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Controlled Trials of Electroconvulsive Therapy

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Electroconvulsive therapy, like every physical treatment in psychiatry with the exception of penicillin for GPI, was introduced on an entirely empirical basis. It became widely adopted before systematic evidence on its efficacy had been collected, and a clinical lore on its indications was built upon a minimal background of objectivity. Slowly a body of evaluation through clinical trials has accumulated, focusing first upon the procedure as a whole and more recently upon the element—the convulsion—that is widely believed to be necessary for the therapeutic effect.

MAJOR CLINICAL TRIALS

Two trials in the 1960s established the efficacy of electroconvulsive therapy (ECT) in depression relative to the then recently introduced antidepressant drugs. One trial in the United States[1] and one in the United Kingdom[2] each examined ECT relative to imipramine, a monoamine oxidase inhibitor, and placebo in a series of at least 250 inpatients with depression. The inclusion criteria of Greenblatt *et al.*[1] were probably somewhat wider than those of Cawley *et al.*[2] (TABLE 1), and the duration of the trial was longer, but the results were remarkably similar. Thus at the end of the first trial 91% were judged at least "moderately improved" and 76% "markedly" so on ECT, and in the second trial 84% were judged "improved" and 71% with no or only slight symptoms. The comparisons with the percentage of patients improved on placebo show advantages for ECT significant at the 1% level. There are also significant differences in favor of ECT with respect to the drug treatments, although in each trial one drug comparison (with phenelzine in Greenblatt *et al.*[1] and with imipramine in Cawley *et al.*[2]) is not significant at the "moderately improved" and "improved" level. Together the trials yield a concensus conclusion that ECT is at least as effective as antidepressant medication and perhaps more rapid in its action.

However it must be noted that neither trial was conducted blind with respect to ECT in the sense that they were blind with respect to the tablets (antidepressant or placebo) administered. Both clinicians and patients knew which patients had received electroconvulsive therapy.

Thus these trials did not eliminate the possibility that some aspect of the treatment procedure other than the induction of the convulsion was responsible for the therapeutic effect. For example there is evidence that the circumstances in which a treatment is administered affect placebo response rates,[3] and the history of the introduction, widespread use, and subsequent decline of insulin coma therapy suggests that in the past the psychological effects of an elaborate physical procedure have been underestimated.[4] For these reasons and also to understand the mechanism of action, a more precise evaluation of the role of the convulsion is desirable.

TABLE 1. Major Random-Allocation (Nonblind) Controlled Trials

		Diagnoses Included	Total Trial Entrants	Group Size	Treatments	Outcome at 8 Weeks: Percent Markedly Improved	p vs. ECT	Outcome at 8 Weeks: Percent Markedly + Moderately Improved	p vs. ECT
Greenblatt, Grosser & Wechsler[1]	1964	Depression occurring in psychoneurosis (18%), manic-depression (27%), involutional melancholia (18%), schizoaffective reactions (20%), and character disorders (16%)	281	63	ECT (>9)	76	—	92	—
				73	Imipramine 200–250 mg	49	<0.01	74	<0.02
				38	Phenelzine 60–75 mg	50	<0.01	79	N.S.
				68	Isocarboxazid 40–45 mg	28	<0.001	56	<0.001
				39	Placebo	46	<0.01	59	<0.01
						Outcome at 4 weeks: Percent None or Slight Symptoms	p vs. ECT	Outcome at 4 weeks: Percent Improved	p vs. ECT
MRC trial Cawley et al.[2]	1965	Primary depression in patients aged 40–69 years of duration less than 18 months without adequate previous treatment	250	65	ECT (4–8)	71	—	84	—
				63	Imipramine 200 mg	52	<0.05	72	N.S.
				61	Phenelzine 60 mg	30	<0.01	38	<0.01
				61	Placebo	39	<0.01	45	<0.01

There have been two phases of interest in this question. A number of studies between 1953 and 1966 incorporated designs in which ECT was either compared with simulated (sham) ECT or was compared with other treatments in such a way as to cast light on the role of the convulsion. Since 1978 there has been further interest in this issue (particularly in the United Kingdom), and five trials have been conducted specifically to assess the role of the electrically induced convulsion.

TRIALS BETWEEN 1953 AND 1966

Data for trials between 1953 and 1966 are shown in TABLE 2. Two of the earliest studies included groups of patients treated with electroconvulsions unmodified by anesthesia or muscle relaxants,[5,6] in one case in comparison with pentothal anesthesia and subconvulsive stimulation under anesthesia,[5] in the other with groups treated with electroconvulsions modified by muscle relaxant and thiopental, and treated with thiopental or nitrous oxide alone.[6] Although the designs were unexceptionable and substantial improvements were seen in all groups in each trial, no significant advantages for convulsive over subconvulsive regimes were seen. However these trials included patients with schizophrenia, a diagnosis that would not now be considered the primary indication for the use of ECT. Thus the trial of Miller *et al.* was confined to chronic institutionalized patients originally diagnosed catatonic schizophrenic,[5] and the study of Brill *et al.* included 67 patients described as suffering from schizophrenic reactions, 14 with schizoaffective disorders, and 16 with depressive reactions.[6] In the latter study the 30 patients with depressive illnesses were analyzed separately; although there was a 67% overall clinical improvement in the shock-treated patients in this group compared to 44% in the nonshock patients, this difference did not reach statistical significance. For size of sample, rigor of design and analysis, and range of assessments employed, the study of Brill *et al.* has hardly been equalled in the literature. The authors' conclusion that "for groups comparable to this one, the more traumatic components of ECT (electricity, convulsions) might be abolished without reducing therapeutic effectiveness"[6] has received less subsequent attention than it deserved.

