

# Massachusetts General Hospital Neuroleptic Biological Therapies in Psychiatry

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## ECT: Controversies and Consensus

ECT - Controversy  
Controversies

A National Institute of Mental Health hospital survey estimated that 33,384 patients admitted to hospital psychiatric services during 1980 were treated with electroconvulsive therapy (ECT), representing approximately 2.4% of all psychiatric admissions. To evaluate the current status of this treatment, a consensus development conference on ECT was held at the National Institutes of Health (NIH) in Bethesda, Md, in June of this year. The consensus panel — consisting of psychiatrists, psychologists, a neurologist, a professor of law, and an editor of lay books — heard descriptions of scientific studies and clinical experience with ECT, punctuated by emotional testimony from former patients who contended that their lives were seriously disrupted by ECT.

### Efficacy

Dr Sydney Brandon of Leicester, England summarized a series of controlled studies of ECT versus sham treatments (no seizure): Almost all have found superior efficacy for ECT (*BTP* 1981;4:9-10, 19-20; 1979;2:10; 1978;1:20). His own recently conducted Leicester ECT trial involved 95 depressed patients randomly assigned to real or sham treatments. At two and four weeks after the beginning of treatments, improvement in depressive symptoms was significantly greater in the group that received real ECT; after that, sham-treated patients could receive real treatment. Treatment effects were most striking in patients with delusions or psychomotor retardation, while patients with "neurotic depression" did not show a clear ECT response. Dr Brandon concluded that the weight of evidence on the effectiveness of ECT makes further placebo-controlled trials unjustified.

### Indications

Dr Jan Fawcett of Chicago reviewed the literature comparing ECT to antidepressants and concluded that ECT generally showed superior efficacy (particularly in the delusionally depressed) and *might work faster*, although the use of *high doses of antidepressants* could be as effective as ECT. The literature documents a clear role for ECT in the treatment of patients *unresponsive to or intolerant of tricyclic antidepressants*. In addition, the use of *antidepressants following ECT* may lower the relapse rate from approximately 50-70% to about 20%. Importantly, most comparisons of drugs versus ECT have focused on short-term therapy (three to four weeks); we know little about longer-term outcome.

Dr Joyce Small of Indianapolis reported that ECT has a role in the treatment of *schizophrenia* when it is relatively *acute* and marked by intense *affective symptoms*. Chronic patients (ie, those ill for five years or more) seem to experience no benefit, while more acute patients improve, but generally require greater numbers of seizures than patients treated for depression. Antipsychotic drugs are thought to be superior to ECT, but the combination (drugs and ECT) might be better still, and ECT is clearly superior to placebo in patients who have been ill for less than two years.

The literature suggests that *ECT is at least equal to lithium in the treatment of acute mania*. In an ongoing prospective study of her own, Dr Small has found bilateral ECT superior to lithium in acutely manic individuals. During lithium maintenance therapy, she has found that patients who had previously been treated with ECT are showing a trend toward a lower relapse rate. Of note, Dr Small avoids administering lithium to patients undergoing ECT so as to diminish the risk of neurotoxicity. In a related comment, Dr Harold Sackeim of Columbia University reported that in his pilot project, 80% of treatment-resistant manics improved following ECT.

Having reviewed the scientific basis for the use of ECT in nondepressive conditions, Dr Small concluded, "The use of ECT as a form of restraint for control of behavior outside of the context of syndromes described poses serious ethical problems and should not be condoned."

Drawing on accumulated clinical wisdom and his own experience, Dr Richard Abrams of the Chicago Medical School opined that patients with melancholic or endogenous depressions typically do better with ECT, particularly when they have had delusions, have previously responded positively, have had a family history of depression, a stable premorbid personality, or "pseudodementia." By contrast, patients with prominent self-pity, a tendency to blame others, and reactivity of mood tend not to respond well.

