Electroconvulsive therapy (ECT) for depressive illness, schizophrenia, catatonia and mania

Authors: **Ms Joanne Greenhalgh, Research Officer, Nuffield Institute for Health**

Mr Chris Knight, Senior Operational Research Analyst, ScHARR

Dr D Hind, Research Associate, ScHARR

Ms C Beverley, Systematic Reviews Information Officer, ScHARR

Mr. Stephen Walters, Medical Statistician, ScHARR

Correspondence to: **Ms Joanne Greenhalgh, Nuffield Institute for Health, University of Leeds, 71-75 Clarendon Road, Leeds, LS2 9PL**

Date completed:

Expiry Date: Expiry date

CONTENTS

LIST OF ABREVIATIONS

APA	American Psychiatric Association
BBB	Blood Brain Barrier
BDI	Beck Depression Inventory
BGT	Bender Gestalt Test
BPRS	Brief Psychiatric Rating Scale
C. TCA	Continuation Therapy with TCAs
C.ATP	Continuation Therapy with antipsychotic drugs
C.MAOI	Continuation Therapy with MAOIs
C.placebo	Continuation therapy with placebo
C.SSRI	Continuation Therapy with SSRIS
CASP	
CEAC	Cost Efectiveness Acceptabilty Curve
CECT	Continuation ECT
CGI	Clinical Global Inpression
CIRS	Cumulative Illness Rating Scale
CODS	Cronholme and Ottoson Rating Scale
CONSORT recommendations	
CT	Computerised tomography
CTCA+LI	Continuation therapy with Lithium and TCAs
DSM	Diagnostic and Statistical Manual
EEG	
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
GDR	Global Depression Rating Scale
GDS	Geriatric Depression Scale
GRSD	Global Rating Scale for Depresision
HAD	Hospital Anxiety and Depression Scale
HADS	Hamilton Depression rating
HAM-D	Hamilton Rating Scale for Depression (same as HRSD)
HRSD	
ICER	Incremental Cost Effective Ratio
Li	Lithium
Loss TF	Loss to follow up
MADRS	Montgomery and Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MMPI	Minnesota Multiphasic Personality Inventory
MMSE	Mini Mntal State Examination
NHS EED	
NICE	National Institute for Clinical Excellence
NMS	Neuroleptic Malignant Syndrome
NNH	Number needed to harm
NNT	Number needed to treat
NRS	Nurses Rating Scale
OHE HEED	
PIRS	Psychological Impairments Scale
PSE	Present State Examination
PSQI	Pittsburg Sleep Quality Index
RCP	Royal College of Psychiatrist
RTMS	repetitive Transmagnetic Stimulation
SCI	Science Citation Index

SMD	Standardised Mean Difference
SNRI	Serotonin and Norepinephrine Reiptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
SURE	Service User Research Enterprise
TCA	Tricyclic Antidepressants
TRS	Treatment Resistant Schizophrenia
VAS	Visual Analogue Scale
VPI	Value of Perfect Information
WAIS	Weschler Adult Intelligence Scale
WBIS	**WESCHLER-BELLEVUE INTELLIGENCE SCALE**

SUMMARY

DESCRIPTION OF PROPOSED SERVICE

Electroconvulsive therapy (ECT) has been available for use since the 1930's. It involves passing an electric current through a person's brain while they have been given a general anaesthetic and muscle relaxants in order to produce a convulsion. There is a complex interplay between the stimulus parameters of ECT, including position of electrodes, dosage and waveform of electricity, and its efficacy.

EPIDEMIOLOGY AND BACKGROUND

ECT is rarely used as a first line therapy, except in an emergency where the person's life is at risk as a result of refusal to eat or drink or in cases of attempted suicide. Current guidelines indicate that ECT has a role in the treatment of people with depression and in certain subgroups of people with schizophrenia, catatonia and mania. In England between January and March 1999 there were 16, 482 administrations of ECT to 2, 835 patients(2). Eighty five percent of all administrations were within an inpatient setting. There were important variations in the rates of administration of ECT by gender, age and health region. Women received ECT more frequently than men and the rates of administration for both genders increased with age. Rates of administration of ECT are highest in the North West of England and lowest in London.

METHODS

17 electronic bibliographic databases were searched, covering biomedical, health-related, science, social science, and grey literature. In addition, the reference lists of relevant articles were checked and 40 health services research related resources were consulted via the Internet. These included HTA organisations, guideline producing bodies, generic research and trials registers and specialist psychiatric sites. All abstracts were reviewed to ascertain whether they met the inclusion criteria for the review. The study quality of relevant articles was assessed using standard checklists and data was abstracted by two people using standardised forms in Access. Where relevant, results from studies were pooled for meta-analysis using Rev Man.

NUMBER AND QUALITY OF STUDIES

We identified two good quality systematic reviews of randomised evidence of the efficacy and safety of ECT in people with depression, schizophrenia, catatonia and mania. We also identified 4 systematic reviews on non randomised evidence, though only one of these could be described as good quality. There was no randomised evidence of the effectiveness of ECT in specific subgroups including older people, children and adolescents, people with catatonia and women with postpartum exacerbations of depression or schizophrenia.

SUMMARY OF BENEFITS/DIRECTION OF EVIDENCE

In people with depression, real ECT is probably more effective than sham ECT but stimulus parameters have an important influence on efficacy; low dose unilateral ECT is no more effective than sham ECT. ECT is probably more effective than pharmacotherapy in the short term but the evidence on which this assertion is based was of variable quality and inadequate doses of

pharmacotherapy were used. Limited evidence suggests that ECT is more effective than rTMS . Limited data suggests that continuation pharmacotherapy with TCAs in people who have responded to ECT reduces the rate of relapses. ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED. There was much less evidence regarding the efficacy of ECT in schizophrenia and no randomised evidence of the effectiveness of ECT in catatonia. ECT either combined with antipsychotic medication or as a monotherapy is not more effective than antipsychotic medication in people with schizophrenia. The evidence did not allow any firm conclusions to be drawn regarding the efficacy of ECT in people with catatonia, older people or younger people with psychiatric illness or women with psychiatric illness during pregnancy or postpartum. ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.

COST EFFECTIVENESS

No previous analysis has been undertaken on the cost-effectiveness of ECT treatment in depression or schizophrenia. Two economic models were developed primarily based on evidence from the clinical effectiveness analysis and limited quality of life studies.

DEPRESSION

The economic model for depression was based on a severely depressed population requiring hospitalisation. As clinical opinion differs to whether ECT should be used only as a last resort treatment or whether it could be used earlier in the treatment hierarchy the model was constructed to allow the evaluation of the cost-effectiveness of ECT being provided as a 1st, 2nd, or 3rd line therapy.

Different scenarios where developed that incorporated ECT as a treatment and compared to a pharmacological only treatment. The economic modelling results did not demonstrate that any of the scenarios had a clear economic benefit over the others. The main reason for this was the uncertainty surrounding the clinical effectiveness of the different treatments and the quality of life utility gains. Sensitivity analysis surrounding the cost of ECT and the quality of life utility values had little effect on the overall results.

Further economic analysis, such as Expected Value of Perfect Information (EVPI), may be able to identify areas in which research would be best targeted by identifying parameters where reducing the level of uncertainty would have the most effect in helping make the decision on whether ECT is a cost-effective treatment in the hospitalised severely depressed population.

SCHIZOPHRENIA

The main schizophrenic population for which ECT is indicated in the APA and RCP guidelines is patients resistant to pharmacotherapy(3;4).Therefore, economic model constructed for schizophrenia was based on a pharmacological model constructed by Oh (5) which was the only cost-utility study identified in the treatment of schizophrenia. This model analysed the cost-effectiveness of clozapine compared to haloperidol/chlorpromazine treatment in treatment resistant schizophrenia. The model was adapted to incorporate an ECT arm to the decision tree analysis. The results of the adapted model including ECT suggest that clozapine is a cost-effective treatment compared to ECT. However, for patients who fail to respond to clozapine ECT treatment would be the preferred therapy to the comparative treatment of haloperidol/chlorpromazine. Although it should be stated that the clinical evidence underpinning the ECT assumptions in the model is weak.

1   AIM OF THE REVIEW

The aim of this review is to establish the clinical and cost effectiveness of ECT for depressive illness, schizophrenia, catatonia and mania.

ECT has been available for use since the 1930s. The therapy involves the passage of an electric current through a person's brain while they are under a general anaesthetic and have been given a muscle relaxant. This normally produces a convulsion. A course of ECT usually consists of six to twelve treatments given twice a week. ECT is indicated for severely depressed patients, but is also has a role in the management of those with schizophrenia, mania and catatonia, often when drug therapy has proved ineffective or is not suitable.

There is considerable variation in the use of ECT within the UK and current opinion is divided between those who consider ECT to be the most effective treatment within psychiatry and completely safe (6) and those who consider that ECT is probably ineffective and almost certainly causes brain damage (7).

The specific questions addressed by this review are:

- The effectiveness of ECT for people with depression, schizophrenia, mania and catatonia

- The effectiveness of ECT in specific subgroups of people including older people, pregnant women and children and adolescents

- The impact of ECT stimulus parameters (including dosage, frequency of electricity, number of treatments and electrode placement) and technique of administration on the effectiveness of ECT

- The duration of the effects of ECT

- The use of ECT as a maintenance therapy, emergency therapy and the role of concomitant therapy in the overall effectiveness of ECT

- The setting in which ECT is administered and its impact on the clinical and cost effectiveness of ECT

- The costs of additional infrastructure and training required for the optimal delivery of ECT

- Patient acceptability and choice in ECT treatment and how these may affect outcomes

2   BACKGROUND

2.1   DESCRIPTION OF THE UNDERLYING HEALTH PROBLEM

2.1.1   SCHIZOPHRENIA

Schizophrenia is a major psychotic disorder.   It is characterised by a constellation of symptoms and signs that have been present for a significant length of time during the last month with some signs of the disorder persisting for at least 6 months (3). The symptoms and signs of schizophrenia have been conceptualised as falling into three categories – positive, negative and disorganised. Positive symptoms include hallucinations and delusions, negative symptoms include loss of initiative, interest in others or sense of enjoyment and blunted emotions and limited speech. Disorganised symptoms include disorganised speech and behaviour and poor attention. DSM-IV (8) describes 4 major subtypes of schizophrenia that are defined by the predominant symptoms at the most recent evaluation.   These subtypes include paranoid type characterised by delusions or auditory hallucinations; disorganised type in which disorganised speech, behaviour and blunted affect predominate; catatonic type characterised by immobility, excitability and mutism and undifferentiated type which is a non-specific category in which none of the other subtype signs and symptoms   are   prominent.

2.1.2   DEPRESSION

The DSM-IV (8) criteria for a major depressive syndrome are that at least five key symptoms should be present during the same two week period and one should be depressed mood or loss of interest or pleasure. The key symptoms are:

- Depressed mood most of the day nearly every day
- Markedly diminished interest or pleasure in all or almost all activities most of the day, every day
- Significant weight loss or weight gain when not dieting
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation every day (observable by others)
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive inappropriate gilt nearly every day
- Diminished ability to think or concentrate or indecisiveness nearly every day
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation or suicide attempt or specific plan.

According to DSM-IV (8), mild depression is defined as five or six symptoms and only minor impairment in occupational functioning or usual social activities or relationships with others. Severe depression is classified as either with or without psychotic features; without psychotic features it is defined as several symptoms in excess of those required to make a diagnosis and marked impairment in functioning; with psychotic features also includes delusions or hallucination. Moderate depression is defined as symptoms or functional impairment between "mild" and "severe".

2.1.3 MANIA

Manic symptoms are considered to be part of bipolar disorder. The DSM-IV (8) minimum criteria for bipolar affective disorder is a single episode of mania or mixed disorder (both episodes of mania and major depression occur). The DSM-IV (8) criteria for mania are:

- Distinct period of elation, irritability or mood disturbances lasting at least one week (or for any period of hospitalisation)
- Three of the following:
    Inflated self esteem
    Decreased need for sleep
    Increased talkativeness or pressure of speech
    Flight of ideas or racing thoughts
    Distractibility
    Increase in goal directed activity (eg social, at work) or psychomotor agitation
    Indiscreet behaviour with poor judgement (sexual, financial)
- Symptoms that do not meet the criteria for a mixed episode (fulfils criteria for both mania and major depression)
- Marked impairment in occupational or social function
- Not due to drug abuse (or other medication) or a physical illness

According to DSM-IV (8), bipolar affective disorder may be mild, moderate or severe and severe forms may be with or without psychotic features. Bipolar disorder may also be associated with catatonic features or have a postpartum onset. DSM-IV (8) also describes the long term clinical course of bipolar disorder, which may be with or without full interepisode recovery, with a seasonal pattern or with rapid cycling (4 or more affective episodes per year).