Some studies which have focused more directly on depression have included smaller sample sizes. Thus in the study of Harris and Robin more patients on ECT improved than those in the comparison groups treated with hexobarbitone and phenelzine or placebo[7] but the trial was not fully blind and the groups were too small for statistical analysis. McDonald *et al.* included a group of four patients treated with simulated ECT in their control group but these patients were not separately analyzed.[8] In the trial of Wilson *et al.* a significant difference in Hamilton scores ($p < 0.05$) was observed between the two groups of patients treated with electroshock and two given anesthetics, but the differences between individual groups were not significant and the shock vs. imipramine group differences disappeared in a second phase of the trial in which the drug dose was increased.[9] A larger study of depressions of moderate severity compared electroconvulsive therapy with thiopental-induced sleep and showed a difference in favor of the former,[10] but this difference was not significant and the patients were not blind to the nature of the treatments.

Two studies that appear to give a favorable result with respect to the therapeutic effect of the convulsion include faults of design with respect to random allocation.[11,12] Thus the study of Ulett *et al.* compared photoconvulsive and electroconvulsive treatments with subconvulsive photic stimulation and quinalbarbitone sedation.[11]

Although the outcome in the convulsive groups together was significantly superior to that in the two nonconvulsive groups together, allocation to groups was achieved by a mixture of matching and random allocation; in addition it is not clear to what extent the patients were aware of the differences between the treatments.

In a brief report of a trial comparing 16 patients treated with biweekly anesthetics and imipramine tablets and 15 patients treated with ECT and placebo tablets, Robin and Harris present clinical findings (TABLE 2) that show a significant ($p < 0.01$) advantage for the latter after two weeks of treatment.[13] Symptom ratings (data not presented) also apparently showed advantages for ECT, but nurses' ratings did not. The design of this study (similar in some respects to that of Wilson *et al.*)[9] is of interest in that it is of potential value in assessing the relative efficacy of tricyclic antidepressants and ECT with respect to different types of depressive illness, although neither trial included sufficient numbers of patients to make this possible.

RECENT TRIALS

Although between 1966 and 1978 no studies bearing directly upon the role of the convulsion have appeared, since that time five studies in which real ECT (modified by anesthesia) has been compared with simulated (sham) ECT (i.e., the induction of anesthesia and muscle relaxation as for ECT but without the passage of current) have been published (see TABLE 3). Major interest attaches to the question of the extent to which the results of these trials are in conflict or agreement. Since there are substantial differences in trial design and conduct, each must be separately discussed.

Freeman, Basson, and Crichton, 1978

Freeman *et al.* adopted an experimental design in which patients with a diagnosis of primary depressive illness were randomly allocated either to a course of real ECT or to a course of ECT in which the first two treatments were simulated.[14] Outcome was assessed both by depression ratings obtained at weekly intervals throughout the course of treatment and by the decision of the clinician (who was blind to treatment) to terminate the course. The authors concluded that "ECT is significantly superior to simulated ECT in the treatment of depressive illness"[14] on the basis that there were significant differences in Hamilton ratings after two treatments, and that the number of treatments administered to the simulated group was significantly greater.

However there are obstacles to accepting this conclusion without qualification. These arise partly from the design which permitted flexibility with respect to number of treatments administered but also attempted to assess the effects of different treatment schedules as if this had been an independent variable. Criticisms that may be made of the two outcome criteria are:

1. *Number of ECTs prescribed.* The principal difficulty here is that unequal numbers of patients were lost for reasons other than satisfactory response from the two groups: 2 were lost from the simulated ECT group because they developed hypomania, but a total of 6 were lost from the real ECT group—2 for hypomania, 2 because they refused further treatment, and 2 because they had an "inadequate response." Obviously this imbalance makes the use of "number of ECT to satisfactory response" problematic. Presumably the 2 patients who developed hypomania in each group can be eliminated, but the remaining 4 (20% of the randomized sample) lost from the real ECT group must be taken

