

# Electroconvulsive therapy for severe depression: evaluation



Can electroconvulsive therapy make a meaningful contribution in the treatment of Severe depressive illness? The work of mental health nurses.

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## **References**

Abstract

This dissertation seeks to explore the evidence base for electroconvulsive therapy. It does so by considering the historical background to the procedure

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and its evolution to the present. It considers the professional and legislative guidelines which govern its use and contrasts the regulations in the UK with those in other cultures, notably the USA.

In order to assist the exploration, the literature review is subdivided into five sections, each exploring a different area of interest. Electroconvulsive therapy is placed within a therapeutic spectrum of treatment for patients with major depressive illness and psychosis and is compared with other modalities of treatment. Its use in both acute treatment and its role in disease prevention and relapse is discussed.

Current hypotheses of its possible mode of action are explored, and conclusions drawn about the strength of the evidence base in this area.

There appears to be considerable discussion about the site of optimal stimulation for electroconvulsive therapy. This area is discussed in depth with a critical analysis of the studies which inform the evidence base in this area.

The literature review concludes with an examination of the various side effects of the treatment. There is an element of discussion of the evidence and conclusions are drawn from the evidence extrapolated and presented.

The whole dissertation is fully referenced.

## Introduction

Electroconvulsive therapy was introduced into clinical practice in the late 1930s

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and rapidly gained a place in the standard treatment of major depressive illness.

It was originated by the Hungarian, Dr Meduna, who mistakenly believed that schizophrenia and epilepsy were mutually exclusive conditions. He argued that epilepsy was never seen in schizophrenic patients and therefore artificially inducing fits (epilepsy) in patients would cure schizophrenia. (Mowbray R M 1959). The effects on schizophrenia were soon recognised to be minor and the most marked effect appeared to be in the patients with major depressive illness.

The advent of effective classes of antidepressant, antipsychotic and mood stabilising drugs has seen a marked decline in the use of electroconvulsive therapy, but recent figures suggest that it is still used in over 10, 000 cases per year in the UK (ECT Survey 2003).

Currently the main use of electroconvulsive therapy is in major depressive illness although it also is considered still to have a place in the treatment of schizophrenia and some other mood disorders (UK ECT 2003), psychosis (Corruble E et al. 2004), and overt suicidal intent (Kellner C H et al. 2005).

The Mental Health Act of 1983 allowed Psychiatrists to give electroconvulsive therapy to inpatients without consent if they were sectioned. This should be contrasted to the situation after the 1959 Mental Health Act, where psychiatrists had no clear guidance and a number of litigation cases forced a change in legislation. (Duffett R et al. 1998)

The procedure itself involves anaesthetising the patient with a general anaesthetic and a muscle relaxant and then a small, brief pulse current (typically about 800 milliamperes) is passed between two electrodes applied directly to the scalp. This generates a seizure and there are a number of demonstrable biochemical changes in the brain after the event. (Nobler M S et al. 2001)

Electroconvulsive therapy is usually given as a course over several weeks. The evidence base for length of time of treatment is not strong and appears to vary considerably between authorities. (Lisanby S H 2007)

In 2003 NICE investigated the evidence base for electroconvulsive therapy and issued guidelines which suggested that it should only be used “ only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening in individuals with severe depressive illness, catatonia or a prolonged manic episode”. (NICE 2003)

One of the most extensive recent reviews on electroconvulsive therapy concluded that it had been demonstrated to be effective short term treatment for depressive illness in otherwise healthy adults. Many studies were cited and had shown it to have a greater effect than drug treatment. The authors noted shortcomings in many of the trials cited, especially in areas such as drug resistant depressive illness where electroconvulsive therapy is believed to be particularly helpful. (UK ECT Review Group 2003)

One of the major side effects of electroconvulsive therapy is short and long term memory loss cited in many trials and studies (viz Gupta N 2001)

### Methodology of the review

Cormack suggests that “ Ultimately all good research is guided by and founded on a critical review of all of the relevant literature published on the subject.” (Cormack, D. 2000). It is therefore important not only to define what is currently believed about a subject, but also to place this in a historical context. This is particularly important in the field of electroconvulsive therapy, as the introduction to this dissertation has suggested, with great fluctuations in both understanding and application of this type of therapy over the years.

