessments of mental status including evaluation of suicidality, orientation, and memory will help monitor changes in both therapeutic and adverse effects over the course of treatment. The history and effects of previous treatment with ECT should be obtained. Also, this time, decisions must be made regarding ongoing psychotropic medications particularly those increasing the risk of toxicity in combination with ECT, for example lithium, and those affecting seizure threshold, such as benzodiazepines and anticonvulsants—and steps instituted to adjust, taper, or discontinue these medications, when appropriate.

Other Medical Considerations

History and physical examination should focus on the cardiovascular and neurological systems, the areas of greatest risk. The consulting internist, anesthesiologist, or other physician should advise the treatment team regarding cardiovascular risk of ECT and the need for any modifications in treatment technique, such as medications to moderate hemodynamic changes (Dolinski and Zvara 1997). The safety of possible treatment adjuncts, such as intravenous caffeine, should also be addressed where baseline cardiovascular function is compromised. Appropriate pretreatment optimization and monitoring of medical conditions that may be affected by ECT, such as diabetes, should be arranged at this time.

In the uncomplicated situation, the routine laboratory workup for ECT is that indicated for any procedure involving general anesthesia: complete blood count, serum electrolyte levels, and electrocardiogram (ECG) (American Psychiatric Association 2001, Chaturvedi et al. 2001). Chest X-ray is often obtained as well. The need for further pretreatment workup, such as serum chemistries, urinalysis, HIV antibody titers, and medication blood concentrations,

is determined on an individual basis (Lafferty et al. 2001). Given a normal neurologic and fundoscopic examination, computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain is not indicated. Lumbosacral spine films, historically routine prior to institution of muscle relaxation in the ECT premedication protocol, have become optional for many patients. This remains appropriate for older patients with a history of or at risk for osteoporosis, and for any patient with a history of bone trauma. A formal anesthesiology consultation should result in an assignment of the degree of anesthesia risk and recommendations for any necessary modification in the ECT protocol (Folk et al. 2000). A personal or family history of anesthesia complications may call for assessment of the hydrolyzing capacity of plasma pseudocholinesterase to determine the safety of succinylcholine. The condition of dentition should be routinely assessed to avoid the treatment-associated risk of aspiration or fracture of loose teeth or bridgework. Especially in elderly patients, a formal dental examination may be helpful to assure proper protection of the teeth during ECT.

Informed Consent

Among the unique features of ECT compared with other standard psychiatric treatments is the requirement for written informed consent by the patient or legal guardian or other substitute. Guidelines regarding the content of a standard informed consent form for ECT have been published (American Psychiatric Association 2001). Supplemental information regarding ECT for patients and their families in a variety of media is also available and its distribution is encouraged (Fink 1999, American Psychiatric Association 2001). Informed consent entails the patient being provided the rationale for the recommendation for ECT, along with information regarding the potential benefits and risks of available alternative treatments, including no treatment. The consent form encompasses information regarding the series of treatment sessions that constitute a course of ECT, with the explicit understanding that consent may be withdrawn and treatments terminated at any point, at the patient's discretion. A separate consent form is necessary for continuation or maintenance ECT following completion of the (acute phase treatment) course (see further). In some locales specific procedures for obtaining consent for ECT are regulated by the state, a recent example being legislation passed in Vermont in 2000. As with all medical procedures, special challenges attend the informed consent process for children and adolescents. In addition to seeking the parents' or guardians' consent, and, if possible, the patient's assent, current professional (and, in some locales, regulatory) standards call for consultation with an independent colleague prior to initiating ECT in a young person (American Psychiatric Association 2001, Taieb et al. 2001). Reviewing the current knowledge of the potential benefits and risks of convulsive therapy for adolescents with severe mental disorders, child psychiatrists in France have warned that "the consequence of overprotection is that the adolescent may remain untreated because of unrealistic fears regarding ECT" and conclude that "there is no ethical reason to ban the use of ECT in adolescents" (Cohen et al. 2000a).

The NIH/NIMH Consensus Development Conference on ECT (1985) emphasized that informed consent is a process that continues throughout the treatment course. Given the transient cognitive impairments common in depression and during an ECT course, it is particularly necessary to maintain a dialogue with the patient as treatment progresses to assure that all of the patient's questions and concerns are addressed, even if repetitive discourse ensues. With appropriate modification of the presentation of information, including use of nonverbal demonstration of the procedure, even patients with mental retardation often can make informed decisions about consent for ECT (Van Waarde et al. 2001).

Most candidates for ECT are voluntarily admitted inpatients. Questions about the capacity of the patient to make treatment decisions or the refusal of the dangerously ill patient (e.g. catatonic, malnourished, continually suicidal) to agree to ECT that is medically indicated constitute legal issues, for which judicial intervention should be sought promptly; this appears to be more common in public rather than private settings. Despite local variations in relevant laws and regulations, many ECT practitioners can cite instances of court ordered ECT in carefully selected cases where the potentially life-saving necessity of ECT had been clearly demonstrated to a judge. At the same time, good communication with the patient's family or friends is imperative in dealing with the complex dynamics involved in considering an intervention over the patient's objections (Boronow et al. 1997).

Initiation of Treatment

Once informed consent has been obtained, the initiation of treatment involves several decisions. These include selection of ECT device, electrode placement, dose of electricity, choice of premedications, and frequency of treatment.

Several different types of devices for administering ECT have been used. They differ in two major respects: the waveform of the stimulus delivered, and whether they deliver constant current, constant voltage, or constant energy (Stephens et al. 1991, Abrams 1982). The waveforms available for delivering stimuli in the US include sine wave and brief pulse (Abrams 1997b, 2000). The older sine wave devices have the disadvantage of requiring more energy, thereby producing greater cognitive side effects than the more recently developed, and now standard, brief pulse devices (Weiner et al. 1986, Stephens et al. 1991, Abrams 1997b, Sackeim et al. 1994).

The other respect in which ECT devices differ is whether constant current, constant voltage, or constant energy is delivered. With constant current devices, the current is set and the device dynamically adjusts the voltage to maintain that current. In devices where the voltage is kept constant, an increase in resistance results in a decrease in the current delivered, which may lead to induction of subtherapeutic seizures. Lastly, with constant energy machines the amount of energy delivered is kept fixed. Increased resistance, such as poor skin contact, will also decrease the amount of current delivered and possibly result in a subtherapeutic or missed seizure (Sackeim et al. 1994). Research is now underway regarding the possible role of various components of the electrical stimulus waveform, for example, pulse width in determining the therapeutic and adverse effects of brief pulse ECT.

In choosing electrode placement there are two important factors to consider: antidepressant efficacy and cognitive side effects. The choices of electrode placement can be divided into unilateral placement over the nondominant (generally right) hemisphere and bilateral electrode placement (Figure 92–1), traditionally bifrontotemporal. The advantage of unilateral placement is that there is less memory loss and confusion than with bilateral electrode placement (Horne et al. 1985, Weiner et al. 1986, Abrams 1982). The disadvantage of unilateral ECT is that it appears to be less effective when the dose of electricity given is close to seizure threshold (Sackeim et al. 1993), and the seizure threshold can vary more than 40-fold from individual to individual (Sackeim et al. 1987a, 1991). With bilateral placement, seizure threshold is less of a concern, and the degree and speed of response appears greater with (high dose) bilateral than unilateral ECT (Nobler et al. 1997, Sackeim et al. 2000b). Although bifrontotemporal placement has been more widely used, a limited number of studies suggest that bifrontal electrode placement may offer comparable treatment efficacy with fewer cognitive side effects (Weiner 1994). NIMH-supported research currently underway seeks to compare the efficacy and cognitive safety of standard bilateral (bifrontotemporal) electrode placement with high-dose right unilateral ECT and with bifrontal electrode placement. In short, electrode placement should be individualized based on the relative benefits and risks for a given patient (Abrams 1997b, 2000, Farah and McCall 1993). Individuals who are unresponsive to several adequately dosed unilateral treatments may benefit from a switch to bilateral electrode placement.

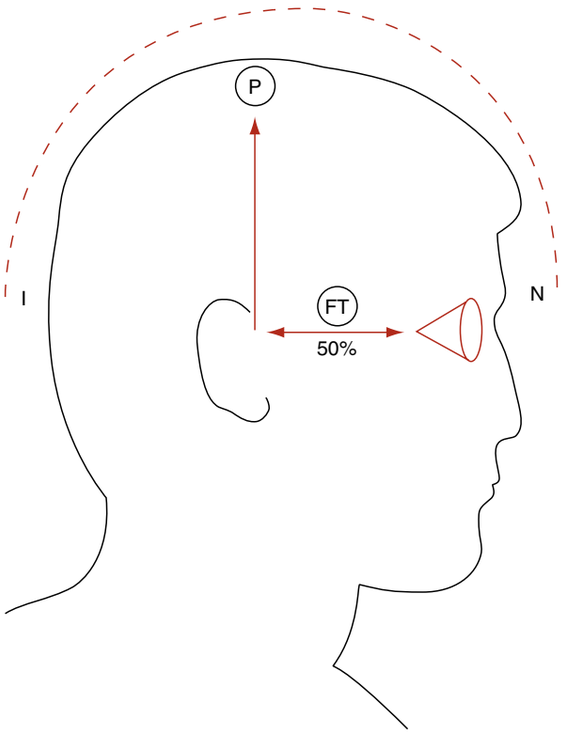

Figure 92–1 *Positioning of stimulus electrodes with bilateral and right unilateral ECT. For the standard bifrontotemporal (bilateral) placement, the electrodes are placed in position FT (frontotemporal). The midpoint of the line connecting the external canthus and the tragus is determined on both sides of the head. The center of the electrode is positioned 1 inch above this point. In the US, stimulus electrodes are typically 2 inches in diameter, so the bottom of the electrode is adjacent to this point. For the commonly used d'Elia placement with right unilateral ECT, one electrode is in the FT position on the right side. The other electrode (P) is over parietal cortex and is positioned by determining the intersection between the line connecting the left and right tragus and the inion (I) and nasion (N). The center of this electrode is 1 inch below this intersection. (Source: American Psychiatric Association [2001] The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging—A Task Force Report, 2nd ed. American Psychiatric Press, Washington DC.)*

As potential but still experimental alternatives to traditional bifrontotemporal electrode placement, novel bifrontal and asymmetric placements are undergoing investigation as to whether they confer cognitive advantages by reducing electrical stimulation in left temporal areas while retaining therapeutic efficacy (Bailine et al. 2000). The bifrontal placement of Lawson and coworkers (1990) positions the center of each electrode approximately 5 cm above the lateral angle (external canthus) of each orbit, about 14 to 16 cm apart. The asymmetric (anterior bilateral) placement of Swartz (1994) positions the left-sided electrode above the left eye, with the lateral edge bordering the bony ridge between the forehead and the temple. The right-sided electrode is placed in an identical position to that used for the right-sided electrode in the traditional bifrontotemporal placement.