TABLE 2

Authors	Year	Diagnoses Included[a]	Treatment Comparisons[b]	Group Sizes	Allocation	Assessments	Outcome	Significance
Miller, Clancy & Cumming[5]	1953	Catatonic schizophrenia	ECT (× 15) Pentothal (A) Pentothal (A) + subconvulsive shock	10 10 10	Random	2/4 raters blind	All groups showed behavioral improvements	No significant between-group differences
							No. recovered / No. markedly improved	
Ulett, Smith & Glesser[11]	1956	Involutional psychotic (18), manic-depressive (8), psychotic depressive (20) & psychoneurotic depressive (8) reactions; 1st episode catatonic and schizoaffective psychoses (20)	Photoconvulsive shock Subconvulsive photic shock ECT (12–15) Quinalbarbitone (S)	21 21 21 21	Matched/random (i.e., not fully random)	Raters blind	7 / 5 1 / 3 5 / 2 2 / 3	ECT group not significantly different from other 3 groups: 2 convulsive groups superior to 2 non-convulsive groups
							Percent improvement	
Brill, Crumpton, Eidusson, Grayson, Hellman & Richards[6]	1959	Schizophrenic reactions (67), depressive reactions (30)	ECT (× 20) ECT + scoline ECT + thiopental (A) Thiopental (A) N_2O (A)	19 20 20 20 18	Random	Raters blind	63 60 } shock: 53% 35 35 55 } no shock: 47%	No significant differences between groups, between shock and no-shock groups or between the shock (67% improvement, $n = 21$) and no-shock (44% improvement, $n = 9$) depressive subgroups
							No. slightly or greatly improved after 2 weeks	
Harris & Robin[7]	1960	Depressive reactions	ECT (× 4) + hexobarbital (S) Hexobarbital (S) Hexobarbital (S) + phenelzine	4 4 4	Random	Not fully blind	4 1 —	Sample size too small for statistical analysis
Cronholm & Ottosson[12]	1960	Endogenous depression	ECT (× 6) ECT shortened by lidocaine	24 23	Sequential (i.e., not random)	Not fully blind		Significantly less improvement in group receiving lidocaine
							Withdrawn/slight or no improvmt. / Mod. or marked improvmt.	
Robin & Harris[13]	1962	Depression	ECT (× 6) + placebo Anesthesia + imipramine	15 16	Random	Blind	3 / 12 13 / 3	$p < 0.01$
							No. improved/recovered	
Fahy, Imlah & Harrington[10]	1962	Nonreactive depression	ECT (× 6) Imipramine Thiopental anesthesia	20 20 20	Random	Patients not blind	12 10 8	Between-group differences not significant
							No. of responders	
Wilson, Vernon, Guin & Sandifer[9,c]	1963	Manic-depressive, involutional and reactive depression	ECT (× 6) + imipramine ECT (× 6) + placebo Thiopental (A) + imipramine Thiopental (A) + placebo	4 6 6 6	Random	2/3 raters blind	4 6 5 3	Between-group differences not significant
							Adjusted percent improvement	
McDonald, Perkins, Marjerrison & Podilsky[8]	1966	Depression	Amitriptyline ECT (× 8) Placebo/sham ECT	10 12 4 + 4	Random	Blind	29 36 15	ECT-sham ECT differences not separately analyzed

[a]Brackets indicate numbers of patients with each diagnosis.

[b]ECT, brackets indicate numbers of treatments; drugs, A indicates anesthesia, S indicates sedation.

[c]In Wilson *et al.*'s study, convulsive/nonconvulsive differences were present but these disappeared in phase 2 when imipramine dosage was increased.

[**Note added in proof:** Fink (1982. Br. J. Psychiatry **141:** 213–214) gives brief details of a comparison of convulsing with subconvulsive shock in a group of mixed psychotic patients, with greater therapeutic effects in the convulsive group.]

TABLE 3

Author	Year	Sample Assessed for Entry	Selection Criteria	Comparison Groups	Trial Sample: Starters	Withdrawn	<4 ECT	Unaccted. for	Completors
Freeman, Basson & Crichton[14]	1978	Not stated	Primary depression (Hamilton & Beck >15)	2 sham + real ECT	20	6			14
				2 real ECT	20	2			18
Lambourn & Gill[19]	1978	38 patients referred for ECT	Depressive psychoses	6 sham ECT	16	—			16
				6 real ECT	16	—			16
West[20,21]	1981	Not stated	Primary depression (Feighner criteria)	6 sham ECT	12	1			11
				6 real ECT	13	2			11
Northwick Park[17,22]	1980, 1984	128 depressed inpatients[a]	MRC 1965 Newcastle and Feighner criteria	8 sham ECT	35	4			31
				8 real ECT	35	4			31
Leicester[27]	1984	143 depressed inpatients[b]	Patients referred for ECT including those with retardation, delusions & neurotic depression	Up to 8 sham ECT	42	10	2	1	29
				Up to 8 real ECT	53	6	0	4	43

[a] 19 patients did not meet trial diagnostic criteria; 6 outside age range; 13 had ECT in previous 6 months; 12 refused; 2 detained; 6 poor anesthetic risk.

[b] 48 patients did not give consent for various reasons.

into account. If the 2 patients can be assumed to have had an unsatisfactory response, the proportion of 4 of 18 in the real as compared to 0 of 18 in the simulated ECT group (Fisher's exact test $p = 0.052$) might support the paradoxical conclusion that real ECT is less effective than simulated ECT.[15] Freeman *et al.* adopted the strategy of excluding the two patients who refused further treatment and calculated that the number of ECTs given to the real ECT group (presumably including the two patients who were withdrawn because of "inadequate response," but whether or not including the patients who became hypomanic is unclear) is significantly less ($p < 0.05$) than the number given to the group given simulated ECT.[14] The data presented in the paper do not allow other assessments (e.g., with the inadequate responders excluded) of this variable to be made. It would seem that if the treatment course could be terminated either by satisfactory or by inadequate response, the number of treatments given is not a suitable dependent variable.