2.1.4 CATATONIA

Catatonia is a condition that is associated with both schizophrenia and affective disorders. It is characterised by marked changes in muscle tone or activity, which may alternate, between extremes from a deficit of movement (catatonic stupor) or excessive movement (catatonic excitement). The ICD-10 (9) diagnostic criteria for catatonic schizophrenia state the one or more of the following symptoms must be present:

- Stupor (marked decrease in reactivity to the environment and in spontaneous movements and activity) or mutism
- Excitement (apparently purposeless motor activity, not influenced by external stimuli
- Posturing (voluntary assumption and maintenance of inappropriate or bizarre postures)
- Negativism (an apparently motiveless resistance to al instructions or attempts to be moved, or movement in the opposite direction)
- Rigidity (maintenance of a rigid posture against the efforts to be moved)
- Waxy flexibility (maintenance of limbs and body in externally imposed positions
- Other symptoms such as command automatism (automatic compliance with instructions) and preservation of words and phrases.

Although catatonia is most often thought to be associated with schizophrenia, recent studies have also found that it is associated with mania (10).

2.1.5 EPIDEMIOLOGY

In 2000, the prevalence of depressive episode in England, Wales and Scotland was 2.6 per 1000(11). Depression is more common in women than in men. The age standardised prevalence of

depression treated in general practice in England between 1994 and 1998 was 24.9 per 1000 in men and 61.4 per 1000 in women (12). The age-standardised prevalence of treated depression in Wales between 1994 and 1998 was 24.0 per 1000 in men and 57.4 per 1000 in women. These figures may under represent the true prevalence of depression since it is estimated that on a typical GP's list, over 100 patients suffer from depression but half go unrecognised (13).

The lifetime prevalence of schizophrenia is 1% and the incidence of first onset schizophrenia is approximately 1 per 10,000 population per year(14). The age standardised prevalence of schizophrenia treated in general practice in England between 1994-1998 was 2.0 per 1000 in men and 1.7 per 1000 in women(12). In Wales, the age-standardised prevalence of treated schizophrenia was 1.9 per 1000 in men and 1.3 per 1000 in women.

Standardised mortality rates in schizophrenia are 5 times higher than those for the rest of the population; 10-15% of people with the disorder eventually commit suicide(14).

2.2   CURRENT SERVIC PROVISION

2.2.1   *DESCRIPTION OF INTERVENTION*

ECT has been available for use since the 1930's. The practice of ECT has undergone a number of modifications since its introduction with the use of general anaesthesia and muscle relaxants. Current practice of ECT involves the passage of electricity through a person's brain while they have been given a general anaesthetic and a muscle relaxant. This normally produces a convulsion. It was initially believed that the production of a generalised seizure was both necessary and sufficient for the antidepressant effect of ECT as sub convulsive stimuli were without therapeutic benefit. Later, it was demonstrated that generalised seizures of adequate duration could be reliably produced that lack therapeutic effect in depression (15;16). Thus the role of seizures in the therapeutic efficacy of ECT is still open to debate and there is currently no universally accepted theory to explain the mechanism of action for ECT. Current opinion on ECT ranges between those who consider ECT to be the most effective treatment within psychiatry and completely safe (6) and those who consider that ECT is probably ineffective and almost certainly causes brain damage (7). ECT is a complex intervention and its efficacy and safety are affected by a number of parameters including the placement of electrodes, dosage and waveform of the electrical stimulus and the frequency with which ECT is administered.

2.2.2   *PATIENT POPULATIONS*

2.2.2.1   Overall indications for ECT
Current guidelines from the American Psychiatric Association (APA) (17) and the Royal College of Psychiatrists (RCP) (18) on the patient populations for whom ECT is indicated are summarised below. The APA (17) guidelines recommend that ECT should primarily be used where there is need for a rapid response because of the severity of a psychiatric condition, where the risks of other treatments outweigh the risks of ECT, where there is a history of poor medication response or a good response to ECT or where the patient requests it. Secondary indications are in cases of treatment resistance or adverse side effects.

A survey of psychiatrists in the North West of England indicated that 93% of respondents were in favour of the use of ECT for appropriate patient populations(19). The balance of opinion favoured the use of ECT at some point in only three conditions - depressive psychosis, schizoaffective disorder and depression with dementia.

The second phase of an audit of the use of ECT in Scotland (20) between 1997 and 1998 found that 85% of the people who received ECT suffered from depressive illness whereas only 7.8% were diagnosed with schizophrenia, 2% a manic illness and 1% a neurotic (anxiety) illness. These figures were also similar during the third phase of the audit that took place between 1998 and 1999 (87%, 6.3%, 3% and 1.5% respectively). Among all those who received ECT during 1997 to 1998 in Scotland (20), the most common reason for receiving ECT was resistance to antidepressant medications (55%), followed by a previous good response to ECT (39%), severe retardation (38%), being too distressed to await response to medication (38%), resistance to other drugs (27%) and suicidal ideation (27%). In only 6% of cases was ECT used as an emergency, life saving treatment.

2.2.2.2   ECT in depressive illness

For depressive illness, first line treatment in the acute phase is the use of antidepressant medication (21). The APA guidelines indicate that the effectiveness of antidepressant medications is generally comparable (21) although a recent meta-analysis (22) suggests that serotonin norepinephrine reuptake inhibitors (SNRIs eg venlafaxine) are more effective than SSRIs (for example fluoxetine) or TCAs (for example imipramine). A meta-analysis of 36 open and double bind trials suggest that 29% to 46% of depressed patients failed to respond fully to antidepressant treatment of adequate dose or duration (23). The minimum does of TCAs known to be effective is 100mg per day (24) and treatment resistance has been defined as failure to respond to a trial of more than one antidepressant drug in a dose equivalent to 250-300mg of imipramine given for a duration of 6-8 weeks each (25). The APA (26) advises that ECT should be considered only for patients with major depression with a high degree of symptom severity, for cases in which psychotic symptoms or catatonia are present, or for cases in whom there is an urgent need for response such as patients who are suicidal or refusing food. The RCP (4) suggest that ECT may be particularly effective in depressive illness with psychotic features or in patients who have not been responsive to antidepressant drug treatment. However, studies have shown that response rates following ECT for depressive illness are lower (50%) in people who previously received adequate antidepressant medication than in those people who received inadequate treatment (86%) (27;27).

A survey of psychiatrists in the North West of England (19) found the most common indication for the use of ECT in depressive illness was in cases of refusal to eat of drink (89% agreed it was the treatment of choice), followed by cases that were responsive in the past to ECT but not to drugs (85%) or had a high suicidal risk (67%). ECT was considered the treatment of choice for psychotic depression by 61% of respondents, for depression not responsive to antidepressant medication by 53% and for depression with severe agitation by 52%.

Repetitive transcranial magnetic stimulation (rTMS) was developed in the 1980s and has been reported to have an antidepressant effect but data on efficacy and optimal stimulation parameters are still conflicting (28). The technique involves the induction of a current in the brain using a magnetic field. The stimulus is a magnetic field that is generated by a current passing through a coil of copper wire that is encased in plastic and held over the patients head. rTMS involves the administration of trains of stimuli to the same area of the brain several times per second. The number of stimuli per second, the strength of stimulus, the duration of the train of stimulation, the interval between trains, the total number of trains and the total number of stimuli in a given sessions are stimulus parameters than can be varied. The adverse effects associated with rTMS are its potential to induce a seizure, muscle tensions, headaches, ringing in the ears and memory problems. It is not currently used in clinical practice.

2.2.2.3 ECT in schizophrenia

For schizophrenia, first line treatment is with antipsychotic medication (3). There are two main types of antipsychotic medication. Typical antipsychotics include chlorpromazine and haloperidol which have both shown to be more effective than placebo in the treatment of schizophrenia (29;30) but can produce a range of unwanted side effects including sedation, dry mouth, tachycardia and extrapyramidal symptoms (medication induce parkinsonism). Atypical antipsychotics such as clozapine have been shown to be more effective than typical antipsychotics (31) and have fewer extrapyramidal side effects but cause potentially fatal agranulocytosis in about 1% of patients (3). Adequate doses of typical antipsychotic medication are considered to be the equivalent of 300 to 600mg of chlorpormazine a day (3). The APA (3) recommend that ECT could be used when patients are treatment resistant or in a catatonic state and when the psychotic symptoms in the current episode have an abrupt or recent onset (17). Similarly, the RCP (4) advise the practical usefulness of ECT in schizophrenia is limited to acute catatonic states, schizo-affective disorders, acute paranoid syndromes and people with type I schizophrenia who are either intolerant or unresponsive to a dose of a neuroleptic equivalent to 500mg of chlorpromazine daily.

2.2.2.4 ECT in mania

In mania, lithium and divalproex are first line treatments (32). The RCP (4) recommends that ECT may, in occasional circumstances, be used for people with severe mania or in less disturbed people with mania who have a slow or inadequate response to medication and may be a safe alternative to high dose neuroleptics. The APA guidelines (32) reserve ECT as a 6th line treatment for euphoric or mixed mania if residual symptoms are still severe following treatment trials with lithium, divalproex with the addition of benzodiazepines, atypical antipsychotics or carbemazepine (32) and as a 5th line treatment for psychotic mania and almost the last resort for rapid cycling mania. Some clinicians believe ECT needs to be administered more frequently to people with mania in order to achieve a therapeutic effect (Paul Birkett, personal communication). Although there is no clear agreement on this, the RCP guidelines recommend that this should be considered (4).

2.2.2.5 ECT in catatonia

First line treatment of catatonia is usually with benzodiazepines (for example, Lorazepam) (33)and the APA (32) and RCP (4) guidelines recommend that catatonia is an indication for the use of ECT in people with schizophrenia or mania.

2.2.2.6 ECT in other subgroups

Other subgroups for which ECT is indicated as a treatment option include older people, psychiatric illness associated with pregnancy and the puerperium and children and adolescents, although it is rarely used in the latter population (4).

2.2.3 STIMULUS PARAMETERS AND ADMINISTRATION OF ECT

2.2.3.1 Frequency and schedules

Although schedules of treatment vary, it is commonly administered twice weekly in the UK (19), but three times a week in the US (4). The courses range from 4-12 treatments (34). Less commonly, it is given fortnightly or monthly as 'continuation ECT' or 'maintenance ECT', to prevent relapse of symptoms.

2.2.3.2 Electrode placement

ECT can be administered by placing electrodes on both sides of the head (bilateral placement) or placed on one side of the head (unilateral), either on the dominant side of the brain or the non dominant side. Unilateral ECT was introduced in order to reduce the cognitive side effects associated with ECT but also has a lower antidepressant effect (35). The RCP (4) recommend that unilateral ECT should be used where the speed of response is less important or where minimising cognitive side effects is especially important, or where there has been a good previous response to ECT. They advise that bilateral ECT should be used where speed and completeness of response have priority, where unilateral ECT has failed, where previous use of bilateral ECT has produced a good response with no memory impairment or where determining cerebral dominance is difficult. A recent survey of psychiatrists in the North West of England found 57% usually used bilateral ECT, 22% used unilateral and 16% used either (19).

2.2.3.3 Stimulus

Early ECT machines delivered an alternating sine-wave stimulus at mains frequency and constant voltage. Modern machines, however, deliver a constant current, variable frequency brief -pulse stimulus. Both efficacy and cognitive side effects are related to the amount of electricity passed through the brain. Modern machines utilise less electrical energy with the aim of maintaining therapeutic efficacy and reducing cognitive side effects.

2.2.3.4 Seizure threshold

This refers to the minimum electrical stimulus required to elicit a generalised seizure. It has been shown to vary 40-fold between individuals, and to increase over the course of ECT (16). Factors that raise seizure threshold, and make it more difficult to elicit seizures, include the use of benzodiazepine anxiolytics and hypnotic drugs, anticonvulsant medication, anaesthetic drugs, older age, male sex, dehydration, low oxygen saturation of blood, and electrical parameters that raise impedance such as poor contact between electrodes and the scalp. The APA (17) recommend that ECT doses should be tailored to the individual. The individual's seizure threshold should be determined using empirical titration and ECT should be delivered at a moderately suprathreshold dose, optimally at 50% above seizure threshold (4).

2.2.3.5 Seizure duration

In clinical practice, generalised motor seizures less than 15 seconds long are considered inadequate. Seizures of 25 to 30 seconds duration are aimed for, and monitored either via EEG or by observing and timing motor convulsions in extremities or in a forearm isolated from muscle relaxants by an inflated blood-pressure cuff (17).

2.2.3.6 Equipment and staffing

Both the RCP (4) and the APA (17) recommend that minimum requirement for ECT facilities is three rooms; a quiet, comfortable waiting area, a treatment room and a recovery area of sufficient size to accommodate the rate and number of patients treated per session (possibly up to six patients lying on trolleys). They advise that rooms should contain the necessary equipment to monitor patients and treat them in an emergency. The staffing levels advised are 2 trained nurses, plus 4 untrained nurses, an anaesthetist, a psychiatrist and an operating department assistant (4). The machines currently recommended for use by both the APA (17)and the RCP (4) are Mecta SR2 and JR2, Thymatron-DGx and Ectron series 5A Ectonus machines.