One of the prime reasons for conducting a literature review is to establish the current evidence base for a particular subject. A critical review of the literature must be preceded by a careful literature search. It is often believed that searching the literature is a linear or “ single episode” process. Current thinking suggests that this is seldom an optimal strategy. Bowling advises that a good literature review is “ primarily a cyclical recursive process that mirrors the thinking and research process, where the discovery of new information results in new ideas, new knowledge and possibly new understanding. Once an overview, or initial opinion has been formed, it then becomes possible to revisit the initial reviews from a more informed perspective which, in turn, allows for a more perceptive interpretation of the data. (Bowling A 2002).

The methodology used in this particular review was to allow for an initial period of reflection on the subject matter and to consult a small number of reference books to achieve an overview of the area. (Taylor, E. 2000).

References were noted and some followed up in order to ascertain the main themes of the review. Once these were established, then methodical searches of a number of databases were carried out utilising the facilities of the local University library, the Post-graduate library (Client to personalise here) and a number of on-line search engines and literary sources including Cochrane, Cinhal, Ovid, BMJ and Lancet archives, Royal College of Psychiatrists archive and various NICE publications. Papers were accessed in both hard back and electronic forms. (Fink A 1998)

Search terms included electroconvulsive therapy; evidence base; evolution; history; schizophrenia; psychosis; major depressive illness; mental health nurse; antidepressant drugs; Mental Health Act; psychiatrist. These terms were used in various combinations to sift papers with varying degrees of relevance to the topic under consideration. (Carr LT 1994)

Inclusion criteria were papers less than 10 years old (unless there were specific reasons for older paper inclusion). UK sources were preferred to other ones. It should be noted that a substantial proportion of the body of literature on the subject of electroconvulsive therapy is American based. A number of authorities have suggested that this may be because the USA currently uses electroconvulsive therapy more frequently than the UK and therefore has a greater experience with it. Papers were only considered from peer reviewed sources unless making a historical point. (Bell J 1999). Each paper considered was then ranked according to its evidential value (See <https://assignbuster.com/electroconvulsive-therapy-for-severe-depression-evaluation/>)

Appendix 1) and the highest value paper was presented for each point to be made.

### Critical Review of the literature

#### The place of electroconvulsive therapy in the therapeutic armamentarium

A good place to start this literature review is with the Olfson paper. (Olfson M et al. 1998). This is an authoritative overview of the place of electroconvulsive therapy in the treatment spectrum. It has to be noted that this paper is already 10 years old and reflects clinical patterns of usage in the USA. The reason that this paper is selected for discussion is primarily on the vast size of its study cohort, which is 6.5 million patient contacts (249,600 with a diagnosis of depressive illness) spread over mainland USA.

Critical analysis of the paper suggests that the authors reveal their viewpoint in the first few sentences of the paper and therefore the opinion part of the review must be understood on the basis that the authors consider electroconvulsive therapy a “ safe and effective treatment for patients with all subtypes of major depression” citing the authority of the APA for this statement (APA 1997)

The paper suggests that there is a strong evidence base to confirm that electroconvulsive therapy is at least as effective as antidepressant drugs pharmaceuticals for the treatment of major depressive illness. (Weiner R D 2004)

The authors make the point that despite this general belief,

electroconvulsive therapy is not as widely used as it should be due to three  
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major misconceptions namely public concern about the safety of the procedure, reactive regulations and guidelines and the belief that it is not cost-effective. They then set about addressing each of these concerns

Rather worryingly, the authors cite evidence of safety with the unqualified comment that “ None of the depressed patients who received ECT died during the hospitalisation. In contrast, 30 (0. 14%) of the depressed patients who did not receive ECT died in the hospital. (Schulz K F et al. 1995)

Although this may well be the case, it is entirely possible that patients who were ill with other comorbidities (and therefore at greater risk of death) were not offered electroconvulsive therapy, as it required a general anaesthetic. One cannot jump to the implied conclusion that these figures suggest that electroconvulsive therapy is therefore intrinsically safe. (Mohammed, D et al. 2003)

The authors draw a number of conclusions, perhaps the most significant of which is that current practice tends to reserve electroconvulsive therapy for the elderly, and those with comorbidities such as schizophrenia, dementia, and general medical (nonpsychiatric) disorders. They also comment that prompt use of electroconvulsive therapy is associated with shorter in patient stays and, by definition, more rapid resolution of the depressive state.

