Annotation

The Onset and Rate of the Antidepressant Effect of Electroconvulsive Therapy
A Neglected Topic of Research

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This annotation is concerned with how soon and at what rate antidepressant effects become apparent over a course of electroconvulsive therapy (ECT). The first question is of importance in the design and interpretation of biological studies of the mode of action of ECT. The second question is of practical interest to the treating psychiatrist when we ask how the speed of recovery is influenced by what the psychiatrist prescribes, that is, the number and frequency of treatments. These questions are little better answered now than 20 years ago. This may come as a surprise to many readers, who have been advised to use ECT when "seeking rapid improvement" in depressive disorders (ECT Sub-Committee of the Research Committee of the Royal College of Psychiatrists, 1989). This lack of progress is attributable to a dearth of appropriately designed ECT studies.

Clare (1980) recognised that clinical impression, sometimes referred to less charitably as dogma, remains an important influence on the development of psychiatric practice in the absence of appropriate empirical studies. This point is particularly relevant to the use of ECT. Clinical impressions of the answers to these two questions are far from uniform.

The prevailing research climate augurs ill for research studies to guide practice. The last study of the efficacy of ECT for depressive illness in the UK was completed in 1983 (Gregory et al, 1985). Although research interest has not waned to the same extent in the USA, the National Advisory Mental Health Council (1988), in its report to Congress on the 'Decade of the Brain', did not include ECT as one of the treatments for major mental illness that merited further research. The total research budget was over $100 million per annum and the failure to identify an important, widely used treatment must indicate the low priority given to ECT research by the single largest grant-giving body.

Recommended practice: 1969 and 1989 compared

It is relevant to contrast the lack of progress in this important aspect of ECT practice with other changes in the recommended practice of ECT in the last two decades, many the result of empirical findings.

Table 1 summarises the earlier recommendations that are taken from the third and last edition of *Clinical Psychiatry* (Slater & Roth, 1969). These recommendations are compared with those published by the ECT Sub-Committee (1989). One notable area where the recommendations have not changed concerns the frequency of treatments, and no mention is made of the relationship between the frequency of treatment and antidepressant efficacy or timing of antidepressant effect. Attempts to reduce the adverse effects of ECT on memory figure importantly in the history of ECT research (Abrams, 1988). The 1989 recommendations add that treatment frequency should be only weekly if post-ECT confusion is marked, and daily ECT is not recommended because of severe memory impairment.

Empirical studies relevant to the 1989 recommendations

The selection of depressed patients to be treated by ECT has been influenced by a series of studies of the clinical prediction of ECT response (Abrams, 1982). Over 80% of depressed patients with endogenous features of depressive illness improve with ECT, but few specific symptoms or signs are of predictive value. Exceptions may be the presence of depressive delusions and, to a lesser extent, retardation (Crow et al, 1984). Contrary to the Slater & Roth recommendations, empirical studies have also showed that depressive illness in bipolar disorder responds just as well as (Abrams, 1982) or better than (Perris, 1966) that associated with unipolar disorder, and a good response to ECT may be associated with a short illness (Black et al, 1989).

Brief-pulse electrical stimulation causes less post-ictal confusion and anterograde and retrograde amnesia than sine-wave stimulation, yet induces cerebral seizure activity at least as effectively as traditional stimulation (Abrams, 1988). Likewise, unilateral electrode placement causes less severe adverse cognitive effects than bilateral electrode placement. Consequently, the Royal College's

Table 1
Recommended ECT practice in depressive illness: 1969 and 1989 compared

Procedure	Slater & Roth (1969)	ECT Sub-Committee (1989)
Patient selection	Most benefit in 'involutional melancholia'; depression associated with manic–depression less responsive, especially early in episode	Based on a number of signs and symptoms of depressive illness, irrespective of syndrome; delusions and/or retardation particularly relevant
Consent	None	Detailed procedure and documentation for informal and compulsory patients
Electrical stimulus	Alternating sine-wave	Brief-pulse
Electrode placement	By inference, bilateral	Brief-pulse, bilateral; sine-wave, unilateral
Optimal seizure length	None	25 seconds
Seizure monitoring	Observation of facial and/or toe twitching	Observation of tonic–clonic activity or forearm isolated by cuff
Frequency of treatment	Twice or thrice weekly	Twice or thrice weekly
Number of treatments	Recommendations conflicting: if no improvement, stop after 6 treatments; additional 1–3 'prophylactic' treatments upon recovery	Assess after each treatment to see if more needed; if no improvement, stop after 8–12 treatments; additional 'prophylactic' treatment of no value