The initial dose of electricity should therefore be chosen to deliver a moderately suprathreshold stimulus. A dose that excessively exceeds the seizure threshold is likely to cause unnecessary memory difficulties and confusion (Abrams 1992, Sackeim et al. 1993). One method used to individualize the starting dose of electricity is to determine the initial seizure threshold using a titration method such as that described by Sackeim and colleagues (1987b) and then choose settings for unilateral ECT which are sufficiently above those required to elicit an adequate seizure. Previous recommendations for unilateral ECT dosing at 150% above initial seizure threshold have been revised upwards in light of recent data showing a continued dose–response relationship for unilateral ECT up to 5- to 12-times above seizure threshold (Sackeim et al. 2000b, McCall et al. 2000). Sackeim and associates (2000b) demonstrated an equivalent clinical response to bilateral and high-dose (500% above seizure threshold) right unilateral ECT, but with more severe and persistent retrograde and anterograde memory disturbance associated with bilateral electrode placement. For most patients, a reasonable balance between efficacy and cognitive toxicity can be achieved with right unilateral ECT beginning with a stimulus intensity 250% above seizure threshold. It must be kept in mind that the seizure threshold rises during a course of ECT (Sackeim et al. 1987a) and a dose that was adequately suprathreshold at the start of treatment may be inadequate by the end of the course. Stimulus parameters should be reevaluated if the patient does not continue to improve throughout the course of ECT.

A contemporary survey of ECT practices (Farah and McCall 1993) revealed that several methods for determining initial parameters are used in clinical practice. Some of them include adjusting dosage on the basis of age and sex, to compensate for the effects of these parameters on seizure threshold; others utilize a fixed set of parameters for individuals which does not take into account the range in variation of seizure threshold (Farah and McCall 1993, Abrams 2000). The main conceptual point is that dose of electricity relative to seizure threshold is an important variable (especially with unilateral electrode placement) and that optimum clinical results are most likely to be obtained when the stimulus intensity is significantly higher than seizure threshold (Sackeim et al. 1993, Weiner 1994).

From the start of the treatment procedure (see Table 92–3) EKG, heart rate, and blood pressure are monitored and oxygen saturation is measured via pulse oximetry. Pure oxygen by mask is typically administered after the induction of anesthesia and until the return of spontaneous respiration. Depending upon the preference of the treatment team, patients may or may not be premedicated with an anticholinergic agent. Atropine and glycopyrrolate are the agents most commonly used (Abrams 1997). The rationale for using these premedications is twofold. First, they reduce the bradycardia observed immediately after the delivery of the stimulus, and second, they dry secretions during anesthesia (Sommer et al. 1989). The decrease in heart rate initially observed during seizure induction is the result of increased vagal tone which occurs immediately after the stimulus (Elliot et al. 1982).

The patient is rendered unconscious with a short-acting general anesthetic. Methohexital 0.75 to 1.0 mg/kg given intravenously is the agent most commonly used (Folk et al. 2000). Other agents in use include thiopental, propofol, etomidate, and ketamine. The usual, but in this context undesired, elevation of seizure threshold associated with the use of barbiturate anesthetics such as methohexital or thiopental has fueled the search for alternative anesthetic agents (Swartz 1993, Weiner 1994). Thiopental may also be associated with an increased risk of postictal cardiac arrhythmias. Propofol attenuates the hypertension and tachycardia during the seizure (Elliot et al. 1982) but also decreases seizure duration (Boey and Lai 1990, Villalonga et al. 1993) with uncertainty regarding possible decreased efficacy of ECT (Swartz 1993, Nishihara and Saito 2002). In animal studies, ketamine lengthened seizure duration relative to animals administered ECS without anesthesia, but in human use may cause patients to hallucinate in the postoperative period (Lunn et al. 1981). Etomidate compares favorably with the barbiturates and may be a useful alternative for ECT anesthesia (Kovac and Pardo 1992); while repeated dosing of etomidate may suppress adrenal function, this is unlikely to be clinically significant when given for brief periods as in ECT (Kovac and Pardo 1992).

Once the patient is unconscious, a muscle relaxant is administered. Intravenous succinylcholine 0.5 to 1.0 mg/kg is almost always used for this purpose. The goal of the muscle relaxant is to dampen the tonic–clonic movements from the seizure and reduce the risk of musculoskeletal injury (Elliot et al. 1982, Lippmann et al. 1993, Weiner 1994). The *cuff technique* (Fink and Johnson 1982) may be applied to an ankle or forearm, preventing localized circulation of the muscle relaxant, thereby facilitating monitoring of the motor seizure duration. The degree of relaxation is somewhat dependent upon the preference of the practitioner; however, when there is a history of skeletal disease the paralysis should be nearly complete. The fasciculations induced by succinylcholine can cause myalgias which can be prevented by administration of a small dose of the nondepolarizing agent, curare, prior to dosing with the succinylcholine. When curare is used in this manner it is necessary to increase the succinylcholine dosage by approximately 25% to achieve the same level of muscle relaxation as previously.

When the patient is unconscious and relaxed, the stimulus is delivered, using the desired electrode placement. Initially, the jaw will clench as a result of direct electrical stimulation. The heart rate will slow and the patient will generally have tonic contraction of the extremities (Elliot et al. 1982). This initial period, which lasts anywhere from 2 to 5 seconds, is usually followed by a marked increase in blood pressure and heart rate (McCall 1993). This is secondary to a centrally mediated catecholamine surge (Elliot et al. 1982, Swartz 1993). The extremities change to tonic–clonic contractions, the intensity of which depends on the degree to which they have been modified by the muscle relaxant.

Excessive increases in heart rate and blood pressure can be reduced by a number of prophylactic agents (Elliot et al. 1982, Lippmann et al. 1993, McCall 1993, Weiner 1994). Esmolol is an ultrashort-acting beta-blocker with a half-life of approximately 9 minutes. Because of its receptor selectivity, it is usually more effective for controlling heart rate than blood pressure. However, it is often sufficient to keep the cardiovascular response within an acceptable range. Labetalol is another beta-blocker which is frequently used as an alternative to esmolol. Doses of esmolol in excess of 200 mg and labetalol doses > 20 mg may decrease seizure duration (McCall 1993). When the beta-blockers are sufficient to control the increase in heart rate, but not blood pressure, a calcium channel blocker such as nifedipine may be used (Abrams 1991). Alternatively, nitroglycerin, which is more specific for blood pressure, may be helpful. Caution must be taken when using these agents to avoid excessively decreasing blood pressure and heart rate, particularly in the context of subconvulsive stimulation (Decina et al. 1984); as noted earlier, anticholinergic premedication may be helpful in this regard.

During the treatment, seizure duration should be monitored via a one- or two-channel electroencephalogram (EEG), an integral component of modern ECT devices (Stephens et al. 1991). Combining motor movement timing with EEG monitoring yields the most reliable seizure duration determinations in the clinical setting (Lippmann et al. 1993). Although dose of electricity relative to seizure threshold is the important variable, in general, an adequate seizure is usually between 20 seconds and 2 minutes in duration. Seizures lasting over 3 minutes are considered prolonged. Should this occur the practitioner may attempt to terminate the seizure with an intravenous benzodiazepine. Diazepam given intravenously enters the brain within seconds and can terminate status epilepticus within 1 minute (Bauer and Elger 1994, Fink 1994b). Peak heart rate during ECT has been proposed as an index of seizure quality (Swartz 2000).

Although many practitioners continue to seek a minimum "therapeutic" seizure duration, for example 25 seconds, a growing body of evidence points to a more complex neurophysiological mediation of ECT response (Nobler et al. 1993, Krystal et al. 1993, Weiner 1994, Delva et al. 2000). Once the seizure terminates, the patient is continuously supported and monitored until breathing spontaneously and responsive to voice commands, with return of muscle strength. The patient's vital signs are monitored every 15 minutes until stable.

This process is repeated for an average of 6 to 12 sessions in the treatment of depression. In the US, ECT is usually performed three times per week, while in the UK and Europe twice-a-week schedule is more common. The

available data suggest that the twice-a-week schedule produces an equivalent therapeutic response with fewer treatments, but the speed of clinical improvement is slower than the three times per week schedule (Lerer et al. 1995, Shapira et al. 2000). On the other hand, the more rapid therapeutic response to thrice weekly ECT is accompanied by greater cognitive adverse effects than those associated with the slower rate of treatments (Lerer et al. 1995, Shapira et al. 2000).

A small percentage of ECT practitioners utilize a treatment schedule known as *multiple monitored ECT*, or just *multiple ECT* (MECT), as today EEG and EKG monitoring capability is integral to all modern ECT devices. In this paradigm, multiple seizures are elicited per anesthesia session, resulting in a course of fewer sessions (but similar or increased number of seizures) than in standard ECT. In the recent New York area survey, only 15% of responding centers reported some use of MECT (Prudic et al. 2001). Although the intent of MECT was to speed clinical response, this potential advantage appears to be overshadowed by an increase in cognitive and cardiovascular adverse effects (Weiner 1994). Most of the literature on MECT is anecdotal and uncontrolled. Indeed, the seven published comparative studies on this approach include only a single randomized controlled trial (Roemer et al. 1990). In that study, depressed patients were randomly assigned to standard or "double-seizure" bilateral ECT. Although a more rapid reduction in depression scores occurred in the MECT group, by the end of the treatment course depression ratings in the two treatment groups were not significantly different. However, even though cognitive effects were rated only on the basis of chart notes, clinically significant confusion was reported for 10 of the 16 MECT patients, but only 2 of 13 patients receiving standard ECT (Roemer et al. 1990). While other retrospective studies and case reports are rife with methodological limitations, and in spite of the risk of observer bias, the literature is replete with unexpected and severe adverse effects associated with MECT, including instances of myocardial infarction and prolonged seizures and confusional states. Research on MECT appears to have ended. Weighing the knowledge of the potential benefits and risks of MECT, most professional societies now recommend against its use for the treatment of mental disorders (NIH/NIMH Consensus Conference (1985), American Psychiatric Association (2001)). Although the database is anecdotal, under limited, urgent conditions there may remain a role for MECT (up to two seizures per session) in the treatment of NMS or intractable seizures (American Psychiatric Association 2001).