Delirious febrile mania — also known as lethal catatonia or catatonic excitement — consists of acute mania with clouded sensorium, fever, dehydration, tachycardia, and insomnia. It may be unresponsive to or even aggravated by neuroleptics, according to Dr Abrams, and can end in death unless ECT is rapidly administered. Catatonia, particularly in the face of temporary clearing during an amobarbital (Amytal) interview, also responds well to ECT,

as does acute schizophreniform ("good prognosis" schizophrenia) psychosis — according to clinical lore, rather than rigorous studies.

Dr Abrams considers ECT the *initial* treatment of choice (preferred to medication) in patients who are seriously suicidal or psychotically depressed, in a catatonic stupor, pregnant, have medical disorders that would make antidepressant drugs hazardous, or have PCP-induced psychosis. As a second-line treatment, he employs ECT for manic or depressed patients who are unresponsive to drug therapy. Emergency ECT, he feels, is justified when there is imminent threat to life or limb. Drawing on increased national attention to various prospective payment schemes for hospitalization costs, Dr Abrams wonders whether the more rapid response associated with ECT might not eventually increase its use over antidepressant drugs.

### Systemic Complications

Reviewing systemic effects of ECT, Dr Trevor Price of Dartmouth Medical School noted that while the death rate in the first few decades of ECT was 0.1%, it is now as low as 0.03% per patient treated, or 0.0045% per treatment administered — comparable to mortality associated with short-acting barbiturates alone (as administered for dental surgery). (Along these lines, Dr Ferris Pitts of the University of Southern California has experienced no fatalities in approximately 60,000 treatments.) ECT-related deaths, which are more common in the elderly and the medically ill, are usually cardiovascular. In the past, up to 40% of patients suffered serious complications, most commonly vertebral compression fractures. Now, significant medical complications with modified ECT occur only with a frequency of 0.045% to 0.46% and are most commonly cardiac, but also include aspiration, musculoskeletal injuries, prolonged seizures, laryngospasm, prolonged apnea, skin burns, damaged dentition, and oral lacerations. Contraindications to ECT include space-occupying intracranial lesions, abdominal aortic aneurysms, and the immediate period following a myocardial infarction.

### Memory Impairment and Cognitive Effects

Dr Peter Breggin of Bethesda has written for many years on putative brain-damaging effects of ECT. In contrast, however, Dr Agnete Dam of Denmark gave a critique of neuropathological studies in this area, emphasizing many methodological pitfalls that can give rise to confusing artifacts. Her own work in humans and several animal species suggests that while spontaneously occurring convulsions can be associated with specific types of neuronal loss, there is *no convincing evidence that ECT causes brain injury*.

Addressing the acute cognitive side effects of ECT, Dr Sackeim stated that the amount of time required for a patient to become reoriented following a treatment was shorter after nondominant unilateral stimulation than after a bilateral treatment. Reorientation tends to take longer as more treatments are administered and as treatments become more closely spaced; however, with a low stimulus intensity and electrically efficient wave form, this cumulative deterioration may not occur. In Dr Sackeim's study, patients receiving right unilateral ECT

actually showed a significantly progressive improvement in orientation time throughout the treatment course. These findings suggest that a prolonged organic brain syndrome is not a necessary part of the therapeutic process.

Both anterograde and retrograde memory for verbal material are more disrupted by bilateral than by right unilateral ECT, but nonverbal information processing may be equally affected by the two treatments. Again, the electrical dosage and wave form appear to substantially affect the intensity of postictal memory deficits.

In a related report that appeared in June's *American Journal of Psychiatry*, Miller et al wrote that among 29 patients given unilateral treatments, nonverbal memory got worse as seizure duration increased, but not verbal memory.<sup>1</sup> Also, *memory was worse with greater doses of methohexital (Brevital)*. In contrast with earlier work, these investigators in San Antonio found no evidence that the antidepressant efficacy of ECT is a function of seizure duration.

