

# Electroconvulsive Therapy in Treatment-Resistant Depression

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## Focus Points

- Electroconvulsive therapy (ECT) is the most effective form of treatment for patients with treatment-resistant depression.
- Relapse after ECT is commonly observed. The combination of lithium and nortriptyline has been shown to reduce the rates of relapse.
- While bilateral ECT is commonly administered in the community, newer modes of unilateral ECT have been developed that are equal in efficacy to bilateral ECT and have less cognitive side effects.

## Abstract

*What is the role of electroconvulsive therapy (ECT) in the treatment of mood disorders, especially treatment-resistant depression (TRD)? While many have thought that ECT has been replaced by pharmacotherapy, ECT is still frequently used, with the number of treatments conducted annually in the United States exceeding coronary bypass, appendectomy, tonsillectomy, and hernia repair. Controlled studies and clinical experience indicate that the short-term efficacy of ECT in major depression is comparable, and likely superior, to that of any other antidepressant treatment. Patients with TRD consume a disproportionate share of medical resources and this condition often presents extraordinary burdens to the individual, family, and society. Relative to any other antidepressant treatments, ECT has the highest rate of response/remission, the fastest onset of symptom relief, and the most complete symptom relief. However, ECT has two major drawbacks that limit its use: its effects on memory and high rate of relapse. Current research is directed at improving cognitive outcomes and identifying more effective prophylactic treatment following ECT. Novel innovations include methods to produce seizures with focal onset and limited propagation. Such modifications have the potential to markedly reduce the adverse effects of ECT without compromising efficacy.*

## Introduction

Electroconvulsive therapy (ECT) is the oldest, continuously practiced biological intervention in psychiatry. It remains our most effective antidepressant treatment despite considerable progress in the pharmacologic treatment of major depression.<sup>1,2</sup> There

was a sharp decline in ECT use in the United States following the introduction of pharmacologic agents to treat depression in the 1950s. In the late 1980s, the utilization rate of ECT stabilized and current estimates are that approximately 100,000 individuals receive ECT in the US each year, with

an annual rate of 1 million–2 million individuals receiving ECT worldwide.<sup>3</sup> ECT is usually administered to patients with severe and medication-resistant major depression, as well as mania, catatonia, and acute exacerbations of schizophrenia.<sup>4</sup> ECT involves a series of treatments, usually administered at a rate of 2–3/week, with most individuals with major depression requiring 6–12 treatments overall to achieve full remission. Thus, nearly 1 million ECT procedures are performed in the US annually and is performed as commonly as tonsillectomy.<sup>3</sup>

All comparator studies have found ECT equal or superior to antidepressant medications in the extent of short-term clinical improvement, with remission rates following ECT on the order of 70% to 90%.<sup>5-7</sup> ECT remains the most effective intervention for treatment-resistant depression (TRD). Factors in its favor include that speed of clinical improvement is typically quicker with ECT and that the quality of symptomatic remission is better (ie, fewer residual symptoms). The latter is important, in part, because there is consistent evidence that the severity of residual symptoms following any intervention for major depression is predictive of relapse.<sup>1</sup>

Despite its strong and unique short-term efficacy, there are two major limitations that restrict the use of ECT: cognitive side effects and the high rate of relapse after response. The magnitude and persistence of cognitive side effects is strongly related to technical factors in how ECT is performed, but also

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varies considerably among individuals. Notably, a small proportion of former ECT patients report profound and persistent cognitive side effects, where objective correlates are sometimes uncertain. Regarding relapse after ECT, optimal methods of prevention have yet to be identified, particularly for TRD.

This review summarizes the clinical indications for ECT and describes the pre-ECT medical and psychiatric work-ups, with a review of the systematic evaluation of TRD using the Antidepressant Treatment History Form (ATHF). The complex relationship between medication resistance and the short-term response to ECT is reviewed, as well as the evidence regarding predictors of response to ECT. For primary care physicians (PCPs) or psychiatrists treating patients following a course of ECT, guidelines are provided for continuation and maintenance treatment based on the empirical literature. New research findings are discussed in the optimization of treatment technique for ECT, with a brief summary of the decades-long controversy regarding the relative efficacy of bilateral versus unilateral ECT. Finally, recent innovations in ECT treatment technique that aim to ameliorate the cognitive side-effect burden are discussed.