Despite these findings, there is a large body of literature documenting the fact that many patients with major depressive illness remain largely unresponsive to therapeutic intervention. With this in mind one should consider the contribution of the Spanish research group under Gonzalez-

Pinto who published a trial of a small group of patients (13) who had proved  
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resistant to both venlafaxine and electroconvulsive therapy separately but who responded to both measures when used in a combined fashion.

(Gonzalez-Pinto A et al. 2002). This was a non-randomised non-controlled trial and therefore constitutes evidence value at level III. Curiously the response was not proportional to the dose of venlafaxine used. The authors however, report the rather worrying side effect of asystole in 3 of the 13 patients immediately after the electroconvulsive therapy.

A number of authorities suggest that there is a definite place for electroconvulsive therapy in the severely depressed patient who is a suicidal risk. The Kellner paper addresses this suggestion directly. (Kellner C H et al. 2005). Suicide remains one of the major associations of major depressive illness and carries a 15% lifetime risk for any patient who has been hospitalised with the same. (Bostwick J M et al. 2000) with symptoms such as profound hopelessness, hypochondriacal ruminations or delusions, and thoughts of suicide or self-harm during depression predict future suicide. (Schneider B et al. 2001).

The Kellner study was a randomised crossover comparative follow-up trial making it evidence value of level 1b. There are a great many result strands from this study, but if one specifically considers the suicidal elements, then one can state that the study showed that of the 444 patients enrolled in the trial as having major depressive illness, 26% had suicidal ideation at a level of 3 or greater on the Hamilton rating scale (the measurement tool used in the trial) and 3% achieving a score of 4 (actual suicidal attempt). This group had a reduction of their scores to 0 in over 80% within the two week course of the electroconvulsive therapy. It was also reported that in the group who <https://assignbuster.com/electroconvulsive-therapy-for-severe-depression-evaluation/>

scored 4, 100% dropped to 0 by the end of the treatment. Despite these impressive figures for short term remission, one would have to note that the trial did not have any significant long term follow-up and there is no information on the rate of relapse after the initial treatment. (Rosenthal R. 1994). The authors state that they were aware of two successful suicide attempts which occurred whilst the trial was running (but after these patients had completed their treatment). The authors suggest that electroconvulsive therapy should be used early in the treatment regime once a diagnosis of suicidal risk has been made.

To provide a balanced argument on the place of electroconvulsive therapy in the spectrum of treatment, one can consider the recent paper by Eranti (Eranti S et al. 2007) who tested out the hypothesis that has recently been published, that Repetitive transcranial magnetic stimulation (rTMS) is as effective as electroconvulsive therapy but does not have the same side effect profile that restricts the use of electroconvulsive therapy in some patients. (viz. Gershon A A et al. 2003 and Loo C K et al. 2005)

This trial was a randomised, blinded comparative trial with a substantial entry cohort (260 patients) being followed up for 6 months after treatment giving it a level 1b significance. (Clifford C 1997). There were a number of possible outcome measures studied but, of relevance to our considerations in this dissertation, one can state that the authors found that Repetitive transcranial magnetic stimulation (rTMS) was not as effective as electroconvulsive therapy in the treatment of depressive illness both at the end of the treatment period and at the end of the 6 month study. The

authors were able to comment however, that the rTMS was virtually free of demonstrable side effects.

The place of electroconvulsive therapy in relapse prevention

It is fair to comment that a brief examination of the literature shows virtually no good quality published material on this topic with the studies that have been done comprising individual case reports (viz Kramer B A 1990), naturalistic studies and small studies of retrospective cases (viz. Schwarz T et al. 1995), none of which have any control element and all of which are evidence level IV at best.