Dr Larry Squire of San Diego addressed the consensus conference on the long-term memory effects of ECT. By six months after treatment, both unilaterally and bilaterally treated patients performed as well on new learning and remote memory tests as they had performed before treatment, and as well as other patients who had not received ECT. However, information acquired for a median of six months before (retrograde) and two months after (anterograde) ECT may be permanently lost. Clearly, bilateral ECT affects the memory to a much greater extent than unilateral, and sine wave more than pulse stimulation. Although memory tests have been unable to confirm the accuracy of patients' complaints about ongoing learning problems many months and even years after ECT, these complaints are more common after bilateral than after unilateral treatment. Perhaps, suggests Dr Squire, such complaints reflect an awareness of and discomfort with the persistent lacunae of memory around the time of ECT, or maybe the memory tests currently used are inadequately sensitive to measure what the patients are describing. Moreover, the sophisticated testing that has been conducted to date has used small numbers of patients who have received relatively modest numbers of treatments (usually no more than 12). Such research has inadequate statistical power to detect uncommon though severe effects of a therapy.

Memory defects represented the greatest singular area of severe criticism from a vocal group of activists seeking to curtail the availability of ECT. On the other hand, the consensus panel was addressed by a small number of former patients who testified to a very favorable (and sometimes life-saving) role that ECT played in their lives.

Dr Christopher Freeman of Edinburgh, Scotland has attempted to systematically assess patients' attitudes toward ECT. When he advertised in a local newspaper for people who felt that they had been damaged by ECT, and also sought such referrals from psychiatrists, Dr Freeman collected a total of 126 patients. Although none of the patients felt that they had suffered brain damage, the commonest complaint was persistent memory impairment. In another sample consisting of 166 patients under the age of 70 who had received ECT at the Royal Edinburgh Hospital over a one-year period, each of

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whom was interviewed about a year after a course of ECT, 78% thought ECT had helped them, and only one patient said that it made him worse. Sixty-five percent would have the treatment again, and 50% felt that a trip to the dentist was more upsetting than ECT. Memory disturbances were reported by 74% of the sample, and 50% believed this was the most troublesome side effect.

→ Twenty-eight percent felt ECT had caused permanent changes in their memory. Importantly, many respondents could not remember being given information about ECT or signing consent forms.

#### Legal Issues

Attorney John Parry from Washington, DC, noted that ECT could not be absolutely prohibited by statute or regulation, but neither could it be administered without informed consent. Patients are to be considered competent to give or refuse consent unless legally found incompetent, in which case a guardian makes the decision. Because amnesia complicates the consent process, Mr Parry and several other participants at the conference suggested the wisdom of an *ongoing consent process*, in which patients are periodically given repeated information about ECT.

Dr Loren Roth of the University of Pittsburgh has systematically studied the consent process for ECT-treated patients and emphasized the importance of *ongoing patient education* as a way to make consent meaningful. Discussions between a physician and patient should take place over time, with the physician repeatedly inquiring as to what the patient has heard and understood, correcting any misconceptions. Dr Roth believes that *consent forms should be educational vehicles* rather than overly complex legal documents. He recommends full disclosure about the ECT procedure to most patients, stating that only in rare instances is this information "toxic or contraindicated." Furthermore, the law expects that patients understand both the procedure they are to undergo and the alternatives. For ECT, points of discussion include bilateral versus unilateral stimulation, psychotropic drugs and nonbiological treatment options, and the risks of no therapy.

#### Technique

Discussing the technique of ECT, Dr Pitts emphasized the safety of *methohexital* anesthesia, which causes  
(See ECT continued on p 32)

## IV Antidepressants

In July (*BTP* 1985;8:26) we featured an article by Pollock et al, in which intravenous (IV) infusions of chlorimipramine (Anafranil)\* produced a dramatic and rapid reversal of depressive symptoms in five patients.<sup>1</sup> Since then, a group from Munich has published preliminary data from a study in which they *failed to find an advantage for IV maprotiline (Ludiomil) over oral administration of the same antidepressant.*<sup>2</sup>

Kissling and co-workers analyzed data on 22 depressed patients (77% of whom were "endogenous"), randomly assigned in double-blind fashion to receive either maprotiline, 150 mg PO daily for 28 days, or daily infusion of the same amount of maprotiline by IV drip for one week.<sup>2</sup> (To maintain the "blind," both groups received tablets and infusions — one active, the other inactive.)