2.2.4 INFORMATION AND CONSENT

The RCP guidelines (4) highlight that under common law in England, valid consent is required

from all patients, whether informal or detained under the Mental Health Act, before ECT maybe given, except where statute specifically overrides it. This consent must be given freely and be based on an understanding of:

- the purpose and nature of the treatment
- the likely risks and effects of treatment, including its likely success
- the alternatives to the treatment
- the likely consequences of not receiving it
- that consent can be withdrawn at any time
- that new consent is required for further treatment

Where a patient does give consent, the RCP (18) advise that this should be for a specific number of treatments and be in the form of a written document that is also signed by the doctor. Where an informal patient refuses to give consent, alternatives must be discussed, but if there is string grounds for the use of ECT the RCP (18) recommend considering whether the person should be detained. In the case of detained patients refusing treatment, the Commission must be asked to issue a certificate in the prescribed form to allow treatment to go ahead. Where a patient is incapable of giving consent, the RCP advises that guidance from the relevant Mental Health Act should be followed. Under common law, ECT may be given if the treatment is "in the patients best interest" after a second opinion has been obtained.

In a recent survey of the use of ECT in England between January and March 1999 (2), 75% of people receiving ECT in the survey were not formally detained under the mental health act. All of these informal patients consented to treatment with 1.4% being treated as an emergency. Of the 709 people who were formally detained, 29% consented to ECT treatment, 12% were treated as an emergency and 59% did not consent to treatment but were treated after a second opinion was gained.

2.2.5   CURRENT SERVICE PROVISION IN ENGLAND AND WALES

A recent survey of ECT use in England (12)reported that between January and March 1999 there were 16, 482 administrations of ECT to 2, 835 patients. Eighty five percent of all administrations were within an inpatient setting. The average number of administrations per patient was 5.6, ranging from 4.8 in the Trent region to 6.6 in London.

The survey (2) revealed important variations in the rates of administration of ECT by gender, age and health region. In the population as a whole, 5.8 people per 100,000 underwent ECT. The rate was significantly higher in females (7.7 per 100,000 females) than for males (3.8 per 100,000). For both genders, the rate increased with age with 15.1 per 100,000 population aged 65 and over undergoing ECT. The highest rate of ECT use was in the North West (7.1 per 100,000 population) and the lowest was in London (3.7 per 100,000 population). The survey did not provide any information regarding the diagnoses of those who received ECT.

A survey of the use of ECT in Wales during 1996(36) found similar increases in the rate of ECT administration with age. The age specific rates of administration of ECT to people aged 20-34, 34-64 and 65 and over were 7.7, 13.2 and 25.5 per 100,000 population respectively.

A survey of the use of ECT in young people during 1996 (37) found the rate of administration to people under 18 was 0.02 per 100,000 total population per year. The age specific rate of administration of ECT to people aged 16 or 17 (0.62 per 100,000 age specific population per year) was over six times greater than for those aged between 12 and 15 years (0.10 per 100,000 age specific population).

An important question is whether these variations in the use of ECT are the result in variations in the need for ECT (for example as a result of variations in the prevalence of depression) or the result of differences in preferences for the use of ECT on behalf of psychiatrists. Although observations of variations in the prevalence of the underlying disorder do not infer a causal relationship between variations in prevalence of a condition and a treatment, it does provide some insight into this issue. With regard to variations by region, between 1994 and 1998 the pattern in the prevalence of treated depression in men and women was similar to the use of ECT. The prevalence of treated depression in men and women was highest in the North West (30.4 per 1000 and 70.3 per 1000 respectively) and lowest in North Thames (18.8 per 1000 and 46.5 per 1000 respectively) and South Thames (20.6 per 1000 and 49.7 per 1000 respectively). As discussed in section 2.1.5, the prevalence of depression is also higher in women than in men.

Without statistical testing it is not possible to draw definitive conclusions regarding trends in the prevalence of treated depression with age in England in men and women. In men, the prevalence of depression in England increases with age until 55-64 years and then drops again between 65 to 74 and then increases again between 75 to 84 and 85 plus years of age. In women, the prevalence of depression in England increases with age until 45-54 years, drops between 55-64 and 65 to74 to comparable levels with people aged 35-44, increases again at 75 to 84 years and drops at 85+ years to comparable levels with people aged 35-44.

Since 1985, the use of ECT in England has been decreasing (12). The estimated 65,930 administrations in 1998-1999 compares with 105,466 reported administrations in 1990-91 and 137,940 in 1985 (12).

2.2.6 TRAINING AND THE QUALITY OF ECT SERVICES

The Royal College of Psychiatrists first issued guidance on the administration of ECT in 1977 (38). In 1981, Pippard and Ellam (39) conducted an audit against those standards and visited about one half of the ECT clinics in the UK (180). They found that the quality of the centres overall was low with some centres using obsolete machines, and the training provision for junior doctors was generally poor. In response to these findings, the RCP issued revised guidance on the administration of ECT in the form of its first ECT handbook in 1989. In 1992, Pippard (40) conducted a second audit of ECT practice in the UK against the 1989 standards, visiting 35 NHS and 5 private ECT clinics in the old North East Thames and East Anglia Regions. Although improvements had been made since 1981 in the standard of ECT facilities and some aspects of practice, a significant number of clinics were still failing to meet the 1989 standards. Again, the training of junior doctors in the practice of ECT and the use of modern ECT machines were areas in which a large number of clinics did not meet with the 1989 standards.

As a result of Pippard's findings, the RCP established a working group on ECT to revise and broaden the guidelines to include both the structures and process of ECT practice. The guidelines were dissemination through the publication of a revised edition of the handbook in 1995 (4) along with a training video and a series of training courses run by the RCP. A third audit against these guidelines conducted by Duffett and Lelliot (36) took place between 1995 and 1996. They visited all 33 NHS clinics and 5 private clinics in the North East Thames and East Anglia regions and 17 NHS clinics in Wales. They also conducted a postal survey of the 165 ECT clinics in England that were not visited. Two thirds of those who responded were at SHO level. At a similar time Hillam et al (41) conducted a postal survey of the experiences of psychiatry trainees at the Royal Free Hospital in 1990 (n = 51) and in 1995 (n = 34).

Duffett and Lelliot (36) found that despite some aspects of care improving, only one third of the clinics rated met the college guidelines. Fifty nine percent of all clinics had ECT machines of the type recommended by the college but 7% were still using machines considered to be outdated in 1989. Only 16% of consultants attended their ECT clinic weekly and only 6% had sessional time for ECT practice.

Duffett and Lellliot (36) report that the training of junior doctors was still of a low quality. Only one third of clinics had clear policies to help guide junior doctors to administer ECT effectively. In a survey of junior doctors, Lelliot and Duffett (42) found that only half of respondents had been supervised by an experienced psychiatrist on their first administration of ECT; a similar finding was also reported by Hillam et al (41). Duffett and Lelliot (42) found that 45% of respondents lacked knowledge about one or more basic issues relating to the administration of ECT. Hillam et al (41) report that 86% of their sample felt confident in their administration of ECT but one fifth admitted to distress or unease when administering ECT.

Although improvements have been made in the practice of ECT during the 20 years since the RCP first issued guidance, there are still many areas of ECT practice that would benefit from further improvement. In particular, the training of junior doctors in the administration of ECT is still an area of concern.

2.2.7 CURRENT MENTAL HEALTH POLICY IN ENGLAND AND WALES

As a recent survey of ECT use in England (12) has shown, the majority (85%) of all administrations of ECT were within an inpatient setting. In contrast, much of recent government policy on the care and treatment of people with mental health problems has focused on providing more care in community settings. The National Service Framework (NSF) for Mental Health (43) advises that people with short term severe mental health problems including severe depression, can be managed in primary care through treatment with drugs and psychological therapies. The NSF (43) recommends that people with recurrent or severe and enduring mental illness, including schizophrenia and bipolar affective disorders, who have complex needs requiring continuing care of specialist mental health services working with other agencies, can also manage well with this support while living in the community.

3   EFFECTIVENESS

3.1   METHODS FOR REVIEWING EFFECTIVENESS

3.1.1 SEARCH STRATEGY: CLINICAL EFFECTIVENESS

The search aimed to identify all references relating to the clinical and cost effectiveness of electroconvulsive therapy (ECT) for depression, schizophrenia, catatonia and mania.

3.1.1.1 Sources searched

17 electronic bibliographic databases were searched, covering biomedical, health-related, science, social science, and grey literature. A list of databases is provided in **Appendix 1**. This includes the Cochrane Schizophrenia Group Trials Register, which was searched on behalf of the review team by the Group's Trials Search Co-ordinator.

In addition, the reference lists of relevant articles were checked and 40 health services research related resources were consulted via the Internet. These included HTA organisations, guideline producing bodies, generic research and trials registers and specialist psychiatric sites. A list of these additional sources is given in **Appendix 2**. Finally, citation searches of key papers were undertaken using the Science Citation Index (SCI) citation facility and the reference lists of included studies were checked for additional studies.

3.1.1.2 Search terms

A combination of free-text and thesaurus terms were used. 'Population' terms (*e.g.* depression, schizophrenia, catatonia, bipolar disorder, mania, mood disorders, adjustment disorders, psychotic disorders, mental disorders, *etc.*) were combined with 'intervention' terms (*e.g.* electroconvulsive therapy, electro convulsive therapy, electroshock therapy, electro shock therapy, *etc.*) Copies of the search strategies used in the major databases are included in **Appendix 3**. Search strategies in electronic format are available on the attached disk.

3.1.1.3 Search restrictions

No date or language restrictions were applied. Where necessary (*e.g.* in the larger databases, such as Medline), searches were restricted to the highest quality of evidence, *i.e.* practice guidelines, systematic reviews and randomised controlled trials, using methodological filters (**Appendix 4**). These were supplemented by strategies designed to pick up other outcomes, such as patient acceptability, side effects and staff training (**Appendix 4**).

3.1.2 SEARCH STRATEGY: COST EFFECTIVENESS

In addition to the searches conducted above, searches were conducted in NHS EED and OHE HEED to specifically identify cost effectiveness literature (**Appendix 3**). Methodological search filters designed to retrieve economic evaluations and quality of life studies (**Appendix 4**) were also applied to the Medline and Embase search strategies.

There were no company submissions.

3.1.3 INCLUSION AND EXCLUSION CRITERIA

3.1.3.1 Populations

Papers were included in the review if they included the following populations: depressive illness (both unipolar and bipolar), schizophrenia and schizo-affective disorder, catatonia and mania. We also aimed to explore the clinical effectiveness of ECT in particular subgroups including people who are treatment resistant to pharmacotherapy, older people (defined as aged 65 and over), younger people (defined as aged 18 or under) and disorders associated with pregnancy and the peurperium. Papers were excluded if they included populations with more than one diagnosis (for example depression and schizophrenia) and did not stratify randomisation by disease type or report results separately for each diagnosis.

3.1.3.2 Interventions

Papers were included in the review if they examined the effectiveness or cost effectiveness of electroconvulsive therapy either as a monotherapy or in conjunction with other appropriate pharmacological or psychological treatment, at all doses and frequency of administration, by any

technique, in all settings, and administered by any health professional. We also included studies investigating the efficacy of adjunctive and continuation or maintenance ECT or pharmacotherapy and interventions that aimed to improve patient knowledge about ECT.

3.1.3.3 Comparators

Papers were included if they compared ECT to any pharmacological or non-pharmacological treatment including sham ECT, psychotherapy or rTMS. Studies that compared one or more types of pharmacotherapy post ECT were also included.

3.1.3.4 Outcomes

Studies were included if they assessed outcomes relating to the efficacy, safety and acceptability of ECT. The primary indicator of the efficacy of ECT were clinically meaningful benefits in symptoms and/or quality of life as measured by a validated rating scale or clinical opinion, secondary indicators were the speed of response to ECT, premature withdrawals by the decision of either the participant, the clinician in charge of their care or the researcher, discharges from hospital and relapses. The primary indicators of the safety of ECT were adverse events including both objective and subjective reports of memory loss (anterograde, retrograde and subjective reports of memory loss) and all cause and cause specific mortality (including suicide). All these outcomes were considered immediately after the course of ECT, at 6 months and 12 month or longer. The primary indicators of acceptability were patients' choice of treatment and their views and experiences of ECT either from questionnaires or interviews.

3.1.3.5 Study methodology

Published papers were included in the review according to the accepted hierarchy of evidence. In the first instance papers were only included if they were systematic reviews, randomised controlled trials and economic evaluations. Where no randomised controlled trial evidence was available, non-randomised comparator studies (for example non-randomised trials, controlled cohort studies and case control studies) were included in the review. Where no evidence from non-randomised comparator studies is available, non-randomised, non-comparator studies (for example case series, case reports, non-controlled cohort studies) were included in the review.

3.1.3.6 Language

Any studies not available in English were excluded as the time scale of the review precluded time for translation.