A notable exception is Keller et al. who made a large UK based study of relapse prevention in major depressive illness with a randomised controlled trial over a seven year period involving over 500 patients. (Kellner C H et al. 2006). The trial is a level 1b evidence level trial and is of a particularly robust structure with great efforts made to achieve standardisation. (Denscombe, M 2002). The structure is a direct comparison between electroconvulsive therapy and a standard pharmacological regime (lithium carbonate plus nortriptyline hydrochloride). Both were given as a therapeutic course (the medication over a six month period) and the patients were followed up with DSM-IV assessments to determine their degree of relapse

The analysis is long and complex but, in essence, the study clearly demonstrated that both groups had better results than a placebo control with similar percentages (about 33%) suffering a relapse and about 46% remaining disease free. The trial suffered from having a large group (about 20%) failing to complete the trial protocol. (Rosenthal R. 1994). This study <https://assignbuster.com/electroconvulsive-therapy-for-severe-depression-evaluation/>

does however, provide firm evidence that electroconvulsive therapy is at least as effective as pharmacological measures in reducing the likelihood of clinical relapse.

Further evidence for longer term efficacy comes from the Gagné study (Gagné G G et al. 2000), which starts by acknowledging the fact that depressive illness tends to be a long term disability with long term pharmacological intervention a comparatively normal treatment strategy. The authors make a subtle distinction between continuance therapy (which is starting a new course of treatment after initial resolution and then relapse) and maintenance therapy which extends beyond the continuation therapy stage and is aimed at preventing relapse.

This paper is noteworthy because, as the authors point out, there is general acceptance by healthcare professionals that long term maintenance therapy with pharmaceuticals is both rational and indicated in patients with a high likelihood of relapse of depressive illness. Treatment with continuation electroconvulsive therapy has failed to gain general acceptance. The authors argue that such an approach is particularly rational, at least in a group of patients who have demonstrated their ability to respond to electroconvulsive therapy in the past, are at high risk of relapse and who may be refractory to pharmacological intervention.

The Gagné study is a retrospective case-controlled comparative study comparing the long term course of electroconvulsive therapy plus pharmacological maintenance therapy with long-term antidepressant treatment alone in a demographically matched group. The two groups

comprised 60 patients. The maintenance electroconvulsive therapy group received the electroconvulsive therapy as a single treatment monthly after the normal intensive treatment course for the acute episode. It has to be noted that this regime is comparatively arbitrary as there appears to be no preceding published evidence base to support it.

The results from this study are nonetheless quite impressive. Both groups are reported to have responded to treatment, but the group who were also maintained with follow up electroconvulsive therapy did markedly better in terms of resistance to relapse being almost doubled at two years (93% vs. 52%), and quadrupled at five years (73% vs. 18%). This result could also be expressed as a doubling of the mean time to relapse in the electroconvulsive therapy group (6.9 years versus 2.7 years for the antidepressant-alone group).

A major criticism of this study would have to be a lack of standardisation of treatment in the electroconvulsive therapy group with some patients receiving univocal and others bipolar electroconvulsive therapy. The number and duration of each was left "to the clinical judgement" of the responsible clinician. This does not reduce the impact of the overall finding, but does make for difficulties in comparison with any other trials which might follow. (Berlin J A et al. 1999)

A critical analysis of the study would also have to conclude that the study suffered from a comparatively small number of patients with assignments to the comparison groups not being random. More importantly, the trial assessor was not blinded to the patients group assignment. These factors

make it difficult to confidently assign an evidence level to this trial. (Denzin, N K et al. 2000)

The authors conclude their study with the comment that a larger, prospective study on the subject is currently underway. One should perhaps regard the results of this study as interesting, but not proven.

In assessing the validity of this paper, one should note comments that it has generated in the peer reviewed press. Gupta makes a number of valid points of criticism (Gupta N. 2001), arguably the most important of which is that the study did not make any measurement of the well recognised effect on memory function that short term electroconvulsive therapy is known to have. (Isenberg K E et al. 2001). Gupta suggests that clinical effectiveness must be assessed only after a risk-benefit ratio has been properly determined. Certainly a valid point and one that was not addressed in the original paper.