Regardless of the treatment schedule, the rate of response will vary for each patient. Often, the patient's vegetative symptoms will respond before the patient feels subjectively improved. In the US, ECT devices are approved for marketing by the FDA as a Class III (most restricted medical device, having been "grandfathered" in based on their use prior to the 1976 medical device regulatory system). A proposed reclassification of ECT devices to the less restricted Class II category has been stalled since 1990, with opponents of ECT arguing against less restrictive regulation and many clinicians concerned about draft language limited the acceptable indication for ECT as major depression with melancholia. Indeed, some practitioners have argued in favor of regulatory change to permit the marketing of more powerful ECT devices, such as those used internationally, capable of delivering an electrical stimulus greater than the present US limit under 600 millicoulombs (Abrams 2000). An estimated 5 to 10% of patients are unable to experience an adequate seizure with one popular current device (Krystal et al. 2000a, Sackeim et al. 2000b), although this figure can be reduced somewhat with the use of a narrower electrical pulse width and longer stimulus duration, as provided on the newest devices.

Clinical Vignette

Mr. A, a 47-year-old married Asian engineer, presented with a 7-month history of depressed mood. The patient reported that he began to feel depressed after he made a "lateral move" at work to another department. In particular, his new job required that he do significantly more conflict resolution and he felt that his performance was below par. In addition, Mr. A's second child had just started college and he was very concerned about finances. At the time of presentation, the patient reported that his depressed mood was 7 on a scale of 1 to 10. Accompanying this low mood, he described middle insomnia nightly, anhedonia, decreased energy and concentration, diminished appetite with a 10 lb weight loss in the preceeding 3 weeks, and passive suicidal ideation. There was no past psychiatric history prior to 7 months earlier, and no history of substance abuse or physical illness. Family history was positive for a poststroke depressive episode in father.

Treatment to date of the presenting episode consisted of three successive medication trials, each lasting 6 to 8 weeks: fluoxetine 20 mg/day, venlafaxine 300 mg/day, and bupropion 300 mg/day (added to ongoing venlafaxine). At presentation, Mr. A was taking bupropion 200 mg qAM and 100 mg qPM. ECT was recommended.

After a discussion of the potential advantages and drawbacks of ECT compared with other treatment options, Mr. A consented to a course of ECT. He expressed concern about possible memory problems related to ECT and the detrimental effect this would have on his work, and was relieved to hear that high-dose unilateral ECT has been shown to be effective with a low risk of cognitive dysfunction.

On the first treatment, a right unilateral d'Elia electrode placement was used. Seizure threshold was titrated to 40 mC after anesthesia was induced with methohexital 80 mg, and premedication with succinylcholine 60 mg and glycopyrrolate 0.2 mg. The stimulus parameters were increased to 192 mC for the next seven treatments, during which a remission of Mr. A's depressive symptoms were achieved. Subsequently, the patient was started on nortriptyline and achieved a steady-state therapeutic plasma level of 78 µg/mL. One month after completion of ECT, Mr. A returned to work and remained in his job. However, 2 months after the last ECT treatment, he relapsed back into depression. Olanzapine was added to his medication regimen for some ruminative thoughts. With worsening of depression, Mr. A then was given two additional ECT treatments within a week on an outpatient basis, with notable improvement. At that point, ECT was continued on a tapering schedule, reaching one treatment session monthly. Mr. A remains in remission, with no adverse effects, on monthly maintenance ECT.

A typical example of the use of ECT in modern psychiatric practice is illustrated in the above clinical vignette.

Adverse Effects

The potential adverse effects from ECT range from mild complications such as myalgias, to serious events such as fractured bones, to catastrophes such as death. In the era that predated anesthesia for this procedure, serious complications occurred in up to 40% of cases. At present, the risk of serious complication is about 1 in 1,000 patients. The risk of death is about 1 in 10,000 patients, which approximates the risk of general anesthesia for a minor surgical procedure (NIH/NIMH 1985) and is actually lower than the spontaneous death rate in the community (Abrams 1997a). The most detailed modern account of ECT-associated mortality is derived from the database in Texas, where all deaths occurring within 14 days of ECT must be reported to state authorities (Shiwach et al. 2001). In the first 5 years since the law's inception in 1993, only one death (of 30 reported), from laryngospasm on the day of treatment, could be clearly associated with the anesthestic procedure. A conservative interpretation of the death reports yielded a mortality rate of two to ten deaths per 100,000 treatments, confirming ECT's status as one of the safest procedures for which general anesthesia is employed (Shiwach et al. 2001). Of note, the two most common fatal occurrences in this naturalistic series, cardiac events and suicide, in no cases were established as caused by ECT.

Nonetheless, cardiac complications are the most frequent medical side effects associated with ECT. The arrhythmias range in severity from the common and benign sinus tachycardia to life threatening or fatal ventricular arrhythmias. The initial parasympathetically-mediated bradycardia during ECT—blocked by atropine or glycopyrrolate premedication—has been associated with clinically insignificant transient asystole in many patients (Burd and Kettle 1998) and at times has led to discontinuation of the treatment (Tang and Ungvari 2001a). However, ECT is not associated with persistent EKG changes or myocardial damage (Dec et al. 1985). The most common cardiovascular effect frequently observed is hypertension, occurring in 6% of one sample of geriatric ECT patients (Kujala et al. 2002). Related to the medically high-risk nature of many candidates for ECT, during most of its history convulsive therapy was frequently complicated by major cardiovascular morbidity in the medically ill (Gerring and Shields 1982) and the most common cause of death during ECT is from cardiac complications. Today, with careful pretreatment evaluation and consultation and the judicious use of prophylactic and therapeutic medications, including beta-blockers and calcium channel blockers, many arrhythmias, dangerous elevations of blood pressure, and other cardiovascular complications may be avoided, even in the medically high-risk patients (Zielinski et al. 1993, Rice et al. 1994, Roose et al. 1994). Indeed, 8 of the 10 cardiac deaths in the Texas series occurred between 2 days and 2 weeks after ECT, with none during treatment (Shiwach et al. 2001). Furthermore, depression per se is now recognized as an important risk factor for coronary heart disease as well as suicide (Rugulies 2002). Data regarding the effect of ECT on some cardiac parameters, for example vagally-mediated heart rate variability, which may be reduced in depression and pose a risk factor to heart disease, are still contradictory (Schultz et al. 1997, Nahshoni et al. 2001). While minor side effects, for example headache, are common in young people given ECT, cardiovascular complications are rare (Rey and Walter 1997).

Table 92–3 Typical Electroconvulsive Therapy Schedule of Events

12:00 AM	Patient begins NPO.
7:45 AM	Patient is escorted to the ECT suite.
7:50 AM	Nurse ascertains that patient has voided, has remained NPO, has dentures and jewelry removed, has clean and dry hair, and orders for ECT are completed properly.
7:55 AM	Psychiatrist and anesthesiologist review medical chart and determine any change in medical or mental status or medications.
8:00 AM	An intravenous line is placed; EKG, EEG, blood pressure, and oximetry monitoring are instituted; stimulus parameters are selected on the ECT device.
8:02 AM	Sites of the ECT electrodes are prepared to reduce impedance.
8:05 AM	Anticholinergic premedication with glycopyrrolate or atropine is given; other adjunctive medications are administered as needed.
8:07 AM	Short-acting barbiturate anesthetic (e.g., methohexital or thiopental) is administered through IV; positive pressure respiratory support is instituted.
8:08 AM	Loss of consciousness is ascertained (eyelash reflex); blood pressure cuff is inflated over a lower or upper extremity to block distribution of the muscle relaxant (succinylcholine), which is then administered through IV.
8:09 AM	Fasciculations are noted in the cuffed extremity; a nerve stimulator may be used to ensure adequate muscle relaxation.
8:10 AM	Electrodes are positioned, and integrity of the electrical circuit is checked; bite block or mouth guard is put in place; electrical stimulus is applied.
8:11 AM	Seizure activity is monitored and duration timed for both motor and EEG manifestations; cardiac status is closely monitored; respiratory support is provided until patient is breathing spontaneously.
8:12 AM	Vital signs are monitored frequently until return to baseline level.
8:20 AM	When the patient is breathing spontaneously, is responsive to commands, and vital signs are stable, the patient is transferred by stretcher to a recovery room.
8:25 AM	Patient is assessed for recovery of orientation; with continued stability of vital signs, the patient is discharged from recovery when reoriented and able to ambulate without assistance, usually 30–60 min following the treatment.

Confusion and memory loss are also commonly occurring side effects. These adverse effects are the major factor limiting the use of ECT. Transient confusion occurs universally as a postictal event. Memory disturbance also occurs quite frequently (Calev 1994). In one typical naturalistic series of ECT-treated geriatric patients, impaired memory was the most common adverse effect (14%), followed by a 6% incidence of clinically significant confusion (Kujala et al.