3.1.4 QUALITY ASSESSMENT AND DATA EXTRACTION STRATEGY

3.1.4.1 Quality assessment and selection of studies

All the abstracts identified by the searches were entered into a reference manager database and reviewed by the relevant author to assess their relevance to the review's objectives in terms of the clinical (JG) and cost effectiveness (CK) of ECT. All potentially relevant papers were ordered and assessed by the relevant author to determine whether they met the study's inclusion criteria in terms of the populations, interventions, outcomes and study quality.

The assessment of study quality was not conducted blindly and used the following guidelines:

- Systematic reviews were assessed according to the User's guides to evidence based practice (44) .

- Randomised controlled trials were assessed with respect to randomisation procedures, blinding, handling of withdrawals and dropouts, guided by Jadad's scoring system (45) and the Cochrane Collaboration Handbook (46).
- Non randomised studies using quantitative data, such as case-control, cohort, case series and case reports were assessed with respect to validity using guidelines from the Centre for Health Evidence based upon the Users Guides to Evidence-Based Medicine (47).
- Qualitative evidence was assessed using the standards proposed by Popay et al (48).
- The quality of the economic literature was assessed according to the Guidelines for authors and peer reviewers of economic submissions to the BMJ (49).

3.1.4.2   Data extraction and analysis

Two reviewers (JG and DH) extracted data on clinical effectiveness using a 3 separate, standard abstraction forms for systematic reviews (JG), randomised controlled trials (DH and JG) and non randomised evidence (JG) respectively. This was not conducted blind to the authorship of the study.

Where we were satisfied that the populations, interventions and outcomes between trials were sufficiently similar, results were pooled in a meta-analysis.

Clinically meaningful improvement in symptoms was abstracted using both binary and continuous data. For dichotmous data we compared the number of responders or relapsers in each treatment arm as defined by the trialists. Other binary outcomes were the number of discontinuations, relapses and deaths. Those leaving the trial early were assigned to the worse outcome and this was tested using a sensitivity analysis. If the definition of responders or relapers used by the trialists was not clear, a clinically meaningful cut off was decided by an independent clinician (PB) who was blind to the trial authors, the intervention, numbers achieving each outcome in each arm and number in each arm. Where trials used different methods to define responders (for example clinical opinion versus scores on the Hamilton Depression Scale), this was tested using sensitivity analysis. The data was deemed unusable if the number of people meeting responder or relapse criteria were not specified separately in each group, or dropouts were not accounted for on a treatment group basis. We calculated relative risks and confidence intervals using the random effects DerSimonian and Laird method(50). All analyses were by intention to treat.

For continuous data group means and standard deviations at baseline, immediately after ECT and at 6 months follow up were recorded. The data was deemed unusable if:
- no standard deviations or standard errors and/or means were reported
- the instrument used had not been published in a peer reviewed journal as non validated outcome measures are a serious threat to the validity of meta-analyses (51).
- baseline and follow up data was based on different samples (for example, baseline data included all participants but follow up data only included the completer sample)
- at least 50% of the sample were lost to follow up

For studies reporting continuous outcome data all measured using the same scale or instrument (e.g. Hamilton Depression rating) the summary statistic used was the weighted mean difference (WMD). Again we used a random effects model with the DerSimonian and Laird method(50).

For studies reporting continuous outcome data when different scales or instruments were used to measure the effect (e.g. Hamilton Depression rating, HADS, BDI) the summary statistic used was the standardised mean difference (SMD). We assumed that these instruments were all measuring the same underlying trait of "depression". Again we used a random effects model with the DerSimonian and Laird method(50).

All analyses were carried out in RevMan v4.0 (http://www.cochrane.de/cochrane/revman.htm).

Heterogeneity was examined both graphically and with a formal statistical test of heterogeneity. If the confidence intervals for the results of each study (typically presented by horizontal lines) do not overlap, it suggests that the differences are likely to be statistically significant. A formal statistical test of homogeneity was also used to examine whether the observed variation in study results is compatible with the variation expected by chance alone. The more significant the results of the test (the smaller the p-value), the more likely it is that the observed differences were not due to chance alone.

3.2   RESULTS

3.2.1   *QUANTITY OF RESEARCH AVAILABLE*

The searches generated 1647 references. Prior to identification of the two systematic reviews (see below), 790 references were included at the title stage and 485 were included at the abstract stage and ordered for review. The number of studies included in the study are described below.

Two, high quality, recently completed systematic reviews of the safety and efficacy of ECT were identified through contacts with experts in the field. One was completed by The Cochrane Schizophrenia Group (52) in 2002 and reviews the efficacy and safety of ECT in schizophrenia. The authors were contacted and gave their permission for the review to be used in this report prior to its official publication. The references of the review were checked and no additional studies were identified.

The second review was commissioned by the Department of Health and reviews the safety and efficacy of ECT in depression, schizophrenia and mania. This review was conducted by the UK ECT Group(53) and completed in 2001 but has not yet been published. Permission was given to use the report provided all data from the report remained confidential. As such, all text relating to this review in the body of the report has been stripped. The references of the report were checked and one additional study was identified (54).

This report is largely based on the results of these two reviews and has been acknowledged as such in the text of the report

A further high quality, recently completed systematic review of non-randomised evidence of consumer's views of ECT was also identified through contact with experts in the field. This report was also commissioned by the Department of Health and was conducted by Service User Research Enterprise (SURE) at the Institute of Psychiatry(55). It was completed in January 2002 and has not yet been published. The authors were contacted and gave their permission to use the review in this report, provided all data from the report remained confidential. As such, all text relating to this review in the body of the report has been stripped.

The populations, interventions and outcomes of included studies in these 3 reviews were compared to the scope of the National Institute of Clinical Excellence (NICE) review to assess the degree of overlap and identify areas not covered (see Table 1). There were several gaps in the coverage between the scopes of the UK ECT group and the Cochrane ECT Review and the scope of the NICE review. We identified additional randomised and non randomised evidence to address these gaps.

For interventions, neither the UK ECT review group nor the Cochrane ECT review included studies comparing ECT with repetitive transmagnetic stimulation (rTMS) and did not include studies evaluating the effectiveness of post ECT drug therapy.

In terms of populations, neither the UK ECT Group review nor the Cochrane review identified any randomised controlled trials evaluating the efficacy of ECT specifically in older people, people with catatonia, younger people or children and women during or after pregnancy. Some of the trials did include people with catatonia and older people and younger people but results were not reported separately and in the UK ECT Group report data was too limited to do reliable subgroup analyses. The Cochrane Review did conduct a subgroup analysis for schizophrenia subtype, including one trial that predominantly (though not exclusively) included people with catatonia.

In terms of outcomes, the UK ECT Review Group and Cochrane ECT review did not identify any trials that explored either quality of life or the impact of consumer choice on the outcomes of ECT. Non randomised studies evaluating this topic were included in the SURE review.

In populations with depressive illness, we identified two randomised controlled trials comparing ECT with rTMS (56;57), 9 randomised controlled trials comparing ECT combined with drug treatment versus ECT combined with either placebo or a different drug (58-66) and 7 randomised controlled trials evaluating the efficacy of continuation pharmacotherapy following ECT (63-69). Four trials (63-66) examined both adjunctive and continuation pharmacotherapy, where participants were randomised to both ECT and pharmacotherapy and then continued taking pharmacotherapy following the course of ECT.

We also identified one additional randomised controlled trial evaluating the impact of an educational video on patient knowledge about ECT (70) that was not included in the SURE review(55).

Due to the lack of randomised evidence, we examined non-randomised evidence for the efficacy of ECT in older people, younger people, people with catatonia and ECT during or following pregnancy. For children and adolescents, we identified 2 systematic reviews(1;71) of case series; the review published in 1999 was an update of a previous review published in 1997 by the same authors. We also identified 1 cohort study(72) published since this review. For older people, we identified one prospective cohort(73;74) study comparing older people who had received ECT with those who had not and 3 retrospective cohort studies(75-77). For catatonia we identified one systematic review(78) of case reports and case series of people with catatonia who received ECT, published in 1995, and 2 prospective(79;80) case series published since this date. For the use of ECT during pregnancy, we identified 1 systematic review of case series(81) and case reports published in 1994 and 3 case reports(82-84) published since that date.

Table 1 outlines the overlap between the NICE scope and the 6 systematic reviews identified. A tick indicates the topic is covered, a cross indicates the topic is not covered and a question mark indicates where the review did not provide sufficient detail to identify whether this topic was covered or not. Table 2 provides an overview of the NICE scope and indicates the sources of evidence used for specific areas.

Tables of all included reviews or studies are shown in Appendix 5. Tables of analysis are in Appendix 6.

Table 1: Overlap between NICE scope and the 6 systematic review identified

REVIEW	UK ECT Group 2002 (53)	Cochrane ECT reviewers 2002 (52)	SURE 2002 (55)	Walters and Rey 1997/ 1999 (1;71)	Hawkins 1995 (78)	Miller 1994 (81)
TYPE OF EVIDENCE						
Randomised evidence	Y	Y	N	N	N	N
Non randomised evidence	Y	N	Y	Y	Y	Y
CONDITIONS						
Depression	Y	N	?	Y	N	?
Schizophrenia	Y	Y	?	Y	N	?
Mania	Y	N	?	Y	N	?
Catatonia	N	Y	?	Y	Y	?
SPECIFIC SUBGROUPS						
Younger people	N	N	?	Y	N	N
Older people	N	N	?	N	N	N
Pregnant women	N	N	?	N	N	Y
COMPARATORS						
Sham vs real	Y	Y	N	N	N	N
ECT vs pharmacotherapy	Y	Y	N	N	Y	N
ECT vs psychotherapy	Y	Y	N	N	N	N
Stimulus parameters	Y	Y	N	N	N	N
ECT vs rTMS	Y	N	N	N	N	N
Adjunctive drug therapy	Y	Y	N	N	N	N
Continuation ECT	Y	Y	N	N	N	N
Continuation pharmacotherapy	N	N	N	N	N	N
SPECIFIC OUTCOMES						
Symptom improvement	Y	Y	N	Y	Y	N
Perceived benefit	N	N	Y	N	N	N
Cognitive functioning	Y	Y	Y	Y	N	N
Suicide	Y	Y	N	N	N	N
All cause mortality	Y	Y	N	Y	N	Y
Brain damage	Y	N	N	Y	N	N
Other adverse events	N	N	N	Y	N	Y
Information and consent	N	N	Y	N	N	N

26

Table 2: Nice scope and sources of evidence used

NICE SCOPE	SOURCE OF EVIDENCE
DEPRESSION	
real vs sham ECT	UK ECT Group review of randomised evidence (53) and NICE reviewers re-analysis of trials identified by UK ECT Group
ECT vs inpatient care	UK ECT Group review of randomised evidence (53)
ECT vs pharmacotherapy	UK ECT Group review of randomised evidence (53) and NICE reviewers re-analysis of trials identified by UK ECT Group
unilateral vs bilateral	UK ECT Group review of randomised evidence (53)
unilateral: dominant vs non dominant	UK ECT Group review of randomised evidence (53)
bilateral: frontotemporal vs tempoparietal	UK ECT Group review of randomised evidence (53)
frequency of administration	UK ECT Group review of randomised evidence (53)
dosage: high vs low	UK ECT Group review of randomised evidence (53)
wave form: sine wave vs brief pulse	UK ECT Group review of randomised evidence (53)
ultrabrief vs standard	UK ECT Group review of randomised evidence (53)
no of ECT sessions	UK ECT Group review of randomised evidence (53)
post ECT nursing care	UK ECT Group review of randomised evidence (53)
ECT vs rTMS	NICE reviewers' analysis of randomised evidence
ECT+pharmacotherapy vs ECT+ placeco/different pharmacotherapy	NICE reviewers' analysis of randomised evidence
continuation pharmacotherapy	NICE reviewers' analysis of randomised evidence
MANIA	
ECT vs pharmacotherapy	UK ECT Group review of randomised evidence (53)
ECT+pharmacotherapy vs pharmacotherapy alone	UK ECT Group review of randomised evidence (53)
SCHIZOPHRENIA	
real vs sham ECT	UK ECT Group (53) and Cochrane Schizophrenia Group ECT Review of randomised evidence
ECT vs pharmacotherapy	UK ECT Group (53) and Cochrane Schizophrenia Group ECT Review (52) of randomised evidence
ECT+pharmacotherapy vs pharmacotherapy	UK ECT Group (53) and Cochrane Schizophrenia Group ECT Review (52) of randomised evidence
ECT vs psychotherapy	Cochrane Schizophrenia Group ECT Review of randomised evidence (52)
continuation ECT	UK ECT Group (53) and Cochrane Schizophrenia Group ECT Review of randomised evidence
bilateral vs unilateral	UK ECT Group (53) and Cochrane Schizophrenia Group ECT Review (52) of randomised evidence
unilateral: dominant vs non dominant	UK ECT Group (53) and Cochrane Schizophrenia Group ECT Review of randomised evidence
dosage	UK ECT Group (53) and Cochrane Schizophrenia Group ECT Review (52) of randomised evidence
frequency of administration	UK ECT Group (53) and Cochrane Schizophrenia Group ECT Review (52) of randomised evidence
number of treatments	UK ECT Group (53) and Cochrane Schizophrenia Group ECT Review (52) of randomised evidence

SPECIFIC OUTCOMES	
severe adverse events	UK ECT Group review (53) of non randomised evidence
patient acceptability and choice	SURE (55) review of non randomised evidence
patient information	NICE reviewers' analysis of randomised evidence and SURE review (55) of non randomised evidence

Table 2: Nice scope and sources of evidence used cont'd

NICE SCOPE	SOURCE OF EVIDENCE
SPECIFIC SUBGROUPS	
catatonia	Cochrane Schizophrenia Group ECT Review (52) review of randomised evidence, Hawkins review (78) of non randomised evidence and NICE reviewers' analysis of non randomised evidence
children and adolescents	Rey and Walters reviews (1;71) of non randomised evidence and NICE reviewers' analysis of non randomised evidence
older people	NICE reviewers' analysis of non randomised evidence
ECT during pregnancy	Miller's review (81) of non randomised evidence and NICE reviewers' analysis of non randomised evidence

3.2.2 QUALITY OF STUDIES IDENTIFIED

3.2.2.1 Randomised evidence

Two systematic reviews including randomised evidence examining the efficacy and safety of ECT were identified (52;53). The discussion here reviews the quality of these systematic reviews and then describes the quality of the trials included as reported by the authors of the reviews.