#### Mechanism of action

A number of papers have been published reporting biochemical changes after electroconvulsive therapy. There seems to be a general agreement that depressive illness is associated with a disturbance in the monoaminergic-cholinergic balance within the cerebral cortex. (Schatzberg A F et al. 2005).

A novel and significant advance was published in 1998 by Avissar (Avissar S et al. 1998) when a correlation with G-protein levels in leucocytes was found and was discovered to be significantly reduced in depressive illness. The significance of this paper was that the authors found that electroconvulsive therapy resulted in a normalisation of the G-proteins level which preceded

(by about a week), and thus predicted, clinical improvement. Patients who did not respond to electroconvulsive therapy did not show a change in G-protein levels. The significance of this finding is enhanced with the knowledge that lithium is also known to alter G-protein levels (Schreiber G et al. 2000), as are some other treatments for bipolar disorder. (Young L T et al. 2003). It is also known the G-protein levels are raised in manic states thereby suggesting that it is a marker for affective mood states. (Schreiber G et al. 2001)

Further evidence of altered metabolism comes from the Nobler study (Nobler M S et al. 2001). This study used Positron emission tomography (PET) to study glucose metabolism in different brain areas. It has to be noted that this was a small study of 10 patients who were assessed before and after a course of electroconvulsive therapy. This study involved highly sophisticated measurements and concluded that certain areas of the brain showed marked reduction in metabolic rate after electroconvulsive therapy and these changes were most significant in the frontal, prefrontal, and parietal cortices. The authors suggest that their results support the hypothesis that electroconvulsive therapy works by suppression of functional (non trophic) brain activity, most prominently in the prefrontal cortex. The authors comment that their findings are consistent with the earlier Drevets study which demonstrated a reduction in brain metabolism after successful treatment with antidepressant drugs. (Drevets W C 1998)

A more modern paper by Sanacora reported alterations in the GABA concentrations in plasma, and cortex after electroconvulsive therapy.

(Sanacora G et al. 2003). It is known that patients with depressive illness <https://assignbuster.com/electroconvulsive-therapy-for-severe-depression-evaluation/>



have reduced levels of the neurotransmitter GABA. This study, again with a small entry cohort of 10 patients, assessed patients before and after electroconvulsive therapy. It was found that the levels of GABA increased with successive treatments. It was also found that the length of duration of the convulsions was proportional to the concentrations of GABA found in the cortex supporting the view that GABA decreases cortical excitability. It may also be significant that GABA concentrations have been found to increase after the use of selective serotonin reuptake inhibitor (SSRI) treatment. (Sanacora G et al. 2002). These findings suggest that enhanced GABA activity may be central to any antidepressant activity

Takano et al. have recently produced a yet more sophisticated study along the lines of the Nobler investigation. (Takano H et al. 2007). This study also uses positron emission tomography (PET) and it studied patients before, during and after the application of electroconvulsive therapy. This is essentially a technical rather than a clinical study. It also has to be noted that all the data was derived from only six patients. The majority of the results are therefore not relevant to this consideration other than the fact that the authors concluded that electroconvulsive therapy exerts its effect by increasing the post treatment blood supply to the anterior cingulate and medial frontal cortex and thalamus. They refine this comment by acknowledging that it cannot be stated that this observed phenomenon is cause or effect, but simply an association with the mechanism of treatment and is associated with a resolution of symptoms.

Preference of site and nature of stimulation

There is a great deal of discussion in the peer reviewed literature about the optimal sites for electroconvulsive therapy application and whether univocal or bipolar stimulation gives better results. Unfortunately the vast majority of it is anecdotal and of poor evidential value. The Bailine study is a notable exception providing a randomised comparative trial with a moderate size of entry cohort (60) making it a level 1b trial. (Bailine S H et al. 2000).

The authors compared the efficacy of bitemporal stimulation with bifrontal stimulation over a treatment period of 12 treatments. The study was assessor blinded. The rationale behind the trial was that bifrontal stimulation avoids direct stimulation of the temporal areas which are directly involved with cognition and memory functions.