2. *Rating scale assessments.* Significant differences ($p < 0.05$) between the groups after two treatments in favor of real ECT were noted on Hamilton, Wakefield,

TABLE 3 (*continued*)

Type of ECT	Fit Ascertainmt.	Blind Procedure Adopted	Previous ECT	Previous Depression	Medication during Trial: TADs[c]	Benzodiaz	Dependent Variables	Follow-up
Ectron Mk 4 bilateral 400 V sine-wave 1.5S	Not stated	Yes	22/40	28/40	Yes	Yes	Hamilton, Beck + visual analogue scales, clinicians decision to administer more ECT	None
Ectron Mk 4 unilateral pulse	Yes	Yes	21/32	26/32	No	Yes	Hamilton scale, global assessment, treatment in follow-up period	26/32 at 1 month
Transycon double-sided unrectified	Yes	No details given	13/22	15/22	Yes	Yes	Clinicians VAS, Beck ratings, nurses' ratings	None
Ectron chopped sine-wave 195V, 1.7S bifrontal	Inflated cuff method	Yes	15/70	47/70	No	Yes	Hamilton scale, Leeds self-rating, nurses' ratings	57/62 at 1 month and 6 months
Ectron chopped sine-wave bitemporal	Yes	Yes	57/95	2.5 mean admissions/ patient	No	Yes	Hamilton scale, clinician's decision to discontinue ECT	70/77 at 1 month; 69/77 at 6 months

[c] TAD is tricyclic antidepressant.

and visual analogue self-rating scales but not on the Beck scale. A significant difference between the groups was not present at later points. The presence of a significant ECT effect at so early a point in time is somewhat unexpected in view of earlier trial results (e.g., References 2 and 16) and later findings (e.g., Reference 17) which suggest that when ECT effects are demonstrable they emerge over a time course of two to three weeks. Moreover patients in this trial were all receiving antidepressant medication and those on simulated ECT would have been expected to benefit from this even if they lacked the postulated benefits of the convulsion. In view of the differential later loss of patients from the two groups, it must be asked whether such patients were included in these early assessments; Freeman has confirmed that this was the case.[18] A further question concerning the interpretation of this trial is why, if the response after two (i.e., two real against two simulated) treatments is recorded as evidence for an effect of the convulsion, the lack of significant differences after four and six treatments is not taken into account in the opposite sense. The lack of a difference (as assessed by the independent raters) after six treatments is surprising in view of the fact that at this point the clinician in charge of the case made a decision to continue with treatment in 12 patients in the simulated group but only 6 patients in the real ECT group.

For these reasons the findings of this trial cannot be as firmly interpreted as the authors have suggested.

Lambourn and Gill, 1978

Lambourn and Gill randomly allocated 32 patients referred with a diagnosis of depressive psychosis to a two-week course of six real or six simulated unilateral brief-pulse ECTs.[19] Antidepressant medication was discontinued, and clinical state was assessed by Hamilton ratings before and after the course of treatment and at one month follow-up. In the follow-up period some patients in each group received further antidepressant medication or real ECT. In Hamilton ratings there was a 66% decrease in scores in the group receiving real ECT and a 42% decrease in the simulated group, the difference being statistically insignificant. In the follow-up period similar numbers of patients in each group received extra ECT or antidepressant medication, and at the final assessment the scores of the two groups were closely similar.

One explanation considered by the authors for the lack of positive outcome (i.e., significant superiority for real ECT) is the use of unilateral rather than bilateral electrode placement. However a bilateral convulsion was noted on each occasion. The authors also consider whether their treatment group was less depressed than those usually treated with ECT. Two outpatients were included (both were randomized to the simulated treatment group), but the pretrial Hamilton ratings suggest that the patients in this trial were as depressed as those in the trial of Freeman *et al.*,[18] and the authors note that all but six of the patients treated with ECT at that center in the course of the trial were included. The results of this trial, which by its design of six real vs. six simulated ECTs and its eschewal of antidepressant medication (but not by choice of unilateral electrode placements) constitutes a more exacting test of the therapeutic effects of the convulsion, stand in contrast to the conclusions of Freeman *et al.*[18]

West, 1981

West randomly allocated 22 patients with primary depressive illness to six real or six simulated ECTs delivered over a period of three weeks and assessed outcome by a psychiatrist's visual analogue scale, Beck's scale, and a nine-point scale applied by nursing staff.[20,21] On all three assessments the patients receiving real ECT are reported as significantly, often highly significantly, more improved than those receiving simulated ECT. After six treatments the trial design allowed patients to be switched on the decision of the clinician in charge to the alternative form of treatment. In the event, 10 of the 11 patients receiving simulated but none of those receiving real ECT were so switched ($p < 0.005$). The results of this trial were therefore interpreted by the author as strong evidence for the efficacy of the convulsion.

Brandon *et al.* expressed reservations about this trial on grounds of "the sample size (22 cases), the unusually unequivocal result (all patients given simulated treatment improved on crossover to real treatment), problems of selection, and doubts about the extent to which blindness was achieved."[27] The latter point is of particular concern since there was apparently only one investigator. No details of the procedures adopted for randomization and blind assessment are given in the final report,[21] although in an earlier publication a research worker is mentioned (but not named) who apparently was involved both in randomization and administering the Beck scales.[20] These uncertainties diminish the weight that can be attached to the findings.