2002). The extent and persistence of the confusion and memory impairment are highly variable—affecting between 0 and 100% of patients across 59 New York facilities (Prudic et al. 2001)—and sensitive to technical factors in ECT, such as electrode placement (Weiner et al. 1986, Sackeim et al. 1993) electrical dosage (Sackeim et al. 1993) stimulus wave form (Weiner et al. 1986) and frequency of treatments (Lerer et al. 1995). In general, during the acute course of ECT, both retrograde and anterograde memory are impaired to some degree (NIH/NIMH 1985, Calev 1994). Retrograde amnesia is generally felt to be more problematic, and until recently, conventional wisdom held that autobiographical memory was specifically disrupted by ECT. However, Lisanby and associates (2000) have demonstrated that in fact, following completion of a course of ECT, memory of impersonal events was more impaired; retrograde amnesia was seen only in patients treated with bilateral, not right unilateral electrode placement, and was not affected by electrical dosage or clinical response. A neurophysiological dissociation between the cognitive and therapeutic effects of ECT has been demonstrated (Sackeim et al. 2000a). Some patients can be shown to experience nonverbal memory impairment with right unilateral ECT, although it is not common for this to interfere with functioning. Learning ability is impaired by depression, but not ECT (Vakil et al. 2000); implicit memory, for example perceptual priming, is also unaffected by ECT. After the treatments end, the memory difficulties gradually resolve over the ensuing weeks to months (Lisanby et al. 2000). Some patients may have permanent spottiness in memory for events that occurred in the weeks to months before, during, and following the ECT course. Rarely, patients have complained of persistent memory difficulties severe enough to interfere with social and/or occupational functioning (NIH/NIMH 1985). However, the infrequency with which this occurs, and certain technical factors such as the lack of nondepressed pretreatment memory and other neuropsychiatric measures, (Coffey 1994) has made it difficult to study these individuals systematically. Subjective impressions of post-ECT memory deficits appear to correlate more closely with clinical outcome and mood state than with objective cognitive measures (Prudic et al. 2000). Although evidence to date points to only a transient and tolerable degree of cognitive impairment with continuation and maintenance ECT (Datto et al. 2001) as these treatment strategies continue to play an increasing role in the long-term treatment of mood disorders, more definitive research on their effects on memory will help guide clinicians. Several decades of appropriately controlled animal and human studies, supplemented in recent years by modern brain scanning techniques (Coffey 1994, Ende et al. 2000) and biochemical analysis of cerebrospinal fluid (CSF) constituents (Zachrisson et al. 2000) have demonstrated that ECT does not cause brain damage (Lippmann et al. 1985, Devanand et al. 1994).

Few formal studies of ECT effects on cognitive functioning in children and adolescents have been conducted in the past 50 years. The limited database in young people—generally with pastgeneration ECT methodology—shows transient confusion and decrements in visuomotor and intellectual performance in some patients, with no lasting deficits (Rey and Walter 1997). Preliminary long-term follow-up data, collected an average of 3.5 years after ECT in a small group of adolescents, found no difference in cognitive testing of these patients compared to controls, even in those individuals who had experienced acute memory problems after treatment (Cohen et al. 2000b).

Moreover, despite continuing negative perceptions of ECT among segments of the public—including many depressed patients lacking personal experience with the treatment (Pettinati et al. 1994)—adults and adolescents whose depression has been treated with ECT report favorable attitudes toward convulsive therapy (Freeman and Kendell 1980, Calev et al. 1991, Pettinati et al. 1994, Manning 1995, Taieb et al. 2001, Hartmann 2002). The majority of surveyed parents of adolescent recipients of ECT would support a physician's recommendation for additional ECT for their child in the future (Walter et al. 1999, Taieb et al. 2001). Patients' positive feelings regarding ECT—comparing it favorably with visits to the dentist (Freeman and Kendell 1980)—are present with both bilateral (Calev et al. 1991) and unilateral (Pettinati et al. 1994) electrode placement and are maintained at 6-month follow-up after completion of the treatment course (Calev et al. 1991, Pettinati et al. 1994).

ECT–Drug Combinations and Interactions

As most patients referred for ECT already are taking psychotropic medications, many ECT–drug interactions result from the inadvertent or intentional continuation of preexisting medication regimens with the initiation of convulsive therapy. Community surveys indicate that fewer than half of patients have discontinued all previous psychotropic medications at the time of ECT (Prudic et al. 2000). Although the controlled database is sparse, substantial anecdotal and case series document possible changes in the efficacy or safety of ECT in the face of concurrent drug treatment of psychiatric or comorbid medical illness (Kellner et al. 1991, Fink 1994). In the face of a dearth of controlled data, expert opinion on the potential advantages and drawbacks of combining psychotropic medications with ECT is mixed and evolving. In the 11 years between the last two editions of the American Psychiatric Association Task Force Report, the 1990 recommendation that antidepressants be discontinued prior to starting ECT is undergoing reconsideration (American Psychiatric Association 2001), based on limited data suggesting possible augmentation of ECT's therapeutic effects with concomitant antidepressants (Royal College of Psychiatrists 1995). The heterocyclic antidepressants are generally thought of as promoting seizures, although they have also demonstrated anticonvulsant effects as well. The cardiovascular effects of the heterocyclics have been an area of concern when they are combined with ECT. However, on the whole there is little evidence that the two treatment modalities pose an excessive cardiac risk (Fink 1994). The only published controlled trial of the past decade on the subject was a Danish study comparing the TCA, imipramine, with the SSRI, paroxetine and placebo in combination with ECT in inpatients with severe major depression (Lauritzen et al. 1996); only patients free of EKG abnormalities were permitted to receive imipramine. Acute antidepressant response in the

ECT + imipramine group was superior to that in the other two groups, although paroxetine proved a more effective continuation treatment after completion of ECT (see further). Bernardo and colleagues (2000) have also specifically demonstrated the cardiovascular safety of combining tertiary amine tricyclics with ECT in physically healthy individuals. While more definitive research is underway, the American Psychiatric Association Task Force recommends that, particularly for patients with a history of treatment resistance, ''concurrent treatment with an antidepressant medication and ECT should be considered'' (American Psychiatric Association 2001).

The limited data on the newer antidepressants suggest that bupropion and the SSRIs beyond paroxetine also may be safely combined with ECT. Despite early concerns of prolonged seizures, the initial studies and most case reports combining fluoxetine with ECT have not found a significant effect on seizure duration (Fink 1994), at least one case of therapeutic lengthening of previously inadequate ECT seizure duration with the addition of concurrent fluoxetine has been described. Double-blind, single-dose administration of the SSRIs fluoxetine or citalopram shortly prior to ECT does not cause adverse effects or change in seizure duration compared to placebo (Papakostas et al. 2000). Initial case reports with bupropion suggest that it may lengthen seizure duration, perhaps related to its dopaminergic action, and caution is recommended, particularly when high doses of bupropion are continued during ECT (Rudorfer et al. 1991, American Psychiatric Association 2001). In one recent case, a single prolonged seizure was reported following the first ECT stimulation of a patient taking therapeutic doses of bupropion, lithium, and venlafaxine (Conway and Nelson 2001); while the exact cause cannot be determined with certainty, venlafaxine alone has been safely combined with ECT (Bernardo et al. 2000).

Although today primarily of historic interest, there remain patients who still take a member of the original class of antidepressants, the MAOIs. For many years, it was standard to recommend that clinicians avoid combining MAOIs with general anesthesia, due to reports of hyper- or hypotension or other serious adverse effects. Although the data are limited, however, several studies have successfully combined ECT with an MAOI without significant adverse effects. Thus, in most cases there is no need for a long washout period after MAOI discontinuation prior to introduction of ECT. However, no increase in efficacy was found with the combination (Kellner et al. 1991). Data are sparse with the newer, selective MAOIs, for example selegiline, but there are no reports of dangerous interactions with ECT (American Psychiatric Association 2001).

The combination of lithium and ECT has been a subject of debate (Rudorfer et al. 1987). There have been several case reports indicating that the combination of the two increases the risk of delirium or prolonged seizures (Rudorfer and Linnoila 1987) but this is not a universal finding (Jha et al. 1996). Conventional clinical practice is to discontinue lithium prior to ECT (American Psychiatric Association 2001, NIH/NIMH 1985) unless a specific indication for the combination shifts the benefit–risk ratio of combination treatment for a given patient (Rudorfer et al. 1987). For instance, patients receiving maintenance ECT who require ongoing lithium for mood stabilization may have one or two doses of medication withheld prior to each ECT session (American Psychiatric Association 2001).

Although not generally used for mood stabilization or antidepressant effect, the calcium channel blocker, nicardipine, was incidentally found to be associated with lower Hamilton depression rating scores when given throughout a course of ECT to nonpsychotically depressed patients in a placebo-controlled trial (Dubovsky et al. 2001); no differences in seizure length or adverse effects between the two groups were noted.

In contrast to lithium, the combination of neuroleptics or atypical antipsychotics and ECT has been reported to be safe and possibly to increase the efficacy of ECT in psychotic patients (Chanpattana and Chakrabhand 2001).

Benzodiazepines and antiepileptic drugs increase the seizure threshold and may decrease the efficacy of ECT (Pettinati et al. 1990, Jha and Stein 1996). Over the past dozen years, conventional practice has been to discontinue benzodiazepines or decrease them to the lowest possible dose prior to the start of ECT, unless there is a clinical contraindication (American Psychiatric Association 2001). If they cannot be discontinued, the bilateral electrode placement may be preferred because with that technique the dose of electricity relative to seizure threshold appears to be less important to a successful therapeutic outcome (Pettinati et al. 1990, Sackeim et al. 1993, Jha and Stein 1996). In some instances, however, it may prove necessary or desirable to continue benzodiazepines in the ECT patient, either to treat an underlying anxiety disorder or to calm fears related to the treatment situation. Low doses of the short-acting benzodiazepine lorazepam have been found in prospective research to lack significant effect on seizure threshold, although lorazepam dose did correlate with decreased EEG-monitored seizure duration during ECT (Boylan et al. 2000). Thus, where clinically necessary, modest daily doses of lorazepam or similarly short half-life benzodiazepine may be continued without interfering with ECT, provided dosing is withheld for 8 hours prior to each treatment (American Psychiatric Association 2001); administration of a benzodiazepine antagonist, such as flumazenil, has been considered for the benzodiazepine-dependent patient, but is not routine at this point. Similarly, usual doses of pre-ECT barbiturate anesthesia are unlikely to impact seizure threshold (Boylan et al. 2000). However, since it is typically difficult to gauge seizure ''adequacy'' beyond duration, it is considered prudent to discontinue anticonvulsants being used as mood stabilizers prior to instituting a course of ECT, or to withhold one or two doses before each maintenance ECT session (American Psychiatric Association 2001).

Conversely, medications that lower the seizure threshold (such as theophylline) and/or prolong seizure duration (such as caffeine) may, in excess, contribute to ECT toxicity, for example status epilepticus. Carefully titrated, however, such agents may be useful therapeutically in augmenting the actions of ECT, particularly during a course when seizure threshold has risen (Sackeim et al. 1987a,b) and seizure duration has shortened (Sackeim et al. 1987b, Young et al. 1991, Calev et al. 1993, Nobler and Sackeim 1993, Fink 1994a).