Recommendations about staffing, treatment facilities and anaesthetic procedures are not included.

recommendations were that when sine-wave electrical stimulation is used, unilateral electrode placement is preferable because of its lesser adverse effects, and that bilateral electrode placement should be standard with brief-pulse stimulation. With brief-pulse stimulation, missed seizures are more common with unilateral ECT (Pettinati & Nilsen, 1985); older patients may respond better to bilateral ECT (Abrams, 1986), and unilateral electrode placement with a stimulus intensity just above seizure threshold may not be effective (Sackeim et al, 1987).

There is now good evidence that generalised tonic–clonic seizures are essential for therapeutic efficacy (Daniel, 1983). A close relationship between the length of individual seizures and therapeutic effect is unlikely, but seizures which last more than 25 seconds are likely to be of generalised tonic–clonic type (Small et al, 1978).

Two extra treatments given once recovery is apparent do not reduce the relapse rate in the three months after ECT in patients without any continuation of antidepressant treatment (Barton et al, 1973).

Antidepressant effect of ECT

Psychiatric textbooks

Statements from recent postgraduate psychiatric textbooks, the Royal College of Psychiatrists and the American Psychiatric Association about the onset and rate of the antidepressant effect of ECT are summarised in Table 2. There is no general agreement on the question of a delay in the onset of the antidepressant effect of ECT. At one extreme, marked improvement after a single ECT is thought

not to be attributable to ECT (Kiloh et al, 1988), or a 'flight into health' to be viewed with caution (Kaplan & Sadock, 1989), and at the other extreme it is stated that a few patients respond dramatically to one or two treatments (Kendell & Zealley, 1988). Partly, this is the result of imprecision in the terminology used to describe treatment outcome in depressive illness (Prien et al, 1991), for example a failure to distinguish clinical response, that is, improvement in depressive symptoms, from recovery, that is, complete remission of symptoms. The intermediate opinion is that there is only slight improvement over the first few treatments, then increasing improvement with later treatments (Gelder et al, 1989). Several sources imply variable rates of improvement among depressed patients, but only Abrams (1988) lists factors that may be associated with such variation. The same author notes that the maximum benefit from an individual seizure may take a week or more to develop, although this view is not supported by a reference.

Unlike some earlier textbooks of psychiatry, those summarised in Table 2 do not mention the durability of improvement after treatments. Sargent & Slater, writing in the first edition of An Introduction to Physical Methods of Treatment in Psychiatry (1944), noted two patterns of response to individual treatments, namely immediate improvement followed by relapse in a few days, and improvement delayed for a day or two but not maximal until about a week after treatment. The authors did not comment upon possible relationships between the patterns of improvement and ordinal number or frequency of ECT, but Forrest, writing in the first edition of The Companion to Psychiatric Studies (1973), stated that after a

Table 2
Statements in recent textbooks about the number and frequency of ECT for depressive illness

Textbook	Relationship of improvement to number of ECT	Recommended frequency of ECT
American Psychiatric Association (1990)	Review after each treatment	2–3 per week; daily, if severely ill
Kaplan & Sadock (1989)	Some improvement after first few treatments, but peak response at 5–10 treatments	2–3 treatments per week; daily, if severely ill
Kendell & Zealley (1988)	A few patients respond dramatically to 1–2; some need 10–12	2–3 per week; no evidence daily ECT gives more rapid response
Abrams (1988)	Depends on previous ECT response and stage of illness; effects of single ECT may take 1 week or more to develop	2–5 per week; 2 bilateral ECT per session if severely ill
Hill et al (1986)	No comment	No comment
Gelder et al (1989)	Little response until 2–3, then increasing improvement	1 per week (bilateral); 3 per week, if severely ill
Kiloh et al (1988)	Recovery after 1 ECT probably natural remission or incorrect diagnosis	No precise rules; 2–6 per week depending electrode placement and individual patient
ECT Sub-Committee (1989)	Response to 1st and 2nd treatments highly correlated with overall change	2–3 per week; daily should not be given

second ECT, the patient was better for part of the afternoon, and after the third and fourth treatments the improvement extended to the next treatment day.