3.2.2.1.1 UK ECT Group Review

The UK ECT Group review(53)covers the efficacy of ECT in people with depression, schizophrenia and mania.

The current authors re-analysed aspects of the UK ECT group report as follows:

1. Reabstracted the trials comparing sham ECT with real ECT and ECT vs pharmacotherapy using dichotomous data.
2. Re-analysed trials comparing real ECT with sham ECT, doing separate analyses for bilateral ECT, unilateral ECT and trials that used both methods.
3. Re-analysed the trials comparing ECT with pharmacotherapy, doing separate analyses by drug class (ie SSRIs and TCA's)

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.2.1.2 Cochrane Schizophrenia Group Review

The Cochrane ECT Review conducted by Tharyan and Adams (the Cochrane Schizophrenia Group ECT Review) (52) includes people with schizophrenia, schizo-affective disorder or chronic mental disorder (non-affective). They identified a total of 24 studies including 1451 participants of whom 779 were treated with ECT. The reviewers provide a description of the participants included in the trials in terms of diagnoses, age, gender, whether participants were treatment resistant and the duration of the disorder. They also describe the study setting and length of the trials.

The review examined the effectiveness of ECT in comparison with placebo, sham ECT, pharmacological interventions and non pharmacological interventions (for example, psychotherapy). They also assessed the effectiveness of continuation ECT compared with continuation pharmacotherapy. The review also examined ECT stimulus parameters including electrode placement (bilateral vs unilateral), dose (threshold vs suprathreshold), frequency of ECT administration (three times weekly vs five days a week) and the number of ECT treatments (long courses vs short course).

The primary outcomes of interest were clinically meaningful benefits in overall functioning, hospitalisation status, changes in mental state, behaviour, social and occupational functioning, remission of symptoms and discharge from hospital or care. Secondary outcomes were premature withdrawal from the trial either by the decision of the participant or the researchers and adverse events including cognitive functioning and mortality. Each outcome was reviewed during the ECT course, in the short term (less than 6 weeks), medium term (6 weeks to 6 months) and long term (over 6 months).

The search strategy of the review was comprehensive and a range of electronic databases were searched using established search strategies from the Cochrane Schizophrenia Group. These

searches were supplemented by citation tracking and the editorial board of the leading journal in the field and first authors of all trials published since 1980 were contacted for additional references and unpublished trials. In addition, the manufacturers of ECT machines were also contacted for additional studies.

The reviewers limited their review to randomise controlled trials only. Two reviewers independently assessed every report identified by the electronic search for its relevance to the review and disagreements were discussed. Where disagreements remained unresolved, the report was ordered and the study added to those awaiting assessment while the authors of the study were contacted for additional information.

Study quality was assessed using guidelines in the Cochrane Collaboration Handbook (46). Two reviewers independently assessed the trials and only those where the method of randomisation was classed as concealed (A) or unclear (B) were included. In cases of disagreement, further clarification was sought from the author.

The Cochrane Schizophrenia Group ECT Review (52) used dichotomous data of global improvement as defined by the trialists as their primary outcome measure of efficacy. They argue that clinicians can better make sense of data indicating whether someone has improved or not. Relative risks and confidence intervals were calculated for each outcome. They also calculated the number needed to treat (NNT) and number needed to harm (NNH). All analyses were undertaken on an intention to treat basis and participants who left the study early were assigned to the least favourable outcome. The effects of this assignment were tested in a sensitivity analysis. For the outcome of global improvements in functioning, the reviewers compared the numbers who did not improve in each arm of the trial. No information is provided regarding how "no of improvement" was defined within the various trials. Trials(85) of pharmacotherapy for depression often use the criterion of a 50% reduction in Hamilton Depression to define responders. Fink(6) points out that trials of ECT often use a different criterion to demarcate responders from non responders. There are two important disadvantages to using dichotomous data. Firstly, it is difficult to know what degree of improvement was made in those people who did improve. Secondly it is not known whether the non responders did not change or got worse. These changes are not taken into account when dichotomous data is used.

Continuous data were excluded if more than 50% of people were lost to follow up and data were analysed as reported by the authors without making any assumptions about those who were lost to follow up. Continuous data were also excluded if the rating scale used had not been published in a peer reviewed journal or if the data did not meet apriori criteria for parametric data.

Data were combined using both fixed and random effects models. Heterogeneity was investigated by the Mantel-Haenszel chi square test of heterogeneity to check whether differences in results were due to chance alone. A significance level of 0.10 was interpreted as evidence of heterogeneity. If heterogeneity remained after the data was combined using a random effects model, the data were not pooled and results reported separately and discussed.

Sensitivity analyses were undertaken in all cases where heterogeneity was detected and the effect of including studies with high attrition rates was also analysed. In addition subgroup analyses were undertake to detect any differences in outcomes between (a) for people with operationally defined schizophrenia as opposed to those diagnosed by clinical consensus, (b) for people with varying degrees of treatment resistance and those whose illness was not designated as such, (c) people having predominantly positive or negative symptoms of schizophrenia and those without this designation; and (c) people ill for less than two years and those at a later stage of their illness. Publication bias was assessed using a funnel plot.

The reviewers pooled data from different classes of antipsychotics including some that are no longer used in current clinical practice. They found little statistical heterogeneity in their analysis and provided the current authors with raw data to allow us to explore this issue in more detail if necessary.

The methods used in this review were of a high quality and the conclusions follow from the results.

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.
Overall quality of trials assessing the effectiveness of ECT in schizophrenia is generally low. The method of allocation is rarely described and blinding is also inadequately explained. Often continuous data was only presented in graphical form or only presented for the completer samples and drop outs were not accounted for. There were also significant gaps in the evidence of the efficacy of ECT for important subgroups that are most likely to receive ECT such as older people and women with post partum depression. There is little randomised evidence of the effectiveness of ECT in people with mania and catatonia. There is also little randomised evidence of the long term efficacy or side effects of ECT with trials rarely following people up beyond the course of ECT. Furthermore, the methods used to measure efficacy and side effects do not adequately represent the views on users who receive ECT. There are no trials exploring the impact of ECT on quality of life. This had important implications for the cost effectiveness modelling within the NICE review.

3.2.2.1.3   Quality of RCTs identified by the NICE reviewers

The quality of the randomised controlled trials we identified was also generally low. Of the trials comparing ECT with rTMS, one used concealed randomisation (57) and both were single blind (56;57). None of 12 trials examining the efficacy of adjunctive or continuation pharmacotherapy adequately described the method of randomisation. Seven of these trials were double blind (61-63;65;67-69), four were single blind (59;60;64;66) and in one it was not clear whether the clinician or the patient were blind to treatment allocation(58). One RCT examining the impact of the educational video on patient knowledge (70) used concealed randomisation but was not blind and only measured knowledge at follow up using an instrument with no evidence to support its psychometric properties. The second trial was also unblinded and it was unclear whether allocation was concealed (86).

3.2.2.2   Non randomised evidence

Due to the gaps in the randomised evidence, we explored the non-randomised evidence. We identified 4 systematic reviews of non randomised evidence that covered different aspects of the NICE scope.

3.2.2.2.1   SURE Review

The review conducted by the Service User Research Enterprise (SURE) at the Institute of Psychiatry (55) aimed to systematically summarise consumers' perspectives of ECT and to understand the sources and nature of controversy about ECT between some user and professional groups.

ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.

3.2.2.2.2   Reviews on younger people and children by Rey and Walters

We identified two systematic reviews (1;1;71) examining the evidence of the efficacy of ECT in younger people and children. The reviews were by the same authors and one review (1) was an update on a previous review (71).

The review included all studies examining the effectiveness of ECT in younger people, defined as people aged 18 or under. The reviewers did not identify any randomised evidence of the effectiveness of ECT in this subgroup and did not restrict inclusion criteria by study type. Studies were only included if they provided sufficient information on diagnosis and individual outcomes.

The outcomes of interest were not defined a priori and appear to be governed by the content of the studies identified. The outcomes covered in the review were the percentage of participants with remission or marked improvement of symptoms immediately after ECT and at 6 months follow up, adverse events including mortality, prolonged seizures, subjective side effects and cognitive functioning.

The reviewers did not provide any information regarding the medical and psychological databases searched or give details of the manual searches so it is difficult to ascertain the comprehensiveness of the review. Language bias was reduced as the reviewers translated papers from other languages into English and included them in the review. The reviewers identified 60 reports describing 396 cases in their initial review and a further 11 reports by 1999. Information on diagnosis and short term outcome was available for 224 cases in 1999 and 154/396 (39%) of cases in 1997. Our own searches did not identify and studies published before 1999 that were not included in the review.

No information is provided regarding how data was abstracted. Two independent reviewers rated the quality of the studies and only included those that provided sufficient information of diagnosis and outcome. However, other elements of study quality were not taken into account when the results of the papers were summarised. The reviewers provided details of how they summarised outcomes. Reviewers defined responders as those who showed marked improvement or recovery both immediately after ECT and 6 months post ECT as defined by the study authors. However, this assessment was not reported as being blind to either the study authors or the results of treatment and was open to some degree of subjective interpretation. The data on efficacy was summarised by adding case series and reports together to produce an overall percentage of these with a good outcome after ECT and at 6 months by diagnosis. However, it is not clear wherther this was undertaken on an intention to treat basis. A qualitative overview of data on adverse effects was undertaken.

Overall, the quality of the studies included in the review was poor and there were no controlled studies. Reviewers' quality ratings ranged from 2 to 17 (minimum possible 0, maximum 20) with a mean of 8.9 and a SD of 3.2. The quality of the reporting within the studies was also poor; 43% of studies in the 1997 review provided no diagnosis for cases and only two reports used quantitative measures of outcome. To examine the quality of studies over time, the reviewers divided reports into those published before DSM-III in 1980 and those published after. Studies published after 1980 had higher quality scores (mean 9.9, SD 2.9) than those published before (mean 7.5, SD 3.2) which was statistically significant at the 0.01 level (t = 3.06, df=58, p = .003).

It is difficult to ascertain whether this review may have missed important studies due to the lack of information on search strategies. The reviewers did rate the quality of studies and only included papers with sufficient information on outcome and diagnosis. The methods of data analysis of the efficacy of ECT are subject to some degree of subjective interpretation and the qualitative analysis of adverse events may be subject to selective reporting. However, given the poor quality of the evidence available, it its likely that these reviews are currently the most comprehensive available.

3.2.2.2.3 Hawkins review (78) of ECT in catatonia

We identified one systematic review examining non randomised evidence of the effectiveness of somatic treatments for people with catatonia (78). This aimed to summarise the literature on the treatment of catatonia.

Papers were included if they provided sufficient information to determine whether cases met DSM-IV criteria for catatonia. Papers were excluded if the clinical descriptions were likely to be due to neuroleptic malignant syndrome (NMS). The review included papers describing any treatment to catatonia although this was not defined apriori but appeared to be governed by the content of the studies identified. The treatments considered included benzodiazepines, antipsychotics, ECT, amobarbital, benztropine, ammantidine, dontrolene, phenytonin, carbamazepine, ECT plus other interventions (not defined) and antipsychotics plus other interventions.

Only one outcome was considered by the review – response to treatment. This was based on the original authors' clinical description of change in catatonic symptoms after treatment. This response was then retrospectively rated by the reviewers on a 3 point scale of none, partial or complete. None was defined as no improvement or worsening requiring a change in treatment; partial was defined as some improvement but incomplete requiring a switch in treatment and complete, defined as resolution of catatonic symptoms but not necessarily the underlying pathology. However, no information is given as to whether these ratings were made blind to either authors or treatment type and as such the results of the review are open to information bias.