Medications to combat the acute cardiovascular effects of ECT, when necessary, have been discussed earlier. Efforts at pharmacological prevention or treatment of ECT-associated cognitive adverse effects have to date been disappointing (Krueger et al. 1992, Dubovsky et al. 2001). The revised American Psychiatric Association (2000) Practice Guidelines on the treatment of major depression identify the potential efficacy and safety implications of combinations of ECT and psychotropic medications as one of the most pressing areas for further research in convulsive therapy.

Continuation and Maintenance Treatment

Among the unique features of ECT is the time-limited nature of its use in the treatment of acute episodes of illness. Following completion of an acute treatment course, ECT is generally terminated abruptly, coincident both with clinical response and, in many cases, impending inpatient discharge. It is now clearly established that left untreated after completion of ECT, at least half of patients will relapse, most within 6 months (American Psychiatric Association 2001, Sackeim et al. 2001a). A questionnaire survey in New York, without independent documentation, reported what may have been an optimistic relapse rate in the year after ECT of only about 20% (Prudic et al. 2001). Naturalistic follow-up of adolescents after ECT has shown a relapse rate of about 40% after 1 year (Cohen et al. 2000a). Risk factors for post-ECT relapse include the change in ECT patient samples over the past generation to a more medication-refractory population (Sackeim 1994) certain clinical features of the presenting illness including the presence of psychotic features (Meyers et al. 2001) or underlying dysthymia (''double depression''), and biological factors, most notably persistent cortisol hypersecretion and dexamethasone nonsuppression (Bourgon and Kellner 2000). Most contemporary authors adhere to the distinction between *continuation* treatment, over 6 months or so, to prevent relapse into the index episode, and *maintenance* treatment beyond that point, with the goal of avoiding recurrence, that is a new episode of illness. Nearly all published data on continuation and maintenance treatment have dealt with ECT administered for the treatment of depression.

Continuation Pharmacotherapy

No longer novel, the use of continuation pharmacotherapy following completion of a course of ECT is now routine, occurring with $>80\%$ of patients in community surveys (Prudic et al. 2001). The strategy of introducing or continuing antidepressant medication following a course of ECT was endorsed by British controlled studies in the 1960s that showed a significant drop in 6-month relapse rate from 50% on placebo to 20% with continuation tricyclic or MAOI treatment (Seager and Bird 1962, Imlah et al. 1965, Kay et al. 1970). A decade later, two studies evaluated post-ECT pharmacotherapy in unipolar depressed patients. In one retrospective review lacking a placebo group, tricyclic or lithium therapy was found effective during 6 months' maintenance (Perry and Tsuang 1979). Another small trial (Coppen et al. 1981) used a placebo control and failed to find benefit from maintenance lithium until after the first 6 months post-ECT. However, subsequent naturalistic studies, both retrospective and prospective, documented a high relapse rate of 50 to 75% during the first 6 months following successful ECT despite clinician's choice continuation pharmacotherapy (Karlinsky and Shulman 1984, Currier et al. 1992) with the highest rate seen in patients who had received ECT for psychotic depression (Spiker et al. 1985, Aronson et al. 1987). Longer follow-up revealed continued occurrence of relapse in one prospective trial (Malcolm et al. 1991) such that nearly 75% of patients were rehospitalized within 2 years of the original ECT course.

Sackeim and colleagues (1990a, 1993) closely monitored two overlapping samples of ECT responders ($N=58$ and 70). At least 50% of each group relapsed, most within 4 to 6 months post-ECT, despite (uncontrolled) continuation pharmacotherapy. Relapse was a function of the adequacy of the unsuccessful pharmacotherapy that had preceded the ECT trial, occurring in patients who had failed an adequate medication trial at a rate (64%) twice that of those who had not received a full antidepressant medication trial before ECT (Sackeim et al. 1990a). This effect was independent of the polarity of depressive illness or the presence of psychosis in the index episode. These results suggested that clinicians would best be advised to use for continuation purposes a class of antidepressant medication or combination treatment that is different from that which failed before ECT (Sackeim 1994). Fewer than half of patients on maintenance antidepressant medication (plus mood stabilizer or neuroleptic where clinically indicated) relapsed during 2-year follow-up post-ECT in another American retrospective study (Gagné et al. 2000); however, patients with the strongest history of previous medication nonresponse at that center were offered continuation and maintenance ECT in addition to medication (see later).

The stage was thus set for a definitive prospective trial to address these issues regarding optimal post-ECT pharmacotherapy for relapse prevention. With NIMH support, the first-ever placebo-controlled maintenance medication trial in the US for this indication was undertaken at three sites throughout most of the 1990s (Sackeim et al. 2001a). Following the achievement of remission from unipolar depression with an open course of bilateral or unilateral ECT, 84 medication-free patients were randomized to one of three treatment groups, stratified by history of medication resistance and psychotic symptoms. In addition to placebo, active double-blind treatment arms were the tricyclic antidepressant, nortriptyline (no longer a first-line treatment by the 1990s), alone or combined with lithium; tricyclic and lithium levels were used to assure therapeutic dosing throughout the trial. As expected, most (84%) patients receiving placebo after ECT relapsed during the 24-week trial, consistent with previous uncontrolled studies. Monotherapy with nortriptyline was somewhat more effective (60% relapse), but only reached trend significance. A statistically significant benefit over placebo was seen for combined lithium (at low therapeutic levels) and nortriptyline, which was associated with a 39.1% relapse rate during the trial. Eight of the 9 patients who relapsed while taking combined nortriptyline plus lithium did so during the first 5 weeks of the trial, while relapses in the placebo and nortriptyline-only groups continued throughout the 6 months of study. Across the treatment conditions, highest relapse rates were observed in patients with the highest post-ECT depression

rating scores, those with a history of medication resistance, and in women. This study thus established without question the necessity of post-ECT continuation treatment, while refuting suggestions from earlier trials that tricyclic monotherapy was adequate for relapse prevention in the modern era. Combined nortriptyline and lithium, while superior to placebo or to the tricyclic alone, nonetheless prevented relapse in only 6 of every 10 patients.

Combined antipsychotic and antidepressant medications, the pharmacotherapy option of choice in the acute treatment of psychotic depression, are also used frequently as continuation treatment after completion of an ECT course in such individuals (Gagné et al. 2000). In a prospective 26-week trial assessing the value of such a combination in preventing relapse, Meyers and associates (2001) randomized older (nearly all >60 years of age) patients whose delusional depression had responded to ECT to one of two active treatment groups: either a tricyclic antidepressant alone (nortriptyline, the same as used by Sackeim et al. 2001a) or nortriptyline plus a conventional high-potency neuroleptic, perphenazine. One quarter of the 28 evaluable patients had relapsed at the 6 months follow-up. Contrary to expectation, combination pharmacotherapy was not superior to antidepressant monotherapy, and, in fact, was associated with a nonsignificantly greater frequency of relapse. Furthermore, the combined-medication group experienced more adverse effects, including falls (even though the nortriptyline dose was adjusted downward in the group to account for pharmacokinetic interactions with perphenazine) and typical neuroleptic-associated side effects, including extrapyramidal symptoms and even tardive dyskinesia, despite the relatively brief neuroleptic exposure (Meyers et al. 2001).

Additional research is necessary to develop even more effective strategies to prevent relapse after completion of ECT. Such approaches could include the use of newer antidepressants and/or mood stabilizers, or atypical antipsychotics, and the introduction of medication (other than lithium) during an ECT course to reduce the latency of pharmacotherapy response once ECT is completed (Sackeim et al. 2001). One trial that did utilize antidepressants concurrently with ECT led to an initial favorable foray into the use of an SSRI post-ECT, with paroxetine more effective than imipramine at preventing relapse in geriatric patients (prevalence of psychotic depression not stated); at 6-month follow-up, relapse rates were 10% for paroxetine, 30% for imipramine, and 65% for placebo (Lauritzen et al. 1996). In that trial, only patients without cardiac disease received the tricyclic. On the other hand, introduction of fluoxetine after completion of successful ECT was associated with a 28% relapse rate over 3 months in a small Israeli study (Grunhaus et al. 2001); the addition of double-blind melatonin to the continuation regimen did not affect the outcome.

Continuation/Maintenance ECT

Given both the logic of continuing the same treatment that achieved acute improvement to prevent relapse or recurrence and the historical reality that ECT achieved widespread use more than a decade prior to the introduction of effective psychotropic medications, it is not surprising that much of the literature on the use of follow-up ECT after completion of an acute course is decades old (Monroe 1991).

However, the chief concern in the earlier eras was the issue of avoiding new episodes of illness. The newer concept of continuation treatment after a successful series of ECT treatments has led to modern case series in patients with a known history of relapse on medications. Decina and associates (1987) offered a detailed protocol of outpatient continuation ECT at progressively longer intervals over several months. This was adapted in one prospective series (Clarke et al. 1989) which avoided a prime confounding factor in most continuation ECT studies, that of concomitant medication (Gagné et al. 2000). In that 5-month series of 27 depressed patients, the rehospitalization rate was 8% in patients who completed an outpatient ECT trial versus 47% in those who did not, a significant difference (Clarke et al. 1989).

In another contemporary series (Petrides et al. 1994) a third of 21 patients with mood disorder treated with continuation ECT required rehospitalization within 1 year of response to a full course of inpatient ECT. Of particular interest were the results in patients with delusional depression, a disorder previously associated with a 95% 1-year relapse rate during post-ECT pharmacological treatment at the same institution (Aronson et al. 1987). In contrast, with the introduction of continuation ECT, the comparable relapse rate in psychotic depressives fell to 42% (Petrides et al. 1994). Marked drops in rate of rehospitalization during extended follow-up periods of 18 months (Thornton et al. 1990) to 4 years (Schwarz et al. 1995) are reported following maintenance ECT in patients with recurrent depression. One of the longest follow-up periods ever monitored for maintenance ECT (mean of >5years) was reported by Gagné and associates (2000) in a retrospective, case-controlled study, though only one of 29 patients was medication free, and a number of the others were on multiple medications throughout the course of maintenance. Compared to a matched group of pharmacotherapy-only post-ECT continuation treatment patients, the combination maintenance ECT + medication patients had higher cumulative survival rates at 2 and 5 years (93 and 73% for ECT versus 52 and 18% for medication), as well as a longer mean survival time (6.9 versus 2.7 years) (Gagné et al. 2000).