Empirical studies

Until recently, in most ECT studies the timing of assessments was ordered to allow comparison with the effects of antidepressant drugs, for example after six administrations of ECT, at four weeks, or at discharge (see reviews by Barton, 1977; Avery & Winokur, 1977). Recent controlled trials of ECT often included more frequent assessments (see Crow & Johnstone, 1986), but did not distinguish between rates of improvement of those patients who go on to recover with ECT and those who make only a partial recovery (or do not improve at all).

Katz et al (1987), writing as part of the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression, emphasised that the process of recovery during treatment for depressive illness must be studied separately in those patients who clearly go on to recover. This point is important and has been neglected in almost all ECT studies. Additionally, most patients in ECT studies also receive concomitant psychotropic drugs, which seems likely to hinder interpretation of results. Even benzodiazepine drugs may confound the pattern of improvement, either by diminishing certain symptoms of depressive illness or by compromising the therapeutic effects of ECT (Pettinati et al, 1990).

Of all the ECT studies specifically designed to assess rate of improvement, only one (Post et al,

1987) concerned drug-free depressed patients who clearly recovered with treatment. Rapid onset of antidepressant effect during a course of bilateral sine-wave ECT was observed in all eight depressed patients studied. There are two other relevant studies, but either patients were not drug-free, or recovered patients were not considered separately from non-recovered. Rich & Black (1985) observed the greatest reduction in depression ratings after the first unilateral brief-pulse ECT, and Price et al (1978) found that the improvement after the first two bilateral sine-wave ECTs was closely correlated with improvement over a course of treatment.

The preceding findings, while clearly preliminary, do not support the views that there is a delay in the onset of the antidepressant effect of ECT and that little improvement occurs early in a course of treatment.

Frequency of treatment

Psychiatric textbooks

Table 2 also shows the recommended frequency of ECT. Usually there is a recommended frequency for routine practice and another for severely ill patients who are either suicidal or refusing to eat or drink. For routine practice, most sources recommend two or three treatments per week, but the recommendations vary from one to six treatments per week. Abrams (1988) and Kiloh et al (1988) noted that unilateral treatments could be given frequently without marked cognitive impairment in routine practice, although neither commented about how this affected

antidepressant efficacy. Abrams (1988) considered differences in the preferred frequency of treatment were more to do with 'personality characteristics' and 'daily routine' of the treating psychiatrists, rather than any theoretical basis.

In the management of severely ill patients, two different approaches are recommended, namely an increase in the frequency of treatments per week and increasing the number of treatments given per anaesthetic. None of the textbooks that recommended either practice cited published studies that supported an increased rate of antidepressant effect. The most recent Task Force Report on ECT by the American Psychiatric Association (1990) supports the use of daily ECT in severely ill patients and, moreover, recommends factors that must be specified in multiple inductions of seizures during the one anaesthetic (multiple monitored ECT, or MMECT). The Task Force noted that a 'substantial minority' of practitioners use MMECT at least occasionally. In contrast, the Royal College of Psychiatrists stated that daily ECT should not be given and made no mention of MMECT.

Variations in recommended psychiatric practice are not unique to ECT. ECT is, however, unique among commonly used treatments in that each application inevitably leads to a variable period of drowsiness, confusion and anterograde amnesia, commonly causes headache and nausea, and may lead to the occasional loss of personal memories; moreover, each application requires a brief anaesthetic that involves additional risks of morbidity and mortality that are slight but never negligible (American Psychiatric Association, 1990). MMECT is also associated with an increased risk of prolonged seizures or status epilepticus (Abrams, 1988). Moreover, Table 2 fails to reflect the variation in routine clinical practice among psychiatrists in the UK and USA; for example, 15% of ECT practitioners in the USA prescribe up to eight inductions of ECT during the first two anaesthetics in severely ill patients (personal communication, Dr Harold Sackeim, member of the APA Task Force). The cost to individual patients of, say, daily treatment is considerably greater than that of weekly treatment.