### Indications for Electroconvulsive Therapy

PCPs and psychiatrists treating patients with major depression are faced with a number of options for treatment and referral. The recommendation of ECT is informed by issues of clinical urgency, particularly the severity of symptoms, including suicidal intent, inanition, psychosis, and marked agitation or retardation. These factors must be weighed together with the patient's medical condition (eg, cardiovascular disease), previous history of side effects on pharmacologic regimens and ECT, previous history of ECT outcomes (cognitive and therapeutic), urgency of life circumstances, and patient preference (Table 1). For example, ECT is particularly useful for patients who are acutely suicidal and hard-pressed to wait several weeks for antidepressants to become effective or for patients who do not tolerate antidepressants. When the rationale for ECT is not compelling, alternative medication strategies are recommended.

While much of the focus for the indications has been on TRD, a variety of

factors may lead to the recommendation to use ECT as a first-choice treatment. For example, in depressed pregnant patients, ECT has proven efficacy and is safer for both mother and fetus than some pharmacologic alternatives. ECT may be used in pregnant women during all three trimesters because the risks of alternative pharmacologic treatment or untreated mental illness exceed those of ECT.<sup>4</sup>

One of the most significant barriers to referral for ECT remains the degree of stigma regarding the procedure in the general population and among medical professionals. Medical students generally have little exposure to or training in ECT, though they commonly express a bias against the procedure.<sup>8</sup> Similar ambivalence in the professional community is evident in the significant variability in regional availability of ECT and in the lack of ECT research in many major psychiatric research centers.<sup>9,10</sup> Interestingly, the majority of patients who have undergone ECT would be willing to go through treatment again, and many consider a trip to the dentist more distressing.<sup>11-13</sup>

### Pre-Electroconvulsive Therapy Evaluation

There are no absolute contraindications for ECT. In fact, ECT is often used in medically compromised patients due to its rapid therapeutic onset and relative safety.<sup>4</sup> All patients should undergo thorough pre-ECT evaluation including psychiatric history, medical history, blood work-up (complete blood count, serum chemistries, thyroid-stimulating hormone, liver function tests), and electrocardiogram. In patients >50 years of age or with compromised dentition, a dental assessment is indicated due to stimulation of jaw musculature by ECT. While not required in all patients, brain imaging studies (magnetic resonance imaging and/or computed tomography scan) may be indicated in patients with a sudden, precipitous change in mental status, or who have notable cardiovascular and cerebrovascular risk factors.

Medical histories of cardiovascular, neurological, or pulmonary diseases should be emphasized as they warrant special care in anesthesia and may also dictate modifications of ECT technique (Table 2). Medication may be administered to reduce treatment-

related hypertension, and additional physiological monitoring during the ECT procedure may also be indicated. In addition, patients starting an ECT course may continue treatment with nondiuretic antihypertensives, anti-anginals, nonlidocaine antiarrhythmics, antireflux agents, nontheophylline bronchodilators, nonacetylcholinesterase glaucoma medications, and corticosteroids. Diuretic and hypoglycemic medications should be withheld until after each treatment. The concurrent use of psychotropic medications during a course of ECT is controversial. For benzodiazepines, which have the potential to reduce seizure duration and expression, it has been shown that lorazepam, in the range of 0-3 mg/day and withheld at least 10 hours before ECT, has no relation to seizure threshold.<sup>14</sup>

**Table 1**  
Principal Diagnostic Indications for Use of ECT<sup>4</sup>

- A. Primary Use of ECT
  1. Severe psychiatric or medical condition requiring rapid, definitive response
  2. Risks of alternative treatments outweigh risks of ECT
  3. History of favorable response to ECT or poor response to medication
  4. Patient preference
- B. Secondary use of ECT
  1. Treatment resistance
  2. Intolerance or adverse reaction to medication
  3. Deterioration of psychiatric or medical condition

ECT=electronconvulsive therapy.