By the mid-1980s, ECT practitioners in one survey (Kramer 1987) reported treating a median of three patients per year with some form of continuation or maintenance ECT. As the use of ECT in outpatient settings increases, in all likelihood so will the application of continuation ECT, now up to one in six patients in the New York City area (Grunhaus et al. 1990, Jaffe et al. 1990, Stephens et al. 1993, Sackeim 1994, Prudic et al. 2001, Fox 2001). Although the optimal methodology for this extension of the traditional ECT course—including electrode placement, frequency, and duration of treatment—is yet to be determined (Scott et al. 1991) it has become the subject of the ongoing NIMH-supported four-site CORE trial (O'Connor et al. 2001). Following an acute course of generally successful bilateral ECT (see earlier), patients in the CORE trial are being randomized for the next 6 months to either a weekly to monthly maintenance ECT trial or to an active control pharmacotherapy condition, consisting of the most effec-

tive post-ECT medication regimen (combined nortriptyline plus lithium) identified by Sackeim et al. (2001a). Moreover, additional data are required on the risk of cognitive and other adverse effects of continuation and maintenance ECT, and the best means of minimizing untoward effects of this potentially valuable intervention (Fox 2001). In the meantime, there is general agreement that new written informed consent, beyond that obtained for the acute series of treatments, must be secured for continuation/maintenance ECT. In the event of prolonged maintenance ECT, the American Psychiatric Association (2001) Task Force recommends that the informed consent process be repeated every 6 months.

Theories of Mechanisms of Therapeutic Action

General Considerations

Despite the early recognition of the essential role of generalized seizure activity in producing the therapeutic effects of convulsive therapy, the exact mechanisms of action of ECT have remained elusive. There are several reasons for this. First, mechanistic research in ECT is difficult to perform, (Rudorfer 1994, Potter 1994) given the myriad of possible confounding variables, including diagnostic heterogeneity, concomitant medications, treatment parameters and severity of patient illness. Study of the acute treatment process, in particular, entails the challenge of accounting for the many physiological changes induced by general anesthesia, muscle relaxation, the evoked seizure, and the subsequent postictal state. Moreover, many of the tools required to investigate human brain function did not exist during most of the life span of ECT. It has proven easier to find changes in various physiological and biochemical processes associated with convulsive therapy than to prove a casual relation with efficacy (Nutt et al. 1989). Ironically, the very high response rate to ECT in some clinical studies removed the opportunity to correlate any biological findings with treatment outcomes (Krahn et al. 2000). Animal studies are proving helpful in understanding the mechanisms of ECT's therapeutic and adverse effects (Fochtmann 1994), but interpretations of preclinical electroconvulsive shock (ECS) are of necessity limited by the species differences between animals, generally rodents, and human patients, as well as the lack of adequate illness models in most such investigations. In one promising line of investigation, ECS shared with antidepressant drugs an ability to restore responsivity to reward that was lost in a chronic mild stress model of depression in rats and mice; interestingly, the response to ECS took only 1 week, versus 3 to 5 weeks for medications, paralleling clinical results in human patients (Willner 1997). In the following text, we review the primary areas of hypothesized mechanisms of ECT's therapeutic action—the neuropsychological, neurophysiological, endocrine, and biochemical—with an emphasis on areas of promising investigation.

Neuropsychological Theories

Early theories related the efficacy of ECT to the harsh physical and psychological conditions of 1940s-era treatment. Psychodynamic interpretations focused on themes of punishment, fear, and pain. Neuropsychological deficits, including confusion and amnesia, which are secondary to the unmodified seizure and accompanying hypoxia, were also invoked as therapeutic correlates. These notions were casualties of the advances in ECT technique, described in detail later. Thus, the introduction of general anesthesia, muscle relaxation, and oxygenation eliminated many of the more traumatic and fearful aspects of treatment. The use of sham ECT procedures in double-blind clinical trials controlled for nonspecific psychological aspects of the treatment, and removed them from consideration as the agents of therapeutic change. Finally, the placement of stimulating electrodes over one cerebral hemisphere (unilateral ECT) clearly demonstrated the independence of therapeutic actions from cognitive adverse effects, as many patients show complete therapeutic response to unilateral ECT with little demonstrable loss of memory (Horne et al. 1985). Thus, theories ascribing the efficacy of ECT to neuropsychological deficits are no longer regarded as credible.

Neurophysiological/Structural Theories

ECT results in a change in brain physiology, including transiently increased permeability of the blood–brain barrier. Recent work has centered on ECT-associated modification of brain electrical activity and regional cerebral blood flow. It has long been recognized that seizure threshold rises throughout a course of ECT (Sackeim et al. 1987a). Support for this phenomenon as a therapeutic mechanism is provided by its correlation with clinical response in both depression (Sackeim et al. 1987b) and mania (Mukherjee 1989) and by the latency of its appearance. This is consistent with preclinical studies in which chronic ECS, but not a single session, produces an anticonvulsant effect (Post et al. 1986). Other preclinical data have demonstrated production of a small anticonvulsant protein with opiate-like properties in the CSF of animals following repeated ECS (Isaac and Swanger 1983, Tortella and Long 1985) as well as GABAergic effects of ECS (Fochtmann 1994). The antimanic and mood-stabilizing clinical efficacy of anticonvulsant drugs, clearly established over the past 20 years, gives new currency to an anticonvulsant mechanism of ECT's therapeutic action, particularly in mood disorders (Post 1990). A related issue is the occurrence of postictal EEG suppression after each ECT session, which appears to correlate with clinical improvement (Nobler et al. 1993). Further investigation of the implications of ECT-associated EEG changes is underway (Krystal et al. 1993, 1998). For example, Krystal and associates (2000b) have developed an ictal EEG model capable of retrospectively distinguishing therapeutically effective versus ineffective seizures during ECT, although the potential clinical utility of this approach is unclear, pending further investigation (Nobler et al. 2000). While some EEG measures, such as intensity of prefrontal seizure intensity during treatment, seem to relate to clinical efficacy of ECT, others, including degree of bilateral generalization of seizure expression, do not (Luber et al. 2000).

Although cerebral blood flow (CBF) is often reduced in untreated depression (Sackeim and Prohovnik 1993) particularly in frontal regions, the effects of ECT on this measure have been inconsistent to date (Milo et al. 2001). Nobler and coworkers (2000) found successful ECT results

in further generalized and regional (primarily frontal) CBF decreases, both in depression and mania. The extent of CBF decline was correlated with degree of clinical improvement, with the CBF changes localized to the side of electrode placement with unilateral ECT (Nobler et al. 1994). Other investigators have reported increased CBF in several brain regions in ECT responders (Bonne et al. 1996). Seeking to resolve this issue, Milo and associates (2001) compared rCBF in 15 patients before and after ECT, as well as 11 healthy volunteers. In the five patients showing excellent clinical response to ECT, following treatment there was both an increase in the initially reduced perfusion in frontal regions and a decrease in blood flow in several hyperperfused areas. While demographic differences between patients and controls confounded interpretation of these findings, they were consistent with a return toward normal rCBF associated with response to ECT (Milo et al. 2001).

Similarly, there are still inconclusive data pointing to a reduction in regional brain glucose utilization following ECS or ECT (Ackermann et al. 1986, Yatham et al. 2000, Nobler et al. 2001). Although still preliminary, positron emission tomography (PET) studies in small patient samples have shown variable decreases in glucose metabolism after ECT, particularly in frontal, prefrontal, and parietal cortexes (Yatham et al. 2000, Nobler et al. 2001, Henry et al. 2001). In at least one trial, changes in frontal glucose metabolism correlated with decrements in depression ratings with ECT (Henry et al. 2001). Moreover, relative increases in glucose metabolism in brain regions with dopaminergic innervation may relate to putative effects of ECT on this catecholamine neurotransmitter (see further) (Henry et al. 2001). Other brain imaging studies have addressed possible toxicity of ECT. For example, the lack of a decrease in the hippocampal *N*-acetylaspartate signal after ECT suggests that any ECT-associated memory impairment is not due to cell death in this brain structure (Ende et al. 2000).

Neurotransmitter/Biochemical Theories

Discerning the therapeutic "signal" from the "noise" created by the plethora of biochemical changes that accompany ECT is daunting (Nutt et al. 1989, Glue et al. 1990, Rudorfer 1994). Advances in methodology in both animal and human studies have been applied to this task in recent years, yielding a number of provisional clues to the mechanisms of action of ECT. This area has been comprehensively reviewed (Lerer and Shapira 1986, Lerer 1987, Fochtmann 1994, Mann and Kapur 1994, Mann 1998). Several areas of ongoing study are of particular clinical relevance.

Both the similarities and differences between the biochemical effects of ECT and those of antidepressant medications are instructive (Rudorfer et al. 1988). Thus, ECS in a rat model produces the familiar beta-receptor down regulation (Kellar et al. 1981a) associated with antidepressant medications, with a time course that roughly coincides with the clinical effects of ECT in patients. The down regulation is complete in about a week, sustained during ongoing treatment, reverses about a week after withdrawal of ECS, but remains unchanged with sufficiently intensive maintenance ECS (Francis and Fochtmann 1993). Pre- and postsynaptic alpha-2-receptors are also down regulated by chronic ECS (Heal et al. 1991, Fochtmann 1994). For instance, a clonidine pharmacologic probe has been used to demonstrate a time-dependent alpha-2-receptor down regulation in rat brain following repeated, but not single, ECS; this receptor effect was sustained with a maintenance ECS schedule (Andrade and Sudha 2000). However, translation of these noradrenergic findings to the clinical situation remains suggestive but unproven. Plasma norepinephrine (NE) is increased about threefold acutely at each ECT session (Cooper et al. 1985, Khan et al. 1985, Mann et al. 1990a, Weinger et al. 1991). However, by the completion of an ECT course, there is little change in plasma NE or CSF and urinary noradrenergic measures (Rudorfer et al. 1988, Rudorfer et al. in press) in contrast to the effects of antidepressant medications. An increase in plasma biopterin after successful ECT has been suggested as the driving force behind accompanying increases in synthesis of amino acids, especially tyrosine, driving catecholaminergic function (Hoekstra et al. 2001).