The Northwick Park ECT Trial

The Northwick Park ECT trial was designed to establish the role of the convulsion in a well-defined population of patients with endogenous depression, to examine predictors of response, and to determine whether the therapeutic effects of the convulsion, if present, are of long duration.[17,22] Seventy patients aged between 30 and 69 years were selected if they met each of three separate sets of criteria—the criteria for depressive illness of the MRC 1965 trial, the Feighner criteria for primary depressive illness, and the Newcastle criteria for endogenous depressive illness and for predicting good outcome to ECT. After consent had been obtained from both patients and relatives, those eligible were stratified by the presence or absence of delusions, agitation, or retardation before randomization to eight real or eight simulated ECTs given over the course of four weeks. Bilateral chopped sine-wave stimulation was applied to the real ECT group, the occurrence of a convulsion being monitored by the inflated cuff method. Particular attention was paid to maintaining the blind procedure in that neither psychiatrist nor anesthetist, nor any member of nursing staff, involved in administering ECT or randomizing patients to treatments was concerned with clinical care or assessment. Outcome was assessed by the Hamilton rating scale administered by clinicians the day before the next treatment was due (to avoid observing the amnesic effects of the last treatment) by Leeds self-rating and nurses' rating scales. Antidepressant medication was not administered during the four-week trial period, but every patient received nitrazepam nighttime sedation and some received additional diazepam during the day. In the follow-up period, with assessments at one and six months after trial completion, additional ECT or tricyclic medication was administered by the clinician in charge who remained blind to the trial treatment the patient had received.

Patients in both groups improved considerably during the course of treatment, but the improvement was greater in the real ECT group ($p < 0.01$ at the end of the fourth week, $p < 0.05$ taking into account the difference in depression ratings before trial entry). Similar trends were seen in terms of Leeds self-ratings and nurses' ratings, but the differences between the groups were never significant. In the one month following the trial, the amounts of extra medication and ECT administered to the groups were closely similar and the difference between the ratings of the two groups had disappeared at this time. On a battery of memory tests, the effects of ECT were clearly apparent but there was no evidence of persisting memory deficit at six months. A more detailed analysis of the nature of the deficits induced by ECT indicated that real ECT induced impairments of concentration, short-term memory, and learning but facilitated access to remote memories.[23] With recovery from depression memory function improved in patients treated with both real and sham ECT.

The conclusions drawn from the findings were that "the improvement in terms of psychiatrists' ratings in the group of patients given real ECT was significantly greater ($p < 0.01$) than that in those given simulated ECT, but the difference between the two groups was small in relation to the considerable improvement of both groups over the 4-week treatment period. . . . the therapeutic benefits of electrically induced convulsions in depression were of lesser magnitude and were more transient than has sometimes been claimed."[17]

Two main criticisms have been directed at this conclusion:

1. *That the patients in the trial were not representative of those who would be treated with ECT in some centers.* This criticism was made by Sandifer,[24] Birley,[25] and particularly by Kendell.[26] It should be noted however that the criteria for selection were in certain respects more rigorous than those of the

trials reviewed already and of the Leicester trial.[27] Patients were selected from a group of 128 patients admitted to hospital for treatment of a depressive episode during the course of the trial by application of three sets of criteria (the MRC 1965 trial criteria,[2] the Feighner criteria for primary depressive illness, and the Newcastle criteria both for endogenous depression and predicting response to ECT). Too little information is provided in the papers of Freeman *et al.*[14] and West[21] to allow any comparison of the samples assessed for those studies with those of the Northwick Park trial. The sample of Lambourn and Gill[19] as that of the Leicester study[27] was defined by clinicians' decision to refer for ECT rather than by independent criteria, but the proportion of patients entering the trial to those considered is comparable in the Leicester and Northwick Park trials (TABLE 3). Moreover an analysis of the trial sample according to various earlier predictive scales indicates that the mean of the trial sample was very comfortably within the recommended range for ECT according to the scales of Hobson,[28] Roberts,[29] and Mendels[30] as well as those of Carney *et al.*[31] (the Newcastle scales). According to his own scale, on which Kendell considers that a higher score predicts likelier response to ECT, the sample had a mean of 15.2 ± 10.9 compared to Kendell's sample of manic depressive patients (International Classification of Diseases 301) in a depressed phase (mean score 9.5) and melancholic (ICD 302) patients (mean score 9.7—see CRC Division of Psychiatry,[22] Table IV). A further misapprehension arises from Kendell's calculation that only 21% of the Northwick Park sample had received ECT previously compared to 55% in the Freeman study,[14] 66% in Lambourn and Gill's,[19] and 59% in West's,[21] from which he argues that "many patients would not normally have received ECT."[26] However this calculation overlooks that one of the entry criteria was that patients should not have received ECT in the previous six months. When the appropriate correction is applied the proportion rises to 37%. It is argued[22] that the discrepancy between this figure and those of other trials is more likely to have arisen from the known and relatively low previous usage of ECT in this part of London than from otherwise inapparent "overgenerous inclusion criteria"[26] which Kendell postulates. He goes on to attribute the lack of difference between the real and simulated ECT groups at one and six months follow-up to a "high relapse rate"[26] attributable to failure to use tricyclic antidepressants routinely in the follow-up period. This criticism overlooks that the lack of difference between the groups at follow-up (with similar amounts of treatment given) was due mainly to the fact that the simulated ECT group had further improved to catch up with the real ECT group in the month after trial completion. For these reasons we consider Kendell's criticisms[26] of the Northwick Park trial to be without substance.