Papers were excluded if either the treatment or the response to treatment were inadequately defined. The authors did not identify any randomised evidence and inclusion was not limited by study type.

Limited search strategies were used and only one electronic database was searched (Paperchase) from 1985 to 1994. Citation tracking from included studies was used but no attempt was made to identify unpublished studies. Our own searches did not identify any further studies published between these dates. The reviewers identified 87 articles pertaining to the treatment of catatonia and 70 (80%) met the inclusion criteria for further analysis. The authors provide specific reasons why certain studies were excluded including not meeting DSM-IV criteria for catatonia, treatment responses not defined, NMS suspected. A total of 270 treatment episodes in 178 patients were included.

No information is provided regarding how the data was abstracted or summarised. The unit of analysis in the review was not explicitly defined but appears to be the treatment episode rather than by case. The percentage of treatment episodes having none, partial or complete response were calculated for each treatment type. However, it is not clear in the case of ECT whether treatment episode implies a single administration of ECT or a course of ECT. It is therefore difficult to interpret the results of the review. Given the poor description of the analysis and the limited search strategies, the findings of this review need to be treated with caution.

3.2.2.2.4 Millers review (81) of ECT in pregnancy

We identified one systematic review of the use of ECT in pregnancy (81). This review aimed to review case reports of the use of ECT during pregnancy to clarify potential risks and modifications of ECT techniques that make the procedure safer for women.

Studies were included in the review if they reported on the use of ECT in women during pregnancy. The primary outcome of interest was any adverse events occurring as a result of ECT during pregnancy. No randomised studies were identified and inclusion was not limited by study type.

The review used a limited search strategy only searching one electronic database (Medline) from 1966 to 1991. However, some reports were identified dating back to 1942 although no information is provided regarding how these were identified. Our own searches did not identify any further studies not included in this review. No information is given regarding whether attempts were made to identify unpublished literature. The reviewer identified 300 cases reported in the literature.

No information was given regarding how data was extracted and no attempt was made to rate study quality. As such the results of the review may be biased due to risk of selective reporting. The prevalence of adverse events in the cases identified was outlined and no information is provided regarding the efficacy of ECT in these cases. It is not stated whether this information was provided in the original studies. Given the limited search strategies employed by this review, the lack of information about how data was extracted and the relatively poor quality of the available evidence, the results of this review should be interpreted with caution.

3.2.2.2.5 *Supplementary non randomised evidence identified by NICE reviewers*

We also identified supplementary non randomised evidence of the efficacy of ECT in subgroups of patients with catatonia, older people, younger people and adolescents and its use in pregnancy that were not included in the above reviews.

In people with catatonia, we identified 2 prospective(79;80) case series. Both used a validated instrument to measure outcomes and ECT was used in participants that had failed to respond to lorazepam.

For older people, we identified one prospective cohort (73;74) study comparing older people who had received ECT with those who had not and 3 retrospective cohort studies(75-77). In one study (75) some control over confounding variables was attained through matching but in two studies the groups were different at baseline(76;77). In the Kroessler and Fogel study(76), participants who received ECT were medically and mentally more ill than those who did not receive ECT. In the Phillibert study(77), the ECT group was more likely to be judged as suffering from psychomotor retardation and to have had prior course of ECT than the pharmacotherapy group. The differences in the Kroessler and Fogel(76) study may be due to the fact that a significant proportion of those who did not received ECT were recruited from a different hospital.

In adolescents we identified on addition cohort study(72). There was a large loss to follow up in the ECT group with only 10/20 adolescents identified as being treated with ECT being included in the study. Although matching allowed some control over confounding variables, the two groups were different with regard to diagnoses and the initial level of severity of their diagnoses. Furthermore, participants were interviewed a mean of 5.2 years post ECT leaving considerable scope for information bias.

Finally, we identified a further three case studies of the use of ECT in pregnancy (82-84). In all 4 cases ECT was used because the women had failed to respond to pharmacotherapy.

Overall the quality of the systematic reviews of non-randomised evidence is poor to moderate. and non randomised evidence is poor. Only two of the systematic reviews(55;71) evaluated the quality of the studies included and only one provided sufficient detail of the search strategies used (55). In three of the reviews (71;78;81) the methods of abstracting outcomes was open to a significant degree of interpretation. However, the reviews are likely to be the best evidence currently available in these specific areas. The quality of the non randomised evidence included in these reviews or identified by ourselves is poor. Most studies were subject to confounding by baseline differences between groups who received ECT and those that did not, or lacks any control group at all.

RESULTS OF CLINICAL EFFECTIVENESS

3.2.3   *DEPRESSION*

We identified one systematic review(53) evaluating the efficacy of ECT in people with depression. The results of this review and out own additional analyses are reproduced here:

3.2.3.1   **ECT vs Sham ECT**

We identified 9 trials {Gregory, 1985 517 /id}{West, 1981 563 /id}{Jagadeesh, 1992 466 /id}{Lambourn, 1978 119 /id}{Freeman, 1978 118 /id}{Johnstone, 1980 113 /id}{Brandon, 1984 359 /id}{McDonald, 1966 188 /id}{Wilson, 1963 2652 /id} comparing real with sham ECT. In 4 trials the position of the electrodes was reported and two used unilateral(90;91), one bilateral(92) and one both(87).   In 4 trials(87;92-94) participants received ECT twice weekly and in the remaining two(90;91) it was administered three times weekly. Two trials reported the waveform of ECT, one used sine wave(92) and the other brief pulse(90). In two trials (54;92) the control arm received also received at least one real ECT. In Jagadeesh (54), participants in the control arm received 1 real and 5 sham ECTs. In Freeman (92), participants in the control arm received two initial with sham ECT and the remaining ECTs received were real.

Efficacy at end of course
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Four trials provided dichotomous data for analysis of improvement at the end of an ECT course (54;90-92). One trial used unilateral ECT (91) while the other three used bilateral ECT (54;90;92) and were analysed separately.   The relative risk of a reduction of at least a 50% in HRSD for unilateral ECT was 1 (95% CI = 0.54 to 1.84, p = 1, n = 32) indicating no statistically significant difference between real and sham ECT.

Data from the three trials using bilateral ECT had a relative risk of improvement as defined by the trialists at the end of a course of 1.21 (95% CI = 0.61 to 2.40, p = 0.6, n = 134), indicating no statistically significant difference between real and sham ECT. There was a significant degree of heterogeneity within these three trials and removal of Freeman et al (92) resulted in a homogenous result with non significant trend in favour of real ECT (RR = 1.64 95% CI = 0.92 to 2.49, p = 0.1., n = 84). The control arm of this trial only received 2 sham ECTs, the rest were real ECTs. A further remaining trial (54) also included 1 real ECT treatment in the control arm along with 5 sham ECT treatments. Removal of this trial (54), leaving one trial only, suggests that real bilateral ECT is more effective than sham ECT (RR = 1.98, 95% CI = 1.05 to 3.73. p = 0.03, n = 70).

Discontinuations by end of treatment

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Efficacy at 6 months follow up
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: mortality
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: cognitive functioning

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.2 ECT vs inpatient care alone

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.3 ECT vs Pharmacotherapy

We identified 18 trials containing 1144 patients that were included in the analysis(88;93;95-110). Bilateral ECT was used in 5 trials(96;97;102;105;106) and unilateral in 2(103;107). ECT was administered twice a week in 4(93;102-104) studies and 3 times a week in 5(88;96;97;107;108) studies. In 5 trials (93;97;102;105) participants were treated with tricyclic antidepressants at doses between 75 and 150mg of imipramine or 150mg of amitryptaline(88). L-tryptophan was used in two trials at does of 3g(103) and 6-8g(104). The remaining trials used paroxetine 40-50mg(107), lithium 800g(106), phenelzine 15-45mg, either imipramine 50g or phenelzine 15mg(98) or a TCA or a MAOI(108). Only 4 studies(96;102;106;107) required participants to have failed to respond to at least one trial of antidepressant drugs for inclusion into the study. Treatment was continued for a range of durations. Three studies(93;106;108) reported the end of treatment at 3 weeks, one for 3-5 weeks(96), 4 trials reported 4 weeks(88;103;104;107), 1 at 5 weeks(102), 1 at 12 weeks(105) and 1 at approximately 2-4 weeks(98). Only three of the 18 trials identified used sham ECT in the pharmacotherapy arm (93;100;110).

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Efficacy at the end of treatment

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

One trial compared right unilateral ECT with an SSRI (paroxetine 40-50mg) in people with treatment resistant depression. The criterion for clinical improvement in the trial was a reduction of at least 50% in baseline HRSD scores. The RR of being a responder was 3.14 (95% CI = 1.39 to 7.11, n = 43, p = 0.006) in favour of ECT.

Fourteen trials compared ECT with a TCA (88;93;95-102;105;106;108;110) and in one trial the TCA was combined with an MAOI (96)and in another it was combined with Lithium (106) in people with treatment resistant depression. Six trials including 394 participants provided dichotomous data for analysis (97-99;102;108;110). The criteria used to define responders varied between trials. Two trials (102) defined responders using different criteria specified apriori based on scores from quantitative outcome measures while the remaining 4 (98;99;108;110) were based on clinical opinion of improvement. To explore whether the heterogeneity in defining responders influences outcomes the relative risk of being both a responder and non-responder was calculated and the trials were analysed separately and together.

Pooled analysis of all 6 trials showed that people treated with ECT were statistically significantly more likely to be defined as a responder by the trialists (RR = 1.42, 95% CI = 1.17 to 1.72, p = 0.0004) and also statistically significantly less likely to be defined as a non responder (RR = 0.47, 95% CI = 0.31 to 0.69, p = 0.0002).

Analysing the two trials (97;102) based on a quantitative assessment of improvement separately results in no difference in the likelihood of being defined as a responder between ECT and TCAs (RR = 1.23, 95%CI = 0.90 to 1.67, p = 0.58, n = 38). Analysis of heterogeneous data from the four

trials (98;99;108;110) based on clinical opinion gives a RR of improvement of 1.63 (95% CI = 1.21 to 2.20, p = 0.001, n = 346) in favour of ECT.

Discontinuations by end of treatment

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Depression at 6 months follow up

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: mortality

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: cognitive functioning

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.4 Unilateral vs bilateral ECT

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Efficacy at end of course

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Discontinuations

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: Mortality

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: Cognitive functioning

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

IMMEDIATELY AFTER AN ADMINISTRATION OF ECT TREATMENT

ORIENTATION

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

RETROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

ANTEROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

SUBJECTIVE DISTRESS

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

AT END OF COURSE OF ECT

RETROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

ANTEROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

OVERALL COGNITIVE FUNCTIONING

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

SUBJECTIVE REPORTS

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

LONG-TERM (>6 MONTHS)

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.5 Unilateral Electrode Placement

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Efficacy: end of course and 6 months

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: cognitive functioning

AS AN IMMEDIATE CONSEQUENCE OF ECT TREATMENT:

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

ORIENTATION

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

AT THE END OF ECT COURSE

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.6 Bilateral Electrode placement

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Efficacy at end of course

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Depression Rating at 6 Month Follow Up

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: mortality

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: cognitive functioning

AS AN IMMEDIATE CONSEQUENCE OF ECT TREATMENT:

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

AT END OF A COURSE OF ECT:

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.7 Frequency of ECT

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Efficacy at end of course

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Discontinuation

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Depression Rating at 6 month follow-up

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: mortality

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: cognitive functioning

AS AN IMMEDIATE CONSEQUENCE OF ECT TREATMENT
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

AT THE END OF A COURSE OF ECT:
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

RETROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

ANTEROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

OVERALL COGNITIVE FUNCTIONING

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.8 Dose of electrical stimulus

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Efficacy

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Discontinuations

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: mortality

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: cognitive functioning

AS AN IMMEDIATE CONSEQUENCE OF ECT TREATMENT:

ORIENTATION

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

ANTEROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

AT THE END OF A COURSE OF ECT

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

RETROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

ANTEROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

OVERALL COGNITIVE FUNCTIONING

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.8 Stimulus wave form

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Efficacy at end of course: depression rating

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: mortality

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: cognitive functioning

AS AN IMMEDIATE CONSEQUENCE OF ECT TREATMENT:

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

ORIENTATION

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

RETROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

AT THE END OF A COURSE OF ECT:

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

RETROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

ANTEROGRADE MEMORY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

OVERALL COGNITIVE FUNCTIONING

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

AT 6 MONTHS

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.10 Ultrabrief ECT vs Standard ECT

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.11 Number of ECT sessions
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.12 Number of seizures per treatment session
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.13 Extra sessions of ECT
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.14 Post ECT Nursing care
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.3.15 ECT vs rTMS

We identified two randomised controlled trials evaluating the efficacy of repetitive transcranial magnetic resonance stimulation with ECT in people with depression including 63 participants (56;57). One trial compared ECT alone with rTMS(56)while the other compared ECT with ECT plus rTMS (57). One trial specifically included people with medication resistant depression(57). Both trials used unilateral ECT placement and only one described the frequency of administration, which was 3 times per week(57). The rTMS methods different between the two studies. In Pridmore (57), a Magtism Super Rapid Stimulator was used with a Magstim 70mm double coil, at an intensity of 100%, frequency of 20Hz and a train length 2 secs. The number of trains was 30 with an intertrain interval of 20 seconds. In Grunhaus(56)the motor threshold was determined daily by electromyographic method and stimulus intensity was the lowest machine power output that would provide five of 10 stimulations an MEP of at least 50 µV. Electrodes were placed over the left dorsolateral prefrontal cortex. During stimulation the coil was held with the handle towards the back of the head. rTMS was administered five times a week for 4 weeks (for a total of 20 stimulations).