Throughout the trial, *oral administration showed superiority* on both self- and physician-rated scales. Patients on the PO regimen did better than their IV counterparts by the second day of treatment, and the difference became even more pronounced by day seven. At the conclusion of treatment, 64% (7/11) of the PO group were judged "free of symptoms" or "considerably improved," versus only 36% (4/11) of IV subjects. No side effect differences were apparent.

According to the authors, there is a widespread clinical impression that IV antidepressant therapy is superior to PO, particularly for patients with refractory depressions. Purported advantages for infusions include a more rapid onset of therapeutic effect, a greater therapeutic effect brought about by achievement of higher plasma drug levels (through bypassing the gut and liver), the possibility of using lower doses and thereby causing fewer side effects, and the assurance of compliance.

Counterposed to the clinical enthusiasm, however, stands the paucity of controlled studies that demonstrate any advantages for IV antidepressants. The only published double-blind study the authors could find, a 1973 report by Escobar and collaborators, failed to find an advantage for IV over PO chlorimipramine.<sup>3</sup> Furthermore, the authors quote a personal communication (1985) from Jungkunz, who found a slight superiority for PO over IV chlorimipramine, analogous to their own results.

We must note that a study of only 22 patients is insensitive to all but the largest clinical differences between two active treatments. Nevertheless, the trend in favor of the PO antidepressant makes it less likely that a clinically significant difference in favor of IV infusion will emerge by the end of the German trial, which is still enrolling subjects. Moreover, despite the enthusiasm of European psychiatrists, rigorous investigation at this stage provides little to no support for IV antidepressant infusions. This leaves the skeptics among us to be convinced that this technique represents anything more than adding medical drama to standard pharmacotherapy.

\*Not currently available in the United States.

<sup>1</sup>Pollock BG, Perrel JM, Shostak M: Rapid achievement of antidepressant effect with intravenous chlorimipramine. (letter to ed.) *N Engl J Med* 1985;312(19):1130.

<sup>2</sup>Kissling W, Moller HJ, Lauter H, Binz U, Wentt G: Double-blind comparison of intravenous versus oral maprotiline: antidepressant activity, plasma levels, side-effects. *Pharmacopsychiatry* 1985;15:96-97.

<sup>3</sup>Escobar JI, Flemenbaum F, Schiele BC: Chlorimipramine: a double-blind comparison versus oral administration in depressed patients. *Psychopharmacologia* 1973;33:111-115.

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fewer arrhythmias and other cardiac effects than thiopental (Pentothal) or diazepam (Valium).

Considerable debate still surrounds the relative efficacy of bilateral versus unilateral electrode placement. Dr Richard Weiner of Duke University reported that most studies of relative efficacy have failed to find differences between the two techniques. Where a trend did occur, however, it always favored bilateral, and in two series, the difference was statistically significant. A recent trial, in which nonresponders after six to ten unilateral treatments were either continued on unilateral or switched to bilateral ECT, found no greater improvement among patients who were switched to bilateral.

In another relevant study recently published, 69 patients in Nottingham, England were assigned randomly in double-blind fashion to receive either bilateral, unilateral, or simulated ECT for the treatment of depression.<sup>2</sup> Although both active treatments were superior to the simulation, patients who received bilateral ECT recovered more rapidly and required significantly fewer treatments (9.64 for the simulated group, 7.91 for unilateral, and 6.59 for bilateral). After completion of the study, 32 went on to receive further bilateral treatment: The simulated group received an average of 4.14 sessions, the unilateral 2.18, and the bilateral 0.91.