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**Table 2**  
Medical Conditions Associated With Increased Risk<sup>4</sup>

- A. Cardiovascular
  1. Recent myocardial infarction
  2. Uncompensated congestive heart failure
  3. Severe valvular heart disease
  4. Unstable angina
- B. Neurological
  1. Increased intracranial pressure
- C. Pulmonary
  1. COPD, asthma, obesity, etc.

COPD=chronic obstructive pulmonary disease.

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## Assessment of Treatment-Resistant Depression

A diagnosis of TRD must satisfy two conditions: the patient had insufficient benefit from pharmacologic antidepressant treatment and the pharmacologic treatments established efficacy for major depression and were administered at sufficient dosage and duration. While standardized measures for assessing depressive symptoms, such as the Hamilton Rating Scale for Depression (HAM-D)<sup>15</sup> and the Beck Depression Inventory,<sup>16</sup> have been available for many years, there have been few attempts to formally assess the adequacy of pharmacologic treatment. However, in recent years substantial evidence has emerged indicating that many patients with major depression never receive treatment trials of adequate dosage and/or duration.<sup>17-19</sup>

The ATHF is one of the broadest and most commonly used clinician-rated instruments for evaluating the adequacy of prior treatments in TRD.<sup>20,21</sup> The ATHF rates each pharmacologic intervention on a five-point scale, with lower scores given to antidepressants administered at inadequate dosage or for <4 weeks. Regardless of dose and duration, a low score (≤2) is given to interventions without established efficacy for major depression. Specifically, positive findings from randomized, placebo-controlled trials must be available for an intervention to be considered an adequate treatment. Higher ATHF scores are assigned to antidepressant treatments lasting ≥4 weeks at doses that meet threshold levels or higher for adequacy. Specifically, the ATHF levels for considering a trial adequate (ratings of 3 or above) use a threshold dosage equal to the dosage used in randomized clinical trials that demonstrated the efficacy of the agent in major depression.<sup>22</sup> An example of ATHF criteria for the commonly prescribed antidepressant citalopram is illustrated in Table 3.<sup>22</sup>

## What are the Factors that Impinge on the Short-Term Outcome of Electroconvulsive Therapy?

Work on the prediction of response to ECT has centered on phenomenology, clinical history, or neurobiological measures. In patients that presently receive ECT, clinical features have shown surprisingly little relation to clinical outcome.<sup>23</sup> The presence or absence

of subtypes of major depression such as melancholia and bipolar depression do not have predictive value regarding likelihood of response to ECT. On the other hand, one factor that portends a relatively poorer outcome following ECT is the presence of axis II comorbidity, particularly borderline or narcissistic personality disorders.<sup>24</sup>

There has been some research suggesting that patients with psychotic depression (or delusional depression) have a superior response rate relative to nonpsychotic depressed patients.<sup>25-27</sup> However, this association is likely due to the low rate of medication resistance in patients referred to ECT with psychotic depression.<sup>28,29</sup> Optimal pharmacotherapy for psychotic depression requires combination treatment with an antidepressant and antipsychotic medication. Even with the introduction of atypical antipsychotics, this combination is rarely administered to patients with psychotic depression at adequate dosage. In particular, due to problems of tolerability, patients with psychotic depression rarely receive adequate dosage of the antipsychotic medication. Consequently, the relative lack of medication resistance among patients with psychotic depression may account for their seeming preferential response to ECT. Treatment history has rarely been evaluated as a predictor of response to subsequent antidepressant treatment, although there are now data suggesting that this factor might be critical to prognosis. Various researchers<sup>30-32</sup> have repeatedly shown that medication-resistant patients have a substantially lower rate of ECT response. Approximately 90% of the patients who have not received an adequate medication trial during the current episode will meet remission criteria when treated with ECT. This rate is reduced to approximately 50% in medication-resistant patients. While medication resistance substantially impacts on efficacy, ECT may nonetheless still have the highest probability of producing remission, as the likelihood of benefit is often lower with pharmacologic alternatives.