2. *That the use of benzodiazepines diminished a therapeutic effect which would otherwise have been apparent.* This point was made by Lennox and Weaver[32] and d'Elia.[33] For reasons that we have already given,[34] we consider that the supposition that a relationship between seizure duration and therapeutic effect has been established rests on a mistaken interpretation of such evidence as is available. It is the case that such trials as have so far been conducted have not attempted to avoid sedative medication,[35] and in most trials substantial and often uncontrolled amounts have been given. For example in Cronholm and Ottosson's study, 31 of the 87 cases received phenobarbitone 25 mg + 0.16 g opium tincture three times a day.[12] We think it likely that current clinical practice is seldom based upon the premise that any sedative antagonizes the therapeutic effect of ECT and that most clinicians allow their patients to receive at least benzodiazepine hypnotics.

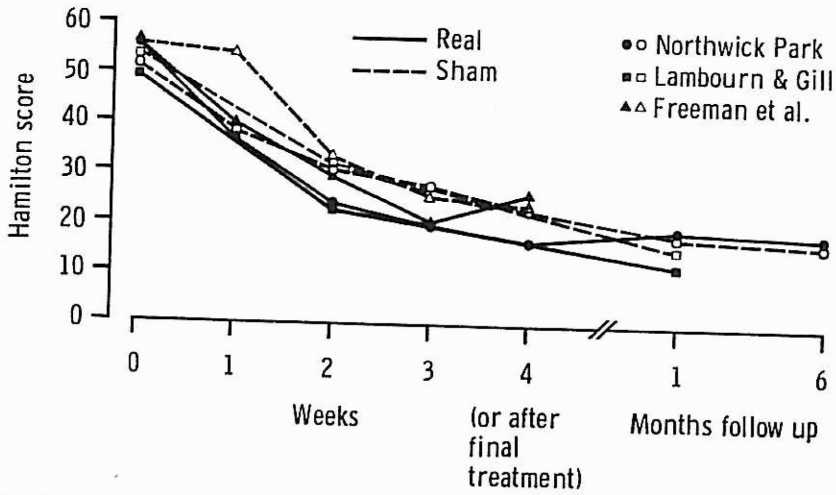

FIGURE 1. A comparison of Hamilton scores in the trials of Freeman *et al.*,[14] Lambourn and Gill,[19] and the Northwick Park trial (Johnstone *et al.*).[17] Groups treated with simulated ECT are shown with dashed lines. The simulated ECT group in the Freeman *et al.* trial received two simulated treatments before going on to real ECT, the total number of treatments being determined by the clinician.[14] Scores after the final treatment in that trial are compared with scores after the fourth week in the Northwick Park trial.

A Comparison of the Freeman et al., Lambourn and Gill, and Northwick Park Trials

West's trial[21] did not use the Hamilton scale,[36] but the other three trials did. Although the scale may not be used by different authors in the same way, some sort of comparison between trials can be made (FIGURE 1).

A number of interesting points emerge:

1. In spite of differences in design and selection criteria, before-treatment scores in the three trials are remarkably similar.
2. The time course of improvement in the different groups is similar. Thus whereas two groups of patients (the simulated groups in the Northwick Park[17] and Lambourn and Gill[19] trials) have received no convulsions at the three- and four-week points respectively, their rates of improvement are not substantially different from the real ECT treated groups (i.e., both groups in the Freeman study[14] and the real ECT groups in the Lambourn and Gill[19] and Northwick Park trials).[17,22]
3. For these reasons extrapolation of the trend in the simulated treatment group in the Freeman *et al.* study beyond two treatments would not be justified.
4. The findings in the Northwick Park and Lambourn and Gill studies at follow-up are closely similar.

The Leicester Trial

The Leicester study was mounted in the wake of the preceding trials to evaluate their apparently discrepant findings. Patients with a wide range of diagnoses (includ-

ing some who were not depressed) referred for ECT were considered, but only those with depression as assessed on Present State Examination were included.[27] Since no specific criteria for endogenous depression or predicted response to ECT were applied, the sample is diagnostically wider than that of the Northwick Park trial.[17,22] Rigorous steps were taken to maintain the blindness of the procedure, and patients were randomly allocated to real or simulated ECT, the stimulation in the former group being of the same form as that given in the Northwick Park trial. As in the Northwick Park and Lambourn and Gill[19] studies, tricyclic antidepressant medication was excluded during the trial, but not in the follow-up. In contrast to these two trials, the length of treatment course was variable. Patients received up to eight real or simulated treatments, the decision to terminate earlier than eight being in the hands of the responsible clinician. Outcome was assessed both in terms of number of treatments given and Hamilton rating scales.