Empirical studies

There are no published studies of the comparative efficacy of different frequencies of treatment by bilateral ECT. In a preliminary abstract, Lerer et al (1991) reported that the rate of improvement was greater in depressed patients treated by three bilateral administrations of ECT per week than in patients treated by two real and one sham treatment. Details

of the assessment methods are not yet available and interpretation of this finding is further complicated by the fact that patients treated thrice weekly also received more treatments.

For unilateral ECT, neither four-times-weekly (Stromgren, 1975) nor thrice-weekly treatment (McAllister et al, 1987) have been shown to induce improvement more quickly than twice-weekly treatment. There are limitations to these studies because clinical improvement was only measured after most patients had been treated with six ECTs, and rate of improvement was not assessed separately in those patients who clearly recovered with ECT.

There are several descriptive accounts of multiple seizure induction, in which up to eight convulsions were obtained during prolonged anaesthesia (Blachly & Gowing, 1966). There are no adequate prospective studies of the comparative efficacy of multiple induction during one anaesthetic with more conventional ECT, but multiple induction may be associated with a greater risk of postictal confusion and prolonged seizures (Abrams, 1988). In a prospective study, Roemer et al (1990) randomly allocated 29 depressed patients withdrawn from psychotropic drugs to conventional or double-induction bilateral ECT given three times per week. Double induction gave more improvement between the outset of treatment and the day after the fourth session of treatment. Double induction was also superior when analysis was carried out separately, both in deluded patients and in patients who clearly recovered with ECT.

There are insufficient data to determine the optimum frequency in clinical practice. In the management of severely ill patients, two different strategies are recommended. The first involves increasing the number of treatment sessions per week, even up to daily sessions, and the second strategy is to increase the number of seizures induced during the one anaesthetic. There are no comparative studies of these two strategies.

Practical and theoretical implications

The presumed relationship between the onset of the antidepressant effect of ECT and the ordinal number of treatments will influence clinical practice. Slater & Roth (1969) noted that some psychiatrists preferred to start a course of ECT with three treatments per week for two weeks and only then to assess the result. A survey of British psychiatrists by Pippard & Ellam (1981) revealed that one in ten psychiatrists prescribed a fixed course of treatment without clinical review between treatments. Presumably, this practice reflects the opinion that the first few treatments in a course

of ECT are without antidepressant effect. This opinion may be apparently self-fulfilling if patients are not reviewed until they have had several treatments in a course of ECT. The prescription of a fixed number of treatments was not recommended by any of the sources reviewed, but a future study to establish the antidepressant effect of early treatments may influence the use of ECT.

The lack of evidence concerning the cost and benefit of various frequencies of ECT means that its use more often rests on personal preference than an adequate theoretical basis (Abrams, 1988). In the UK, ECT is usually given twice per week and an ECT course consists of just over six treatments (Pippard & Ellam, 1981), whereas in the USA, ECT is usually given three times per week and a course consists of ten treatments (Lerer & Shapira, 1986). In recent textbooks, the recommended frequency in the routine practice of ECT varied from one to five bilateral treatments per week. This discrepancy would not be tolerated in the recommended therapeutic dose of a newly introduced antidepressant drug. There is no general agreement on the optimum treatment of patients who are suicidal or refusing to eat and drink and in whom a rapid improvement would be desirable. The recommendations given by several of the textbooks conflicts with that of the ECT Sub-Committee, who noted that there is no evidence that daily ECT speeds recovery.

There is considerable controversy about the significance of any apparent antidepressant effect early in a course of ECT. Several authors suggest this phenomenon is worth studying. Price *et al* (1978) suggest, for example, that the clinical response to the first one or two treatments may prove helpful in forecasting the likelihood of eventual recovery after a course of ECT. Fink (1979) argues further that the identification of characteristics of depressed patients who respond rapidly to ECT may form the basis of a future subclassification of depressive illness. The ECT Sub-Committee's guidelines noted that a few depressed patients make a rapid response to one to two treatments and so make further treatment unnecessary. In contrast, Kiloh *et al* (1988) remark that marked improvement after a single treatment is not related to ECT itself, but probably reflects a natural remission or the incorrect diagnosis of depression. By extension, Pande *et al* (1988), in their study of clinical predictors of response to ECT in depressive illness, excluded from the study any patient who did not receive at least five treatments. These conflicts about the scientific validity, theoretical and clinical significance of an anti-depressant effect early in a course of ECT remain unresolved.