## Relapse Prevention: What to Do After Electroconvulsive Therapy

From the perspective of the referring PCP or psychiatrist, post-ECT care is a critical issue. Optimization of follow-

up care begins during the ECT course, when regular communication between the ECT team and the referring physician is vital, especially if ECT has been conducted on an inpatient basis. When the patient is discharged from the ECT facility, the referring physician should request a summary of the ECT course, including number of treatments, type of treatment (unilateral versus bilateral), pulse width, type of anesthesia, medications administered, documentation of endpoint cognitive status, and formal assessment of depression. Unfortunately, such formal assessments and communication are rarely performed in non-research settings. Patients are often discharged from ECT facilities without appropriate continuation medication, and are given only a general statement to the effect that they are “doing much better.”

Not surprisingly, relapse following ECT response is common.<sup>33</sup> Without active treatment, virtually all remitted patients will relapse within 6 months following ECT, although post-ECT therapy with nortriptyline and lithium reduces relapse rates to approximately 40%.<sup>34</sup> Virtually all cases of relapse with this combination occur within 5 weeks of the end of ECT. In the community, relapse rates are higher than in the research setting, even if the patient achieved remission at the end of ECT (Figure).<sup>34,35</sup> Higher post-ECT relapse rates in community settings are likely due to premature termination of ECT by practitioners unaware of the extent to which improvement is incomplete. Though practitioners in the community typically terminate ECT treatment when they believe maximal therapeutic benefit has been achieved, patients often show considerable residual symptoms at termination.

The preponderance of early relapse may be expected, as standard practice involves abrupt discontinuation of ECT once it is effective. Since antide-

**Table 3**  
**Antidepressant Treatment History Form—Sample Rating of Citalopram<sup>22</sup>**

1	≥4 weeks and dosage 1–9 mg/day
2	≥4 weeks and dosage 10–19 mg/day
3	≥4 weeks and dosage 20–39 mg/day
4	≥4 weeks and dosage >40 mg/day

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pressants generally take several weeks before symptomatic improvement is observed, patients are left vulnerable in the first several weeks following a standard switch from ECT to continuation pharmacotherapy. Continuation therapy with nortriptyline and lithium has shown a markedly lower relapse rate compared to nortriptyline alone or placebo alone in the 6 months following ECT.<sup>34</sup> These findings require replication with different combinations of antidepressants and lithium. The same group is now investigating whether beginning an antidepressant at ECT initiation provides a “head start” and protects against early relapse. The role of continuation ECT as part of the post-acute regimen is being studied in certain patients. Preliminary data from a large, randomized, prospective study comparing the lithium/nortriptyline combination versus continuation ECT has suggested a superior relapse-free interval in the medication group.

The authors recommend the early use of continuation medication treatment in patients who have completed a course of ECT, whether they are remitters, partial responders, or nonresponders. While the combination of lithium and nortriptyline for post-ECT treatment has the most solid research backing, and appears to be more effective than continuation ECT,

other combinations, eg, lithium-venlafaxine extended release, are currently being tested in large-scale studies.

### Innovations in Electroconvulsive Therapy Administration and Technique

In 1980, the view of ECT was that its efficacy depended only on the generalized seizure, while cognitive side effects were determined by the intensity of electrical stimulation. A series of studies<sup>5,6</sup> at Columbia University has demonstrated that the efficacy of right unilateral (RUL) ECT is highly dependent on the degree to which dosage exceeded seizure threshold (ST). It was recently demonstrated that high dosage RUL ECT matches the efficacy of a robust form of bilateral (BL) ECT while maintaining advantages in acute, short- and long-term cognitive effects.<sup>36</sup> These findings have helped resolve the controversy in the field about the relative merits of RUL and BL ECT.