Efficacy: depression at end of course

Only one trial(56) provided usable data on 40 participants for analysis. The efficacy of the treatment was measured using continuous data from the HRSD. The weighted mean difference between ECT and rTMS was 6.8 (95%CI = 1.41 to12.19; n = 40) which was statistically significant at the 0.01 level in favour of ECT. Thus people treated with ECT fared, on average, 6.8 points better on the HRSD than people receiving rTMS. Efficacy was also measured as a dichotomous variable with responders defined as those whose scores at the end of the course were greater of equal to 60 on the Global Assessment of Function and had decreased by at least 50% on the HRSD from baseline but the data was unusable. There were no discontinuations or deaths reported in this trial.

Adverse events: side effects

The two trials only reported data on subjective side effects.

Grunhaus et al.(56) (ECT vs. rTMS) found that 5 patients in the rTMS group complained of mild headache, which responded to analgesics. In one patient and only during one of the treatment sessions a muscular-evoked potential (MEP) discharge was noted 20msec following each magnetic pulse.

Pridmore(57) (ECT vs. ECT + rTMS) used a six-item subjective side-effects questionnaire derived from a report on the side-effects of ECT (Gomez 1975). Over the 2-week study period the ECT only stream was scored 56 positive responses to the side effects questionnaire, whilst the ECT + rTMS stream scored a little over half of that number. None of the observed differences in proportions of patients having side effects were statistically significant. The main symptoms were 'memory problems', 'headache' and 'muscle pains' scored most complaints in both streams. Memory problems were twice as common in the ECT only stream. Because of the small sample, the possibility that these results are due to the play of chance cannot be excluded.

3.2.3.16 ECT + pharmacotherapy vs ECT + placebo/different pharmacotherapy.

We identified 9 trials that compared ECT combined with pharmacotherapy versus ECT combined with either placebo or a different type of pharmacotherapy (58-66). Two trials compared unilateral ECT combined with L-tryptophan versus unilateral ECT and placebo (61;62). Two trials compared ECT combined with imipramine versus ECT combined with placebo (63;64); in one study the dosage of imipramine ranged from 25-50mg(63) while in the other the dosage was 25mg t.d.s (64). Imlah also had an arm in the trial where ECT was combined with phenelzine (15mg t.d.s). Neither trials reported any details of electrode placement. Lauritzen (66) had two arms in the trial who were separately randomised to received either bilateral then unilateral ECT combined with paroxetine (30mg) or placebo (Group A) or randomised to received bilateral then unilateral ECT combined with either paroxetine (30mg) or imipramine (150mg). Kay (65) compared ECT combined with either amitryptaline (50-150mg) or diazepam (4-12mg). Mayur (58) compared unilateral ECT combined with continuation of the antidepressants (either TCAs or SSRIs, dose or type not defined) participants were taking on entry to the trial versus ECT alone. Arfwidsson (60)compared bilateral ECT combined with chlorpromazine (50-150mg) versus bilateral ECT combined with placebo. Shiah (59)compared either unilateral or bilateral ECT combined with pindol (7.5mg) with ECT and placebo. In five trials, the length of ECT treatment was determined by a clinical decision on response to ECT (60;62-64;66) while Shiah (59) fixed the number of treatments at 6 in each arm. In the remaining 3 trials, the length of ECT treatment was unclear (58;61;65). In 4 of the trials, participants continued to take the pharmacotherapy they had been randomised to after ECT treatment and were follow up at 3 months (65) or 6 months (63;64;66) to assess the impact of post ECT pharmacotherapy on relapse rates.

Efficacy: Depression Rating at end of course

Three trials provided dichotomous data on global improvement (59;60;62) but were analysed separately due to the different types of drugs in the comparison. Shiah (59) defined reponders as

those scoring less than 12 on the 29 item version of the HRSD, whereas Arfwidsson (60) and D'Elia (62) defined improvement according to clinical opinion.

In the Arfwidsson (60) trial there was a non significant trend for people treated with ECT plus chlorpromazine to be more likely to have improved than people treated with ECT and placebo (RR 1.13, 95% CI = 0.88 to 1.46; n = 52). Shiah (59) also found a non significant trend for people treated with pindol to have responded after 6 ECTs compared to those treated with placebo (RR = 10.8, 95% CI = 0.66 to 177.33, p = 0.1, n = 20). There was also no difference in the likelihood of being a responder in the D'Elia (62) trial when ECT was combined with either L-tryptophan and placebo (RR = 0.96, 95% CI = 0.83 to 1.12, p = 0.6 n = 61).

Three trials provided continuous data on completer samples for analysis and all used the HRSD; Mayur (58) and Lauritzen (66) used the 17 item version and Shiah (59) used the 29 item version. All trials were analysed separately due to the different drugs involved in the comparisons.

Lauritzen (66) found no statistically significant differences in scores on the Hamilton Depression scale between those treated with ECT plus paroxetine and those treated with ECT plus placebo at the end of the course of ECT. The weighted mean difference was 0.80 (95% CI = -11.54 to 13.4; n = 25)) in favour of paroxetine. The weighted mean difference between paroxetine plus ECT and imipramine plus ECT was –2.80 (95% CI = -5.63 to 0.03; n = 52) which is statistically significant difference at the 0.05 level in favour of imipramine.

Mayur (58) found no statistically significant differences in HRSD scores between ECT combined with antidepressants and ECT alone at 6 weeks follow up (WMD = 1.7, 95% CI = -5.54 to 8.94, p = .6 n = 22).

Shiah (59) found statistically significantly lower scores in participants treated with ECT plus pindol compared to participants treated with ECT plus placebo after 6 ECTs (WMD = -9.10, 95% CI = -16.08 to –2.12, p = 0.01, N = 15).

Adverse effects

Two studies explored adverse effects using the UKU scale of adverse drug reactions and the Columbia side effect checklist (58;66). Lauritzen et al.(66) found only minor differences between the treatment groups on the UKU scale. Paroxetine was associated with increased frequency of dreaming periods at night according to assessments after month 2, but not after 6 months. Imipramine was associated with complaints of constipation, although these only reached significance at month 3.

Mayer et al. (58)found no significant differences between groups in the mean number of side effects at the two or the four week stage of the acute phase as measured by the Columbia checklist. The antidepressant group had significantly higher mean ratings in the anticholinergic sub-scale of UKU. There were no significant differences in any other UKU sub-scale. No patient had significant arrhythmias. There was no intolerable anticholinergic side effect among patients with tricyclic drugs and ECT warranting discontinuation of the drug during the ECT course.

3.2.3.17 Continuation pharmacotherapy

As described above, in four of the trials that examined the effectiveness of adjunctive therapies, participants continued to take the pharmacotherapy they had been randomised to after ECT treatment and were follow up at 3 months (65) or 6 months (63;64;66) to assess the impact of post ECT pharmacotherapy on relapse rates. We identified a further three double blind trials (67-69) (69)

that compared different approaches to antidepressant treatment following successful treatment with ECT. In these trials, participants had to have responded to ECT and were then randomised to different pharmacotherapies. Grunhaus (68) defined responders as those with a HRSD (17 item version) score of less then or equal to 10 that was maintained for a week. Sackeim defined responders as those who had a decrease of at least 60% on the HRSD (17 item version) from baseline. In the trial by Coppen (67), participants had to have a score of at least 16 on the HRSD.

Coppen(67) compared lithium (plasma levels between 0.8 and 1.2 mmol/L) continuation therapy with placebo and Sackeim et al(69) compared continuation with noritryptaline (25mg) alone versus noritryptaline plus lithium (300mg) versus placebo. Grunhaus (68) compared fluoxetine (20mg/day_ combined with melatonin (5mg) with fluoxetine (20mg) and placebo. Coppen (67) did not describe the initial administration of ECT, Sackheim used either bilateral or unilateral ECT and Grunhaus (68) used unilateral ECT that was switched to bilateral if a response was not achieved within 6 treatments. In the Sackeim trial (69), ECT was administered 3 times weekly for a length of time determined on clinical grounds. In both Grunhaus (68) and Sackeim trials (69), seizure threshold was determined using either the method of limits (68) or by empirical titration (69) and in Grunhaus (68) the stimulus was delivered at 2.5 times threshold and 1.5 times threshold in Sackeim (69).

Efficacy: relapses

Three trials (64;68;69) provided usable data on relapses within 6 months for analysis and another trial (67) compared the mean number of weeks spent depressed during the following 6 months. The trials by Sackeim (69) and Imlah (64) both compared continuation imipramine with placebo and were analysed together, while the trials by Coppen (67) and Grunhaus (68)were analysed separately. Withdrawals were assigned to the worst outcome (relapse).

The analyses from the Sackeim (69) and Imlah (64) trials showed that people treated with TCA's were statistically significantly less likely to have a relapse in the 6 months following ECT compared to people treated with placebo (RR = 0.78, 95% CI = 0.61 to 0.99, p = 0.4, N = 158). In the Imlah trial (64), there was no statistically significant difference in the likelihood of relapsing between those treated with TCAs and MAOIs (RR = 0.80, 95% CI = 0.52 to 1.24, p = .3, N = 100). Similarly, in the Sackeim (69) trial, there was no statistically significant difference in the likelihood of experiencing a relapse between those treated with TCAs alone and those treated with TCAs combined with Lithium. A sensitivity analysis revealed no important effect of assuming that withdrawals had a relapse.

In the Grunhaus (68) trial, there was no statistically significant difference in the likelihood of experiencing a relapse in those treated with fluoxetine combined with melatonin compared with those treated with fluoxetine alone (RR = 0.67, 95% CI = 0.29 to 1.52), p = 0.3, N = 40).

Coppen (67) found a statistically significant different in the number of weeks spent depressed during the 6 months after ECT between those taking lithium and those taking placebo in favour of Lithium. The weighted mean difference was 0.90 (95% CI = 0.29 to 1.51), p = 0.004 .

Adverse events

Only one additional study reported data on adverse effects. Grunhaus (68) found no significant differences between fluoxetine-melatonin and fluoxetine-placebo group in cognitive functioning measured by the MMSE or sleep quality measured by PSQI.

3.2.4   MANIA

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.4.1   ECT vs Pharmacotherapy

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.4.2   ECT+Pharmacotherapy vs Pharmacotherapy alone

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.5   SCHIZOPHRENIA

Two systematic reviews evaluated the effectiveness of ECT in schizophrenia(52;53).   The results are reproduced here.

3.2.5.1   Real vs sham ECT

Efficacy immediately after course of ECT

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) identified twelve trials comparing ECT with sham ECT(100;111-121). They report that all but two(114;114) also used additional antipsychotic drugs (chlorpromazine, haloperidol, or trifluoperazine) and one (100) used additional chlorpromazine only for people given sham ECT, while participants allocated to ECT were given placebo. They also identified two trials(122;123) that compared ECT plus placebo with placebo. They analysed the trials together (562 participants, 294 treated with ECT)

The primary outcome measure of efficacy used by The Cochrane Schizophrenia Group ECT Review (52) was dichotomous data of clinical global improvement, classified as the number who had not improved in each treatment group as defined by the trialist.

The Cochrane Schizophrenia Group ECT Review (52) report that nine trials provided usable data for analysis. Their analysis indicated that treatment with ECT was significantly more likely to result in clinical global improvement, at the end of the course than with placebo/sham ECT (n=400, RR 0.77 fixed CI 0.6 to 0.9, NNT 7 CI 4 to 25) but data were heterogeneous (chi-square 13.46 df=8 p=0.097). Using a random effects model made little difference. One trial(121) was clearly statistically outlying. Removal of this good study resulted in a homogeneous result (n=380, 8 RCTs, RR fixed 0.83 CI 0.7 to 1.01). Removal of the study(115) containing people with treatment resistant illnesses, did decrease the heterogeneity (n=370, 8 RCTs, RR fixed 0.74 CI 0.6 to 0.9, chi-square 10.97 df=7 p=0.14).

The Cochrane Schizophrenia Group ECT Review (52) report one trial that (n=30)(119) showed the benefit of ECT on global improvement in the short to medium term was equivocal (RR 0.71 CI 0.3 to 1.8).