Opinions about the relationship between the antidepressant effect of ECT and individual treatments are important in determining the design and interpretation of biological studies of the mode of action of ECT. In an influential article, Kety (1974) stated that a single treatment was insufficient to produce a detectable clinical effect, suggesting that the acute effects of a single seizure on monoamine function were not likely to account for the anti-depressant effect of ECT. This statement was made without reference to any clinical studies, but has been repeated in textbooks with reference to any of the acute biochemical effects of ECT (Fink, 1979; Lerer *et al*, 1984; Kiloh *et al*, 1988) and applied in important studies of the mechanism of the anti-depressant effect of ECT (e.g. Grahame-Smith *et al*, 1978). In other words, this opinion has directed biological studies away from the acute effects of cerebral seizure activity to effects that emerge only after a series of treatments.

It is not disputed that most depressed patients who recover with ECT do so only after several treatments, but the statement that a single treatment is without any clinical effect is, to say the least, contentious in view of the clinical studies above that detected a rapid onset of antidepressant effect during a course of ECT. In the most recent review of the psycho-pharmacology of repeated seizures, Green & Nutt (1987) repeated the statement that a single administration of ECT is insufficient to produce any detectable clinical improvement, but with an added caveat that some biochemical change must be occurring after even a single treatment, which results in the long-term alterations responsible for the antidepressant effect of ECT.

Our own series of studies support the view that a biochemical change after a single treatment can be associated with the subsequent antidepressant effect (Scott *et al*, 1986, 1989, 1991; Whalley *et al*, 1987). We found that a hormonal effect of ECT detectable within two minutes of the first ECT (the release of the oxytocin-associated neurophysin) correlated with the extent of eventual improvement in symptoms of depressive illness over the whole course of treatment. Neurophysin release was not simply an epiphenomenon of cerebral seizure activity (Scott *et al*, 1989). Surprisingly, the release of oxytocin itself may not be related to clinical outcome (Smith *et al*, 1990).

Methodological considerations for future studies

Few ECT studies are designed to study the onset of improvement in symptoms of depressive illness or its relationship to the number and frequency of

treatments. Given the considerable variations in contemporary recommendations and ECT practice, it will be necessary to assign priority to a few questions. Firstly, it is of considerable theoretical importance to establish to what extent treatments early in a course of ECT have detectable antidepressant effects. (Thereafter it may become informative to ask in which type of depressed patient or depressive illness this is so.) An appropriately designed study could simultaneously investigate questions of direct practical relevance. A clear understanding of the effects of treatment frequency on the rate of improvement and final antidepressant efficacy is lacking. Furthermore, there are few data to guide practice in the management of patients in whom the need for clinical improvement is urgent and may be life-saving. Were it to be established that, say, thrice-weekly treatment brings about more rapid improvement than twice-weekly treatment, an appropriate design would be to compare thrice-weekly treatment with a yet more frequent treatment schedule. If twice- and thrice-weekly treatments are equivalent in their rate of antidepressant effect, it would be more appropriate to compare, say, double induction of seizures with single induction, both given at the same frequency. Such studies could not be restricted to the most severely ill or disturbed patients, because patients would be free of psychotropic drugs throughout the course of ECT to assist interpretation of the results. This is not routine in the UK, but has become recommended practice in the USA (Abrams, 1988; American Psychiatric Association, 1990) and should not, in a research context, raise ethical problems.

Frequent assessment of patients would be required, and difficulties would arise in the use of observer rating scales of depression because so few were designed to be sensitive to short-term change. One exception is the Montgomery and Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979), which can be used daily with success, at a fixed time each afternoon (Dykes, 1988). Daily assessment would be complemented usefully by the inclusion of subjective visual analogue scales. An anecdotal report from the earliest days of ECT (Sargent & Slater, 1944) described dramatic improvements in the motor signs of serious mental illness early in a course of ECT, a suggestion supported by a small preliminary study by Browning & Cowen (1986), which suggests that some specific symptoms of depressive illness may show a distinct pattern of improvement during a course of ECT. Unfortunately, such study will require large numbers of patients and the development of new rating scales sufficiently sensitive to small changes in individual symptoms. Whether truly

blind rating by observers (that is, without any knowledge of exposure to real or sham ECT) is feasible is open to question, but raters would be blinded to the different frequencies of real ECT.