The effects of ECT on the serotonergic system are also unclear. Preclinical data have long suggested enhanced responsivity of serotonin-mediated behaviors after repeated ECS, and increased density of 5-hydronytryptamine (5-HT_2) receptors. This is opposite to the 5-HT_2 receptor down regulation obtained with antidepressant medications (Kellar et al. 1981b, Fochtmann 1994). More recent data suggest that there is no alteration in presynaptic functioning of serotonergic neurons with chronic ECS (Blier and Bouchard 1992). In humans, although a course of ECT leads to increased CSF levels of the primary metabolite of serotonin in most patients (Rudorfer et al. 1991, Mann and Kapur 1994, Rudorfer et al. in press) which is opposite to the effect of chronic antidepressants, no consistent change in response to a serotonergic agonist challenge (Manji et al. 1992) or in platelet imipramine binding sites (Langer et al. 1986, Wägner et al. 1987) accompanies a series of treatments. Furthermore, in contrast to the transient reemergence of depressive symptoms to a tryptophan depletion challenge in patients successfully treated with serotonergic antidepressant medications, no such effect was observed in a small group of newly responsive ECT patients, suggesting that maintenance of ECT-induced improvement did not depend on the availability of presynaptic serotonin (Cassidy et al. 1997). Dutch investigators have also reported that initially low plasma tryptophan levels rose in responders to ECT (Hoekstra et al. 2001).

More robust is a significant dopaminergic effect of ECS and ECT. This is reflected preclinically in acute elevation in brain content of dopamine with each ECS (Glue et al. 1990, Zis et al. 1991) increased D_1 receptors in regions of rat brain (Fochtmann et al. 1989) and enhanced dopamine-mediated behaviors (Fochtmann 1994). Although dopamine measures are little affected by most antidepressant treatments, repeated ECT is associated with a significant elevation in CSF concentrations of homovanillic acid (HVA), the main metabolite of dopamine (Rudorfer et al. in press). In delusionally depressed geriatric patients, there was a trend for successful treatment with ECT, but not with psychotropic drugs, to be associated with an increase in initially diminished levels of dopamine beta-hydroxylase, which catalyzes the conversion of dopamine to norepinephrine (Meyers et al. 1999). There may be a strong clinical correlation to these findings, as dopaminergic mechanisms

have been invoked as part of the pathophysiology of a number of the leading indications for ECT, including delusional depression, mania, and Parkinson's disease. Thus, region-specific increases in dopaminergic activity following ECT could be tied to a variety of therapeutic actions (Glue et al. 1990, Rudorfer et al. in press).

Additional preclinical findings of potential clinical relevance are represented by increased opioid and gamma-aminobutyric acid (GABA) activity, correlating with the anticonvulsant effect of ECT (Tortella et al. 1989, Nakajima et al. 1989, Ferraro et al. 1990) and enhanced cholinergic activity, which may relate to the cognitive adverse effects of convulsive therapy (Lerer 1984, Fochtmann 1994). Continuing advances in research methodology, for example PET scans utilizing ligands for specific receptor subtypes, (Rudorfer 1994) may help define further the specific biochemical mechanisms of therapeutic action among these many possibilities.

Neuromodulator/Endocrine Theories

Although the endocrine effects of ECT are legion, most of the observed changes can be accounted for by the nonspecific effects of stress or the seizure per se and are not associated with the therapeutic effects of ECT. Most studied is the acute treatment situation. Within minutes of the ECT seizure, there are increases in plasma levels of prolactin, adrenocorticotropic hormone (ACTH), cortisol, oxytocin, vasopressin, beta-endorphin, and, less consistently, growth hormone (Whalley et al. 1982, Apëria et al. 1984, Abrams and Swartz 1985, Linnoila et al. 1984, Devanand et al. 1989, Papakostas et al. 1990, Kronfol et al. 1991, Weinger et al. 1991, Young et al. 1991, Bernardo et al. 1993).

Among these hormones, prolactin has been studied most intensively, being released acutely with each session of ECT and peaking at 15 to 30 minutes postseizure (Whalley et al. 1982, Apëria et al. 1985, Papakostas et al. 1990, Swartz 2000). This effect is greater with bilateral than with unilateral ECT in some studies (Papakostas et al. 1984) but not others (Kronfol et al. 1991). Attempting to definitively resolve this issue, McCall and associates (1996) controlled for stimulus intensity relative to seizure threshold and did, in fact, confirm the greater increase in prolactin levels with bilateral electrode placement. The absolute levels and pattern of response to prolactin after a session of ECT are not influenced by a single dose of the SSRI, citalopram (Papakostas et al. 2000). During a series of ECT, the acute prolactin response often attenuates over the course (Deakin et al. 1983, Apëria et al. 1985, Abrams and Swartz 1985, Swartz 1985). A number of studies have sought to characterize the kinetics of the prolactin response to ECT (McGuire et al. 1989, Swartz 2000) and to control for some of the myriad of confounding variables influencing this stress-sensitive hormone, which is under multiple neurotransmitter control (Swartz et al. 1988). Despite the heuristic appeal of suggestions that increased postsynaptic dopamine activity developing during a course of ECT might be responsible for inhibition of the prolactin surge late in the treatment series (Apëria et al. 1985, Abrams and Swartz 1985), the data related to both the mechanisms of the prolactin response to ECT and its correlation with treatment outcome remain inconclusive (Abrams and Swartz 1985, Deakin et al. 1983, Swartz et al. 1988, McGuire et al. 1989).

A more promising area of endocrine inquiry into ECT mechanisms may be the thyroid axis. Most investigators have reported an increase in TSH acutely following ECT, with a peak at 30 minutes (Apëria et al. 1985, Papakostas et al. 1990). Reduction in TSH output at the last treatment compared to the first correlates with the expected decline in seizure length during a course of ECT, but not with clinical outcome (Scott 1989). On a preclinical level, rat brain concentrations of thyrotropin-releasing hormone (TRH), a behaviorally active peptide, is increased after ECS (Kubek et al. 1989). A single study found no alteration in CSF concentrations of TRH in depressed patients following a course of ECT (Kirkegaard and Faber 1998, Kirkegaard et al. 1979). Independent of these hypothalamic/pituitary findings, peripheral levels of free T4 (which are normal to high at depressed baseline) decline by 10 to 20%, while remaining within or entering the normal range, during a course of ECT (Kirkegaard and Faber 1986, 1998, Scott et al. 1990). Joffe and Sokolov (1994) have noted that T4 may affect brain function and, thus, the reduction in circulating T4 levels with ECT may be as important to ECT's antidepressant action as changes higher up the thyroid axis. Of clinical significance is a recent study by Stern and associates (1993) who suggest that the addition of triiodothyronine (T3) to ECT enhances the antidepressant response, while also reducing cognitive adverse effects.

The acute increase in oxytocin-associated neurophysine during ECT is worth noting as, unlike many other transient endocrine effects, in some studies its magnitude has correlated with clinical response (Scott et al. 1986, 1991). This hormonal change reflects the intensity of the ECT stimulation of relevant parts of the brain necessary for a therapeutic effect (Riddle et al. 1993). On the other hand, the pattern of increase of beta-endorphin at each treatment is inconsistent (Young et al. 1991) with a long-term decrease in CSF levels of this polypeptide late in the course of ECT (Nemeroff et al. 1991). Similarly, corticotrophin-releasing hormone (CRH) concentrations in CSF are unchanged (Rudorfer et al. 1991) or decline significantly (Nemeroff et al. 1991) after completion of at least most of the course of ECT. In contrast, CSF somatostatin, which has been reported to decrease in untreated depression, increases significantly over a course of ECT (Nemeroff et al. 1991, Mathé et al. 1996). CSF levels of other peptides, including endothelin, neurokinin A, and neuropeptide Y also rise after completion of a course of ECT (Mathé et al. 1996), but the dearth of clinical nonresponders in that study did not permit determination of relations with outcome. Similar findings have been reported in parallel ECS studies in rat brains, but may have been confounded by the effects of the seizure activity per se (Mathé et al. 1996). In a human treatment study, the additional confounding factors of mood change and resulting normalization of circadian rhythms complicate interpretation of a decrease in daily (mainly daytime) excretion of the main urinary metabolite of melatonin after successful ECT (Krahn et al. 2000).

Sprouting of the mossy fiber pathway in hippocampus of animals with repeated ECS and increased hippocampal choline signal in humans after ECT are prompting study of neurotrophic factors in the pathophysiology of depression and the mechanisms of action of ECT and antidepressant drugs (Ende et al. 2000).

Treatment Failure

Given the still widespread view of ECT as a treatment of last resort, it is not surprising that failure to respond to ECT is often regarded as synonymous with "hopeless case." In fact, most patients have other, if less attractive, treatment alternatives available at the time ECT is initially selected, a fact which can be called upon in the event that ECT is not successful.

The total population of patients who are considered ECT treatment failures can be divided into three categories: true nonresponders; relative nonresponders for whom ECT can yet be made to work; and individuals for whom, upon closer inspection and examination, ECT was not the right treatment choice. Thus, the first approach to the ECT-resistant patient is to assure that an appropriately intensive trial of convulsive therapy has been attempted. Then reassessment, removal of any obstacles to treatment responsivity, and, in most cases, entry into a treatment-resistant depression algorithm are indicated.

Adequacy of ECT Trial

A course of 8 to 12 bilateral ECT treatments should be completed before any patient is declared ECT resistant. Patients who fail to respond to several treatments with unilateral electrode placement should be switched to bilateral ECT and offered an opportunity to respond to a full trial of that modality (Delva et al. 2001). The treatment history of the ECT-refractory patient should be reviewed to ensure that seizures were generalized and of adequate duration, and that in the case of unilateral electrode placement, stimulus intensity was sufficiently above seizure threshold. Some patients who are still resistant may respond to an unusually intensive ECT trial. For instance, 79% of the medication-resistant patients who had failed to respond to a standard course of ECT in the Prudic and coworkers' study (1990) improved during a second trial of bilateral ECT at high electrical intensity (Sackeim 1994). Some resistant patients may require additional ECT sessions in order to respond (Sackeim et al. 1990b). Adjunctive treatment, for example intravenous caffeine to prolong induced seizures of inadequate duration, may be considered, although the popularity of this approach has waned in recent years in the absence of definitive evidence of its value in the refractory patient. As noted, despite their frequent empirical use controlled studies of other ECT-medication (e.g. antidepressant) combinations are only now underway (Sackeim 1994).