A more recent innovation involves the narrowing of pulse width (PW). The traditional ECT stimulus is nonphysiologic, depositing energy long after depolarization.<sup>37</sup> A new study indicates that ultra brief (UB) stimulation is far more efficient in seizure induction, lowering seizure threshold by a factor of 3–4. Critically, the differences between wide PW (1.5 ms)

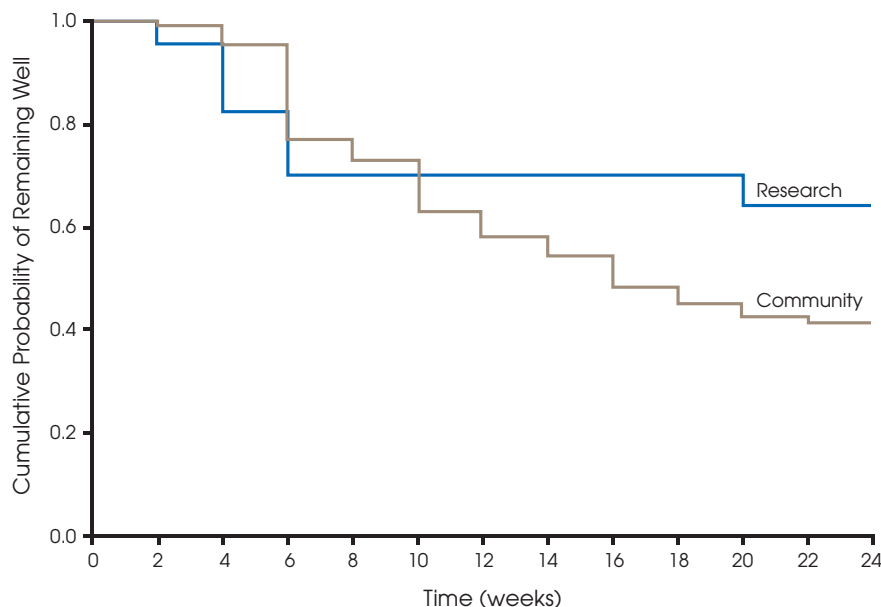
and UB (0.3 ms) PW in cognitive side effects often exceeded the differences between RUL and BL ECT. Given its efficacy and cognitive sparing, UB stimulation may soon become the standard in the field.

Finally, a limitation of current ECT technique is the lack of control over intracerebral current paths and current density. High skull impedance and variation in skull anatomy result in shunting of the stimulus away from the brain with uncontrolled variation in intracerebral spatial distribution. In particular, seizure propagation in medial temporal lobe regions is believed to contribute to the cognitive side effects of ECT, while not contributing to efficacy. The authors are now studying the feasibility of focal electrically-administered seizure therapy (FEAST). Recently, seizures have been elicited in nonhuman primates at a very low dosage (3 mC), which were expressed in frontal electroencephalogram, did not propagate to motor cortex, and did not result in motor convulsions. It is expected that FEAST’s spatial targeting of prefrontal cortex, with reduced involvement of medial temporal lobe, will preserve efficacy and reduce amnesic side effects. Controlled investigations are in progress.

### Conclusion

The practice of ECT remains an important option for patients with TRD, as well as for particular patients who are not treatment resistant. While the efficacy of ECT is comparable to any other intervention and generally surpasses pharmacotherapy in TRD, high relapse rates and cognitive side effects have limited its potential broader applicability. Priorities for future investigation include identification of optimal continuation and maintenance treatments following ECT (whether pharmacologic, psychosocial, or further ECT), optimization of ECT treatment technique to enhance efficacy and limit cognitive side effects, and identification of biomarkers that might predict therapeutic response to treatment. As one example of this direction, the use of non-invasive neuroimaging techniques such as proton magnetic resonance spectroscopy (MRS) would enable the physician to quantify cerebral  $\gamma$ -aminobutyric acid (GABA) prior to treatment. Obtaining serial MRS examinations during the course of ECT

**Figure**  
**Comparative Kaplan Meyer Estimates: Research Trial Versus Community<sup>34,35</sup>**



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would allow quantification and correlation with improvements in depression scores. Instead of simply stating that the patient appears “much better” and discharging from ECT, the treatment team might follow HAM-D scores to remission, while scrutinizing for normalization of GABA. A failure of ECT to normalize brain GABA might indicate that further treatment is necessary, although the patient might appear clinically improved. Future investigations that integrate multiple modes of inquiry (genetics, neuroimaging, clinical phenomenology) are needed to answer fundamental questions regarding the role of ECT in patients with difficult-to-treat mood disorders. **PP**

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