The authors reported that they found both placements to be equally effective in their ability to relieve depressive illness, but the bifrontal positioning achieved statistical significance in reducing cognitive and memory effects. Although not directly tested, the authors comment that right sided unilateral frontal placement has fewer cognitive side effects than bilateral stimulation but needs 2 - 5 times the current to achieve its therapeutic effect. (citing Letemendia F J J et al. 1993)

One area of difficulty which, even a brief overview of the subject illuminates, is the level of stimulus that is required to achieve therapeutic results. Some studies do not specify the level of stimulus, others simply refer to a supra-threshold stimulus, a third group refer to a " titration of stimulus". This makes direct comparison of results difficult. Some authorities have made the comment that not standardising the level of stimulus applied is similar to

conducting a comparative trial of antidepressant drugs to placebo when the drugs are given at a sub-optimal dosage and therefore not achieving their maximal therapeutic effect.

Krystal has attempted to tackle this problem by reviewing the regulations governing the administration of electroconvulsive therapy and also trying to achieve a generally acceptable standard of treatment. (Krystal A D et al. 2000)

The USA limits (by statute) the maximum output charge for clinical applications of electroconvulsive therapy to 576 millicoulombs. The equivalent restriction in the UK is 1, 200 millicoulombs for electroconvulsive therapy devices and this has been determined by the Royal College of Psychiatrists, and this limit is more than double the limit allowed in the USA. As far as the USA is concerned there is no evidence base to ensure that this limit will allow for consistently effective electroconvulsive therapy, which is something of a paradox considering that the USA considers electroconvulsive therapy more mainstream than does the UK.

Krystal published a retrospective study of nearly 500 patients who had received electroconvulsive therapy. Although most of the patients reviewed had a clinically successful treatment, the authors noted that 15% of patients required the maximum stimulus intensity to trigger a seizure and 5% of the total did not have a seizure at all.

The authors comment that the clinicians responsible for the patient had to use enhancing strategies to boost the therapeutic response with caffeine,

ketamine, or hyperventilation. This still left a residual 5% of patients with a sub-therapeutic response at the maximum permitted output charge.

Further problems can be encountered as not only can patients vary with regard to the amount of charge that they need to trigger tonic-clonic seizures, but the amount of charge can vary as the course of treatment progresses in each individual patient. (Coffey C E et al. 2005)

The difficulty that therefore arises in these non-responders, is that there is no greater therapeutic response than placebo if a tonic-clonic seizure is not triggered, but the effects on cognition and memory impairment are still present. (PECT 2000). If this is added to the clinical and economic costs, it is clear that a case can be made for higher limits of initial triggering charge, at least in the USA.

The other factor which may also be relevant and can be a major cause of inconsistency between studies is the pulse width with some electroconvulsive therapy machines delivering a shorter pulse width and longer stimulus duration than others. The majority deliver a pulse width between 0.5-0.75 msec. but other machines are capable of delivering pulse widths considerably beyond these limits. There has been no definitive study which has considered the possible effect of pulse width on either the therapeutic response or the likelihood of triggering a tonic-clonic seizure.

The final point made in the Krystal paper is the fact that one of the reasons that the charge limit was set at the level that it is was the fact that the authorities wanted to minimise the theoretical risk of neuropathological damage. There is now evidence that the levels of stimulus charge necessary  
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to cause such damage is far in excess of the imposed limits. (viz. Weiner R D 1994 and Devanand D P et al. 2004)

The concept of stimulus titration is referred to in many of the clinically based papers reviewed. If this concept is considered in parallel with the comments by Krystal relating to the variation of charge required to produce the seizure, the situation can be clarified in an monograph by MacEwan who advises that it is an important feature of the treatment to allow sufficient time between the initial unsuccessful shock and the attempt at restimulation as the effect of the comparative refractivity after the first shock takes a little time to wear off. (MacEwan T 2002)

#### Side effects of treatment

Considering the rather gross and intrusive physical nature of the treatment, it is quite remarkable that the literature shows very few studies which have specifically explor