Reevaluation

Even in carefully selected patients, lack of response to a course of ECT may occur in 10 to 30% of individuals (NIH/NIMH 1985). Nonetheless, this degree of refractoriness should trigger a reassessment of the patient, with confirmation of the original diagnosis. The additional information learned during a hospitalization may enable a more accurate assessment of the chronicity of illness, presence of medical disease, degree of mood congruence of symptoms, vegetative functioning, mood reactivity, Axis II pathology, alcohol or other substance abuse, and outstanding psychosocial issues than was available on admission. Such data may both help explain the lack of response to ECT and open avenues to further evaluation or treatment efforts.

Alternative Pharmacotherapy Options

Despite the prior history of medication nonresponse in most ECT candidates, the majority of ECT nonresponders will go on to successful treatment with single or combination drug treatment (Sackeim 1994). A careful review of past pharmacotherapy efforts is essential to avoid repeating previous failures and to identify promising untried approaches. While in many cases this will entail antidepressant potentiation strategies, for example with lithium, or creative combinations, for example a tricyclic antidepressant plus an MAOI or SSRI or neuroleptic, often an opportunity for monotherapy will be identified (Sackeim et al. 1990). For instance, it is increasingly common that patients are referred for ECT from the community following two or three unsuccessful trials of SSRIs or other newer antidepressants (Sackeim 1994). Should ECT fail in such individuals, a trial of a tricyclic antidepressant or MAOI alone, then potentiated with lithium if necessary, generally is indicated.

This approach was deemed successful in an Israeli report (Shapira et al. 1988) of 12 ECT nonresponders, most with a prior history of tricyclic nonresponse. All 12 went on to respond to tricyclic treatment (all but two with clomipramine) following the unsuccessful ECT trial, including three potentiated with lithium and one with lithium plus haloperidol combined with clomipramine (Shapira et al. 1988). Sackeim and associates (1990) likewise were able to effect clinical response in a mostly antidepressant, as well as ECT-resistant sample of 19 research patients. Aside from two patients who were rediagnosed and treated accordingly, all but three patients showed response to either an additional course of high-dose bilateral ECT ($N = 8$) or pharmacotherapy with a variety of antidepressants alone ($N = 2$) or combined with lithium ($N = 1$) or a neuroleptic ($N = 3$). Other investigators, however, report less success with pharmacotherapy in ECT nonresponders (Zimmerman et al. 1990). In sum, experience to date suggests that with careful attention to diagnosis and assurance of adequacy of both ECT and pharmacotherapy, the cumulative response rate of ECT-resistant patients can be well worth the effort. As in many of the topics discussed in this chapter, further controlled research is necessary (Rudorfer and Lebowitz 1999).

Novel Somatic Treatments

Coincident with the considerable advances in clinical research aimed at optimizing the use of ECT, the past decade has also witnessed renewed interest in the development of new somatic, nonpharmacologic interventions for mental disorders, particularly depression. Ongoing research supports the antidepressant efficacy of repetitive transcranial magnetic stimulation (rTMS) (Holtzheimer et al. 2001) and possibly, vagus nerve stimulation (Sackeim et al. 2001b). These and other related interventions under study stimulate the brain in manners less direct but more focused than does ECT. Should additional research establish an acceptable benefit–risk ratio for these or related new somatic interventions, they may enter treatment algorithms as options for ECT nonresponders or even as alternatives to ECT. The potential role of new somatic therapies with respect to ECT is specifically under study in the case of rTMS. In contrast to the application of an electrical stimulus to the scalp, as in

ECT, a more precisely localized electrical current can be produced within the brain by pulsing a magnetic wave (generated through a coil on the head), which passes undistorted through the skull. A train of TMS pulses, delivered to the left prefrontal cortex repeatedly but at a subconvulsive rate up to 20 minutes/day to an awake and alert patient, has demonstrated antidepressant efficacy in several small open and sham-controlled trials. To date, antidepressant effects have been relatively modest, and few patients have been medication free or followed systematically beyond a 1- or 2-week rTMS treatment trial. Encouraging further research is the apparent safety of this noninvasive procedure, which does not require anesthesia and has rarely been associated with adverse effects beyond mild headache noise-related discomfort. Although controlled trials to date have been small and not entirely consistent, recently five meta-analyses have confirmed the superior antidepressant efficacy of several weeks' treatment with high-frequency TMS over the left prefrontal area compared to a sham condition. For example, based on a review of 23 such published trials, Burt and colleagues (2002) calculated a combined effect size for rTMS of 0.67 (largest in TMS versus ECT rather than sham procedure studies), consistent with a moderate to large antidepressant effect for rTMS. The threshold for TMS clinical efficacy appears to be 2 weeks of treatment.

Of particular interest are several prospective studies where depressed patients for whom ECT is clinically indicated have been randomized to treatment with either ECT or rTMS. In a mixed inpatient/outpatient sample of 40 subjects with major depression who continued existing medication regimens, Grunhaus and coworkers (2000) found ECT (initially unilateral, switched to bilateral in nonresponders) to be superior to rTMS (up to 4 weeks) in patients with psychotic depression, but the two treatments were similarly effective in nondelusional depression. After replicating this finding in a larger sample, this Israeli group followed 41 patients who had responded to either ECT or rTMS while they received continuation clinician's choice of open-label pharmacotherapy (antidepressants, in several patients combined with an antipsychotic or mood stabilizer). During 6-month follow-up, the relapse rate was low (20%) and did not differ in the two treatment groups (Dannon et al. 2002), suggesting that the clinical gains from rTMS could be sustained with continuation treatment in a manner similar to ECT.

Similar results have been reported by other investigators, including Janicak and coworkers (2002), who randomly assigned depressed patients to either bilateral ECT or 2 to 4 weeks of rTMS; efforts were made to minimize concomitant medications. Using rigorous response criteria, 22 completers showed statistically equivalent response rates to ECT (56%) or rTMS (46%) (Janicak et al. 2002). Pridmore (2000) also found similar antidepressant effects for standard bilateral ECT or a combination of ECT (one treatment per week) and rTMS (4 treatment sessions per week).

If rTMS can achieve the desired efficacy in a given patient, it possesses several intrinsic advantages over ECT, including reduced stigma, elimination of the need for anesthesia, and apparent absence of cognitive toxicity. In the best-case scenario, these desirable properties could translate into increased adherence and cost savings compared to ECT. As the field achieves growing consensus on appropriate treatment parameters for rTMS and true double-blind sham control conditions, it is expected that further research will more definitively determine the relative efficacy and adverse effects of ECT and TMS.

While rTMS is designed as a nonconvulsive intervention, some investigators have begun to explore the possibility of using magnetic stimulation as an alternative to ECT to deliberately induce seizures, which presumably may be therapeutic. This line of research is being most actively pursued in nonhuman primates, and its feasibility in humans has been demonstrated (Lisanby et al. 2001b). Although magnetic seizure therapy, like ECT, requires general anesthesia, if future research demonstrates an ability to more finely control the dosing and localization of the resulting seizure activity, this new intervention could offer advantages over ECT, both in therapeutic action and diminished unwanted cognitive effects.

A different aspect of ECT action is being investigated as a nonconvulsive alternative intervention. Burst suppression therapy (BST) uses repeated administrations of certain general anesthetics—without any brain stimulation—to mimic the transient postictal EEG quiescence that typically follows ECT. While the presumed absence of cognitive adverse effects is appealing, the evidence supporting clinically meaningful antidepressant efficacy of BST is mixed, and definitive trials are still being planned.

Much as anticonvulsant drugs were carried over from neurology to psychiatry for mood stabilization, vagus nerve stimulation (VNS) is an effective treatment of refractory seizure disorders that is showing promise as an antidepressant intervention. Approved by the US Food and Drug Administration in 1997 for selected cases of epilepsy, VNS was first reported to be associated with improved mood in neurology patients and more recently has shown partial efficacy in refractory mood disorders. The afferent connections of the left vagus nerve with locus coeruleus, dorsal raphe, and limbic structures have been implicated in the putative antidepressant effect of this intervention.

An initial surgical procedure is required for implantation of a small pacemaker-like stimulus generator beneath the clavicle, with an attached lead wrapped around the left vagus nerve in the neck. The generator can be programmed to automatically deliver a fixed duration of vagus nerve stimulation, for example 30 seconds of stimulation every 5 minutes. Many patients notice physical concomitants of vagal stimulation, such as coughing or hoarseness (Sackeim et al. 2001b). While this may defeat the masking of no-stimulation programming as a control condition in research studies, the intervention otherwise appears well tolerated. In the event of disturbing adverse effects, a magnet held over the stimulus generator will abort a stimulation. Safety experience thus far with seizure disorder patients has been satisfactory; stimulation of the left vagus nerve has no cardiac effects.

In a published industry-sponsored pilot study (Rush et al. 2000), 30 neurologically healthy patients with nonpsychotic treatment-resistant depression underwent VNS while maintained on stable medication regimens. Device implantation was followed by an initial 2-week no-stimulation recovery period. Then 10 weeks of active VNS

was associated with a 50% or greater drop in Hamilton depression scores in 40% of patients. However, only 17% of patients demonstrated full remission, as reflected in a posttreatment Hamilton depression score < 10 (Rush et al. 2000). With expansion of the trial to include an additional 29 completers, the overall response rate fell to 30.5%, with complete remission in 15.3% (Sackeim et al. 2001b). Those patients with the strongest histories of treatment resistance were least likely to respond to VNS, suggesting that VNS would not be a feasible alternative for the ECT nonresponder. A subsequent industry-sponsored multisite pivotal trial of VNS in major depression was not successful in showing superior efficacy of real versus sham VNS. However, most patients who did respond in the acute trials maintained their improvement, and others converted to responder or remitter status, during a 1- and 2-year naturalistic follow-up (Marangell et al. 2002). Further research is necessary to define those patients for whom an invasive intervention such as VNS is likely to be appropriate and beneficial.

In conclusion, ECT retains a limited but important role in the treatment of selected patients with severe mood and other mental disorders. While efforts to continue to minimize the adverse effects, particularly cognitive, of ECT while retaining its effectiveness, other research is underway at developing additional or alternative nonpharmacologic somatic interventions for depression and other mental illnesses (Rasmussen et al. 2002b). Optimal treatment for a given individual continues to require the determination of the benefit–risk ratio for each particular person and situation.

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