Ninety-five patients (compared to 70 in the Northwick Park trial) entered the study, and 72 (compared to 62) completed it. In a significantly ($p = 0.017$) greater number of cases, the course was terminated earlier than the eighth treatment in the

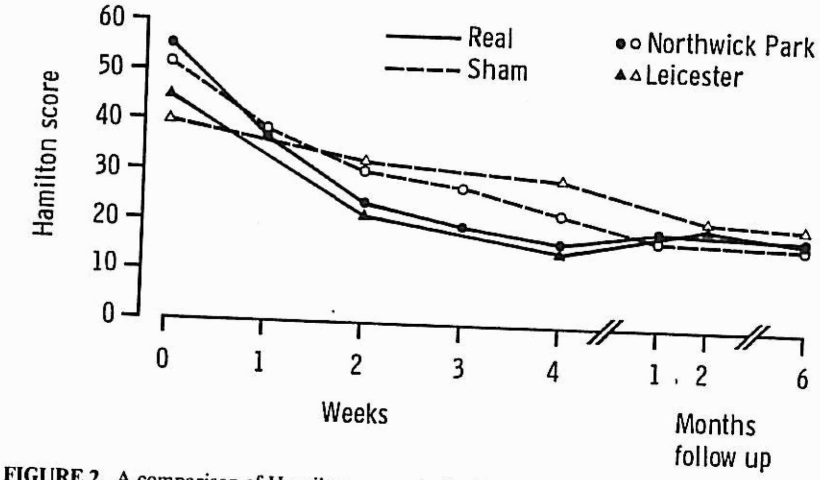

FIGURE 2. A comparison of Hamilton scores in the Northwick Park[17] and Leicester[27] trials.

real ECT group. Moreover on Hamilton rating scores, differences were present between the groups which were significant at the end of the second week ($p = 0.014$) and fourth week ($p = 0.0001$). These differences were not present at 12 and 28 weeks follow-up.

Comparison of the Hamilton scores with those of the Northwick Park study is instructive (FIGURE 2). The pretrial scores of the patients in the Leicester trial are somewhat less than those of the Northwick Park patients, and this is perhaps explained by differences in selection criteria. The rate of improvement in the real ECT groups in the two trials is approximately similar. The main difference between the trials lies in the less good response in the simulated ECT group in the Leicester trial. Again this may be due to differences in the circumstances in which the two trials were conducted—the Northwick Park trial being carried out in a relatively small and well-staffed research ward, while the Leicester study appears to have been conducted in more diverse and perhaps less-well-supervised clinical conditions. If this surmise is

correct it may be supposed that nonspecific therapeutic effects (e.g., due to increased medical and nursing attention) were maximized in the Northwick Park trial.

Although the authors of the Leicester trial interpret their results as indicating that "the difference in outcome in favour of real treatment at two and four weeks was greater than that in the Northwick Park trial,"[27] a reservation concerning this conclusion must be expressed. This is that the number of noncompletors is rather large [23 (24%) compared to 8 (11%) in the Northwick Park trial,[17] 3 (25%) in West's trial,[21] 0 in the Lambourn and Gill trial,[19] and 8 (20%) in the Freeman *et al.* study[14]] and the effects of this cannot easily be assessed from the published account. Thus 16 patients (10 in the simulated and 6 in the real ECT groups) were withdrawn for specified reasons, but a further 2 patients (both in the simulated group) received fewer than four treatments, and were excluded from the analysis. Moreover a further 5 patients (4 in the real ECT and 1 in the simulated group) cannot be accounted for in the numbers included in the Hamilton ratings. If these patients were doing badly (and were not included because for example they were difficult to rate properly), this could affect the size of the difference between the groups. Similarly inclusion of the two patients in the simulated group excluded for receiving less than four treatments could diminish the significance of the between-group difference in treatments administered. Insufficient data have been presented to allow these comparisons to be made. Even without such corrections, the comparison in FIGURE 2 suggests that the similarities between the findings of the Northwick Park and Leicester trials are more striking than the differences.

PREDICTION OF RESPONSE TO ECT

A number of scales have been devised to predict response to ECT, e.g., References 28–31 and 37. However none has been devised on the basis of a comparison of real with simulated ECT and thus all are open to the objection that the clinical observations on which they are based have led them to predict general rather than ECT-specific treatment responsiveness, or even tendency to spontaneous remission. In the Northwick Park trial an attempt was made to examine the ability of each of these scales and other clinical variables to predict response to real rather than simulated ECT.[22] In general the outcome was disappointing. Response to ECT was not predicted by the endogenous stereotype. The most consistent predictor of response was the presence of delusions, which along with agitation and retardation had been used to stratify the sample. Some patients have both delusions and retardation, and when this overlap was allowed for, retardation by itself did not predict response to ECT.

The findings of the Leicester trial appear compatible with this conclusion. Both deluded and retarded subgroups showed significant real-simulated ECT outcome differences but since each of these features has not been examined in the absence of the other, it cannot be determined whether, as in the Northwick Park study, the presence of delusions is the critical factor. If this finding can be replicated, it raises the possibility that delusional depression is, as other workers have suggested, a distinct entity which responds specifically to ECT.