Several factors relating to the patient, the illness, and the details of ECT treatment are likely to affect the relationship of antidepressant efficacy to the number and frequency of treatments. Three are of such importance that they should be considered in the design of the study. Firstly, the rate of response is likely to be different in unilateral and bilateral ECT (Abrams, 1986). However, since bilateral ECT is the laterality recommended by the Royal College of Psychiatrists, it might be preferred to make bilateral ECT the standard. (It is not yet known whether bilateral ECT is similar to unilateral ECT in that stimulus intensity affects the rate of clinical improvement; nevertheless, stimulus intensity would have to be standardised.) Secondly, depressed patients who are psychotic may respond particularly well to ECT (Pande et al, 1990), and allocation of patients should ensure that deluded patients are equally distributed in samples. Thirdly, patients who have failed to respond to a therapeutic dose of an antidepressant drug may not respond so well to ECT (Prudic et al, 1990), and again allocation of patients should take account of treatment resistance.

Such stratifications have considerable implications for the minimum sample size in any proposed study. This point requires further emphasis because of the need to study the pattern of recovery among those patients who clearly recover with ECT, and implies that meaningful results would depend on the recruitment of a large sample of depressed patients.

Conclusions

The selection of depressed patients to receive ECT and the recommended practice of the administration of ECT have changed considerably over the past 20 years. Most recent changes were made with a view to minimising the adverse cognitive effects of ECT. One crucial area of practice that has not been subject to appropriate research concerns the relationship between the antidepressant effect of ECT and the number and frequency of treatments.

Virtually all depressed patients who recover with ECT require at least several treatments to bring about complete remission, but this does not necessarily mean that treatments early in a course of ECT are without antidepressant effect. Some textbooks state that there is such a delay in the onset of antidepressant effect, and this has probably influenced clinical practice, although the few small studies specifically designed to answer this question do not

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support this opinion. Of course, this opinion may be apparently self-fulfilling if psychiatrists delay clinical review until several treatments have been administered, or if several treatments are routinely prescribed at the onset of a course of treatment. (Neither practice is anywhere recommended.)

Contemporary recommendations and practice concerning the optimum frequency of treatment vary to a degree that is undesirable in a treatment where each application leads to a period of confusion and anterograde amnesia. It is not known how best to maximise the rate of antidepressant effect; some authors recommend increasing the frequency of treatment, and others the induction of more than one seizure during a treatment session.

There is a pressing need to establish to what extent the rate of clinical improvement is influenced by the prescribing habits of the treating psychiatrist. Twice-weekly ECT is the usual practice in the UK and three times weekly is the usual practice in the USA. This difference reflects personal preference rather than any theoretical standpoint, although the clinical implications are now under study. Confirmation (or refutation) that increasing the frequency of treatment enhances the rate of antidepressant effect of ECT would be of considerable clinical importance and would help direct research.

Little research into ECT is being conducted in the UK. Whether this low level of research activity is a matter of priority or fashion is open to debate, but these topics are worthy of research. A better understanding of the relationship between clinical improvement and the frequency of treatment would maximise the therapeutic benefit and minimise the cost in terms of adverse cognitive effects. The clinical response to the first one or two treatments may be helpful in predicting which patients will go on to a full recovery. (Refutation of this suggestion will be just as important in clinical practice.) The character-isation of depressed patients who make a rapid improvement with ECT may lead to an improved subclassification of depressive illness, and the identification of which, if any, symptoms or signs of depressive illness characteristically improve early in a course of ECT may provide insights into the temporal sequence of the biological effects of ECT. Questions like these will not be answered properly unless ECT researchers apply and develop methods of clinical rating designed for frequent use and sensitive to small changes in symptoms of depression.

Electroconvulsive therapy is unique among physical treatments for depressive illness, in that the onset of its effects on cerebral function can be defined precisely in time by electroencephalogram, offering many opportunities for the biological study of its antidepressant effects. Biological studies in both man and animal must be designed to take account of the onset and rate of the antidepressant effect of ECT in depressed patients. The opinion that the first one or two treatments are without any detectable anti-depressant effect has directed biological studies away from the acute effects of cerebral seizure activity, yet is without confirmation in an appropriately designed study of a representative sample of depressed patients who recovered with ECT.

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