Dr Abrams suggests that when symptoms are extremely severe or life-threatening, bilateral ECT should be preferred. Moreover, patients who fail to respond to five to seven unilateral treatments should be switched to bilateral. On the other hand, patients who would be particularly sensitive to the amnestic effects of ECT may do better with unilateral treatment.

Dr Weiner believes that the efficacy of unilateral ECT can become comparable to that of bilateral with proper electrode placement (the d'Elia position), proper attention to electrode-scalp coupling, assurance of a suprathreshold stimulus, and incorporation of seizure monitoring to be certain that a convulsion occurs. However, he acknowledges that some subgroups (perhaps manics, for example) might be preferentially responsive to bilateral treatment, and he also raises the possibility that sometimes the bilateral technique might be more effective, rapid, or produce more enduring results.

Although not as striking as the difference between bilateral and unilateral effects on memory, lower energy wave forms can substantially reduce short-term cognitive impairment following ECT. Low energy wave forms appear comparable in efficacy to higher energy stimulation, although ultra-brief pulses (less than 0.5 msec) might be less effective.

The choice of stimulus intensity requires titration for each patient, according to Dr Weiner. Too low a dose can fail to produce a seizure or may require additional stimulation, while an excessive dose produces greater memory and cognitive impairment with no additional therapeutic benefit. Interestingly, an unpublished study from Malitz, Sackeim, and others at Columbia has found that unilateral nondominant ECT with a stimulus barely exceeding

the seizure threshold was significantly less effective than bilateral treatment, suggesting some efficacy attached to the stimulation itself.

### Conclusions

The consensus panel, chaired by Robert M. Rose, MD, professor and chairman of psychiatry at the University of Texas/Galveston, lamented the paucity of adequate studies of ECT. In addition to encouraging more research, the panel urged that surveys be done on the nature of ECT administration in the United States and of patient attitudes and responses to the procedure. They also called for the establishment of hospital review committees to oversee ECT, for the periodic inspection of ECT equipment, and for increased training of medical students and psychiatric residents. The panel emphasized that ECT should be administered only for the benefit of individual patients, and not for the convenience of a professional staff or because of financial considerations. They underscored the controversy that has swirled around convulsive therapies for much of the half-century of their use, finding that at least some of the disfavor attached to ECT stems from its historical use as a means of behavioral management, rather than a specific therapy, and the resulting fears (and actual instances) of its abuse.

Considering all available evidence from both rigorous scientific investigations and testimonials of patients and doctors, we consider ECT a legitimate medical therapy with an acceptable risk/benefit ratio. The high prevalence of mood disorders, coupled with the great morbidity, mortality, and expense associated with them, counterbalance the discomforts and risks commonly associated with ECT. The qualifiers to this conclusion, however, are that patients be appropriate candidates for the procedure (based on all the considerations previously outlined), that the psychiatrist and anesthesiologist be thoroughly familiar with the technique, that the equipment be safe and adequate, and that the spirit of informed consent be observed in full.

Many questions remain to be resolved. Among the more troublesome are the existence, the nature, and the frequency of prolonged memory dysfunction. Toward this end, more and better studies are sorely needed.

We look forward to the time when science will lead us to specific physical/chemical treatments for severe mood and other psychiatric disturbances, so that induction of generalized cerebral convulsions will be retired to the annals of history. Until then, we favor the reasonable availability of ECT, administered by competent and humane clinicians.

<sup>1</sup>Miller AL, Faber RA, Hatch JP, Alexander HE: Factors affecting amnesia, seizure duration, and efficacy in ECT. *Am J Psychiatry* 1985;142:692-696.

<sup>2</sup>Gregory S, Shawcross CR, Gill D: The Nottingham ECT study: A double-blind comparison of bilateral, unilateral, and simulated ECT in depressive illness. *Br J Psychiatry* 1985;146:520-524.