TRIALS OF ECT IN SCHIZOPHRENIA

Some nonblind controlled trials have suggested that ECT has beneficial effects in schizophrenia. Thus Smith *et al.* found that patients with acute episodes of schizophrenia treated with a combination of ECT and neuroleptics recovered more quickly than a group treated with neuroleptics alone;[38] and in May's study

alone did better than those treated with milieu therapy or psychotherapy but in general not so well as those treated with neuroleptics.[39]

Two trials illuminate the role of the convulsion. Miller, Clancy and Cumming in a study already referred to in chronic institutionalized patients found improvements in behavior in those treated with anesthetics as well as those treated with real ECT, and with anesthesia and subconvulsive shock, and no difference between the treatments.[5] By contrast, Taylor and Fleminger found that a group of schizophrenic patients on relatively low doses of neuroleptic medication (chlorpromazine 300 mg or trifluoperazine 15 mg daily, flupenthixol 40 mg or fluphenazine 25 mg monthly) showed greater improvement on a course of 8 to 12 real ECTs than on simulated ECT.[40] Four weeks after the treatment course the difference between the groups had diminished, and 12 weeks later it had largely disappeared. Although the numbers in this trial are small ($n = 20$), the results offer support for the view that the convulsion has some value in the treatment of schizophrenic symptoms. The differences between the findings of Taylor and Fleminger[40] and Miller *et al.*[5] are plausibly attributed to differences in patient populations, the former trial being concerned with a less chronic sample; but the negative findings of Brill *et al.* on more acutely ill patients, the majority of whom suffered from schizophrenic illnesses, must also be borne in mind.[6] It remains to be clearly established that electrically induced convulsions contribute a therapeutic effect which cannot be achieved by neuroleptic medication, but the fact that some symptoms of schizophrenia as well as delusions occurring in the course of depression respond (albeit in the short term) raises the possibility that the indication for ECT is delusional thinking rather than mood change.

OUTSTANDING ISSUES

An issue that has not been addressed by recent trials is whether ECT contributes a therapeutic effect that cannot be achieved by other means. The findings of the Northwick Park and Leicester trials suggest that a requirement for a rapid response is certainly one reason for considering ECT. It remains to be fully investigated whether there are types of depression (e.g., "delusional depression") that respond to ECT but less well to tricyclic medication. A trial design in which this issue could be ethically investigated is that adopted by Robin and Harris[13] and Wilson *et al.*,[9] i.e., that patients are allocated to groups receiving sham ECT and tricyclic medication, on the one hand, and real ECT and placebo, on the other. Such a trial should take into account the effective dose of antidepressant,[9] and might also be designed to address the question of whether neuroleptic medication is of value in deluded depression.

Related to this question is the issue of whether there are types of depressive illness that do not respond to other types of treatment but benefit from ECT over a longer period of time than is apparent in recent studies. These studies have given little support to the notion arising from the retrospective analysis of the literature of Avery and Winokur[41] that the mortality of depressive illness is increased in those not adequately treated with ECT or antidepressant medication. For if, as in the Northwick Park[17] and Leicester[27] trials, differences between the groups are inapparent at one month and six months after a course of treatment, it is difficult to believe that there are long-term benefits beyond this. However perhaps the question deserves further scrutiny in the group of deluded depressed patients, although to obtain a sufficient sample size and duration of follow-up presents difficulties.

Because none of the recent trials has included a comparison group that did not receive repeated anesthetics, they provide no information on the contribution of the nonconvulsive elements of the procedure.

CONCLUSIONS

1. The efficacy of the ECT procedure in the treatment of depressive illness of sufficient severity to require inpatient admission was established in the controlled but nonblind trials of Greenblatt *et al.*[1] and the MRC (Cawley *et al.*).[2]

2. Although the role of the electrically induced convulsion in the therapeutic effect was examined in a series of trials conducted between 1953 and 1966, these studies provided no unequivocal evidence that this was the critical element. Some studies yielded negative findings, or nonsignificant differences between groups treated with real and some form of simulated ECT, while others have defects of design (e.g., nonrandom allocation, failure to establish a blind procedure) which diminish the weight that can be attached to their conclusions.

3. A recent revival of interest in this issue has generated five further trials in which real ECT has been compared with simulated ECT. Although the findings are apparently diverse and criticisms, some pertinent, have been leveled at each study, the following conclusions are probably justified:

   a. Depressed patients treated with simulated ECT show substantial improvements over a three- to four-week course of treatment (as shown by Lambourn and Gill,[19] and the Northwick Park[17] and Leicester[27] trials, and contested only in the findings of the small study of West[21]).
   b. Patients receiving a course of real ECT improve to a significantly greater extent than those receiving simulated ECT (as demonstrated by Hamilton ratings in the Northwick Park[17] and Leicester[27] trials). Although this now appears to be a finding that can be accepted it should be noted that it is not always demonstrable and did not emerge in the study of Lambourn and Gill[19] or in the patient self-ratings and nurses' ratings in the Northwick Park trial.
   c. Some limitations of the studies of Freeman *et al.*[14] and West[21] as indicators of the size of the effect attributable to the convulsion have been noted.

4. The findings of all those studies that have included a follow-up assessment (the Northwick Park[17] and Leicester[27] trials, and the Lambourn and Gill[19] study) are in agreement that the effects of the convulsion are of limited duration.

5. On the evidence available, the most consistent predictor of response to ECT is the presence of delusions. The reliability of this finding, and whether or not retardation is an independent predictor, remain to be established.

6. Whether electrically induced convulsions exert therapeutic effects in certain types of depression that cannot be achieved by other means has yet to be clearly established, as also has the contribution, if any, of nonconvulsive elements of the procedure.

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