Other outcomes

The Cochrane Schizophrenia Group ECT Review (52) also explored a number of other outcomes relating symptoms and overall functioning including short and long term relapses, scores on the BPRS, and behaviour and social functioning. Their results (52) are summarised below

Relapses and discharge from hospital

The Cochrane Schizophrenia Group ECT Review (52) found that results from two trials(111;113) suggested that ECT resulted in less relapses in the short term than sham ECT (n=47, RR fixed 0.26 CI 0.03 to 2.2) and a greater likelihood of being discharged from hospital (n=98, RR fixed 0.59, CI 0.34 to 1.01)(120), though the data on which these outcomes are based is limited. There was no evidence that this early advantage for ECT is maintained over the medium to long term, as assessed by other measures of symptomatic improvement over a six-month and two year follow up period, though the trend favoured ECT. Again, however, the data on which these results are based were sparse.

Leaving the study early

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) found homogeneous data from the 14 trials comparing ECT with sham ECT did not suggest that people treated with ECT dropped out of treatment earlier than those treated with sham ECT (n=495, RR fixed 0.71 CI 0.33 to 1.52).

Efficacy at 6 months

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) report that no data was available for the effects of ECT versus sham ECT in the medium to long term.

Adverse events: cognitive functioning

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) found very limited data from one trial(124) on cognitive functioning. This indicated that visual memory declined after ECT compared with sham ECT (n=24, 1 RCT, WMD -14.0 CI -23 to -5); the results of verbal memory tests were equivocal.

Adverse effects: mortality

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) identified one trial(120)that reported on mortality over a three-year follow up. No deaths were discovered (n=98).

3.2.5.2 ECT vs antipsychotic drugs

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) analysed all trials that compared ECT with antipsychotics together and completed a separate subanalyses of ECT in combination with

antipsychotic drugs. ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED. For this analysis they included five(113;117;119;121;124) of the eight trials that contributed data on clinical global improvement in the comparison of ECT and sham ECT/placebo studied ECT plus antipsychotics against sham ECT plus antipsychotics. ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.5.3 ECT alone vs Pharmacotherapy

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.5.4 ECT in combination with antipsychotics vs pharmacotherapy, plus or minus sham ECT/placebo

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) included eight trials(100;120;122;123;125;126) (127) that compared ECT directly with antipsychotic drugs. They report that four(100;127) of these used chlorpromazine as the comparator drug, Small 1982 (123)compared ECT with thiothixine, May (120) with trifluoperazine and Naidoo 1956 (122) used reserpine, a drug that pre-dated chlorpromazine. Ungvari (126)compared ECT plus low dose haloperidol with very high dose haloperidol, while Janakiramiah (117) compared ECT in two groups of people treated with low dose and high dose chlorpromazine with two other groups given the two strengths of the drug without ECT.

The Cochrane Schizophrenia Group ECT Review (52) report that there was some variability in the doses of antipsychotics used in these trials, as well as in the trials of ECT versus sham ECT that used concurrent antipsychotics. Taylor (121) and Brandon (113) used doses of antipsychotics that were lower than those used in the other trials and lower than those currently recommended for acute phase treatment in people with schizophrenia.

The Cochrane Schizophrenia Group ECT Review report (52) that when ECT is directly compared with antipsychotic drug treatment, the pooled dichotomous results strongly favour the medication group (n=175, 3 RCTs, RR fixed 2.18 CI 1.3 to 3.6). Homogenous data also favoured antipsychotics drugs over ECT with regard to numbers discharged after treatment (n=135, 2 RCTs, RR fixed 1.98 CI 0.97 to 4). The Cochrane Schizophrenia Group ECT Review (52) identified very limited data indicated that people treated with ECT are less likely to relapse than those treated with antipsychotics (n=32, 1 RCT, RR fixed 0.33 CI 0.1 to 0.9). Continuous measures of global improvement from one trial favoured ECT in the short term though the results were equivocal in the long term.

To evaluate whether the addition of ECT is beneficial to those being treated with antipsychotic drugs, the Cochrane Schizophrenia Group ECT Review (52) analysed five of the eight trials that contributed data on clinical global improvement in the comparison of ECT and sham ECT/placebo studied ECT plus antipsychotics against sham ECT plus antipsychotics (see above). Their analysis of heterogeneous data from the first five studies results in a non-significant trend favouring the ECT and antipsychotic combination (n=165, RR random 0.74 CI 0.4 to 1.3).

Efficacy at 6 months

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) found only one study(120) reporting long term outcome of ECT compared with antipsychotic and the results were equivocal.

Discontinuations/leaving the study early
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) found no differences in numbers leaving the study early in the trials that compared ECT to treatment with antipsychotics (n=419, 7 RCTs, RR fixed 0.99 CI 0.8 to 1.3). They report that similar numbers remained in the trial by May(120)five years after treatment with ECT or antipsychotics though by this time 73% of the people in both arms were lost to follow up.

Adverse effects: mortality
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) found one patient who had not received ECT died within the three-year follow up by May (120) (n=149, 1 RCT, RR 0.63 CI 0.03 to 15).

Adverse affects: cognitive functioning

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.5.5 ECT vs Psychotherapy

The Cochrane Schizophrenia Group ECT Review (52) report limited data from one study comparing ECT alone with individual psychoanalytic psychotherapy alone(120) showing a consistent, though non-significant, trend favouring ECT (both short term and two years later) on several outcomes. When antipsychotics were added to psychoanalytic psychotherapy, however, a significant advantage of the drug group over ECT is seen in the short term (n=90, WMD -5.0 CI -0.54 to -9.46) with a continuing trend two years later.

3.2.5.6 Unilateral vs Bilateral ECT
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) identified three trials (128) (124) that compared unilateral with bilateral ECT.

Efficacy
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) found neither unilateral nor bilateral ECT was superior in terms of global improvement (n=78, 2 RCTs(124;128), RR not improved at end of course of ECT 0.79 CI 0.5 to 1.4).

They report that none of the 3 trials reported long term efficacy data

Discontinuations/leaving the study early

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: mortality

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Adverse events: cognitive functioning

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.5.6   Unilateral placement

The Cochrane Schizophrenia Group ECT Review (52) identified one trial (128) that compared the effect of dominant and non-dominant electrode placements on schizophrenic patients. Brief Psychiatric Rating Scale scores were available for pre- and post-treatment. The change in scores was greatest in the non-dominant group by more than two points. No deaths were reported in this trial.

3.2.5.7   Dose of ECT

The Cochrane Schizophrenia Group ECT Review (52) identified one trial(129) of 67 participants. In this study, people with treatment resistant schizophrenia were administered variable numbers of ECT at stimulus intensities just above the seizure threshold (T) twice the seizure threshold (2T), or four times threshold (4T). Endpoint average scores for global impression (GAF), mental state (BPRS), and cognitive function (MMSE) were not extractable.

Efficacy
The Cochrane Schizophrenia Group ECT Review (52) reported that the three stimulus doses did not differ in numbers improved at the end of the course of ECT (~50% in each group). In the subgroup of people given ECT who met criteria for remission (n=22; 34% of sample), those given ECT at twice the threshold required fewer doses of ECT to attain remission than those given threshold doses (WMD 6.1 CI 2.4 to 10). Similarly those given 4T required fewer treatments than those treated at threshold doses (WMD 9.4 CI 6.3 to 12.5). Treatment at 4T was non-significantly superior to treatment at 2T in reducing the number of treatments required to achieve remission (WMD 3.23 CI 0.8 to 5.6). Similarly, those treated at 2T and 4T required fewer days to attain remission than those given threshold stimuli, but those treated at 4T required on average fewer days of treatment than those given ECT at 2T (WMD 9.4 CI 2.1 to 16.8).

Leaving the study early
The Cochrane Schizophrenia Group ECT Review (52) report that only five out of 67 people left this study before completion, with no clear trend favouring any one group.

Adverse events: cognitive functioning
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.5.8 Frequency of administration

The Cochrane Schizophrenia Group ECT Review (52) identified only one study(130) comparing unilateral ECT given thrice a week versus five days a week that included only 10 participants. This trial had usable data for cognitive functioning only. Average endpoint scores on the MMSE indicated no significant advantage for the less frequent treatments, and not one developed clinical evidence of cognitive impairment.

3.2.5.9 Number of ECT treatments

The Cochrane Schizophrenia Group ECT Review (52) report limited data from one trial(131)showed a significant advantage for 20 treatments over 12 treatments in numbers globally improved at the end of the ECT course (n=43, RR fixed 2.53 CI 1.1 to 5.7). Not one had concurrent antipsychotics. **ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.**

3.2.5.10 Continuation ECT (CECT)

The Cochrane Schizophrenia Group ECT Review (52) identified one trial(132) that compared continuation ECT alone with antipsychotics, with continuation ECT added to antipsychotics, for people with treatment resistant schizophrenia.

Efficacy
The Cochrane Schizophrenia Group ECT Review (52) reported that when CECT was compared with antipsychotics at the end of the 6 month trial, results for overall functioning as measured on the GAF scale were equivocal (n=30, 1 RCT, MD -1.24 CI -6.4 to 3.9). However, when CECT was added to antipsychotic drugs, the combination was clearly superior to the use of antipsychotics alone (n=30, WMD 19.1 CI 9.7 to 28.5), or CECT alone (n=30, WMD -20.3 CI -11.5 to -29.1). Similarly, at six months, CECT was no better than treatment with antipsychotic drugs in reducing BPRS scores, though the combination of CECT and antipsychotics was superior to CECT alone (n=30, WMD 18.6 CI 8.6 to 27.6), or antipsychotics alone (n=30, WMD -19.8 CI -10.3 to 29.2).

Relapses
The Cochrane Schizophrenia Group ECT Review (52) report that equal numbers (14/15) of people on CECT alone or antipsychotics alone relapsed over the six month trial period. The addition of CECT to antipsychotic drugs, however, was clearly beneficial in reducing relapses compared with antipsychotics alone or CECT alone (n=30, RR fixed 0.43 CI 0.23 to 0.81, NNT 2 CI 1.5 to 2.5).

Leaving the study early
The Cochrane Schizophrenia Group ECT Review report (52) that few people (6/45) left the study early, with no clear pattern emerging to suggest a trend in favour of any of the three comparisons.

Adverse effects: mortality
No death occurred in this trial.

Adverse effects: cognitive functioning

The Cochrane Schizophrenia Group ECT Review reported (52) that no significant differences were seen in cognitive impairment scores between those treated for six months with CECT or antipsychotics. CECT added to antipsychotics resulted in non-significant trends favouring antipsychotic drugs used alone and the combination versus CECT used alone.

3.2.6 *SPECIFIC OUTCOMES NOT COVERED BY THE RANDOMISED EVIDENCE*

The randomised evidence reviewed by the UK ECT Group (53), The Cochrane Schizophrenia Group ECT Review (52) and the current authors did not address two key areas of outcome: (1) long term adverse effects of ECT including suicide, all cause mortality and brain damage and (2) consumer's views and experiences of ECT and whether these experiences influenced the outcomes of ECT. We therefore identified sources that reviewed the non-randomised evidence for these outcomes

3.2.6.1 Severe adverse events

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

All cause mortality

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Cause-specific mortality

SUICIDE

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Brain scanning and ECT

COMPUTERISED TOMOGRAPHY (CT)
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

MAGNETIC RESONANCE IMAGING (MRI)
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

EXPERIMENTAL INVESTIGATION OF ACUTE EFFECTS OF ECT ON BRAIN IMAGES
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

3.2.6.2 Patient acceptability and choice

We identified one good quality systematic review of non randomised evidence relating to users' views and experiences of ECT conducted by SURE at the Institute of Psychiatry(55).

Persistent memory loss

ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.

Information and consent

ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.

Felt compulsion

ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.

Perceived benefit

ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.

Interventions to improve patient knowledge about ECT

We identified two RCTs (70;86) that assessed the impact of a video on knowledge about ECT. A pooled analysis of knowledge scores in the two trials revealed significant statistical heterogeneity and results are therefore reported separately.

In the trial by Westreich (70), participants were psychiatric inpatients who had received in ECT in the past and the intervention was delivered during the consent procedure for a further treatment of ECT. One group was randomised to watch a video (n = 11) in addition to receiving a written consent form while the other group received the written consent form only (n = 7). Post consent knowledge was assessed using an instrument with no assessment of its psychometric properties. There was no statistically significant differences between the two groups in the mean number of items answered correctly (WMD = -.81; 95%CI = -1.86 to .24, p = .13, n = 18).

In the other trial (86), the intervention was delivered to a group of psychiatric inpatients who were not about to have ECT and it was not clear how many had personally experienced ECT in the past. One group was randomised to watch the video (n = 40) while the other group did not (n = 40). Knowledge was assessed before and after the video using an instrument with limited assessment of its psychometric properties. There was no statistically significant difference between the two groups in the mean knowledge score after watching (or not watching) the video (WMD = 1.28, 95% CI = -2.3 to 2.79, p = .1, n = 69).

3.2.7 *THE EFFICACY OF ECT IN SPECIFIC SUBGROUPS*

ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.

The Cochrane Schizophrenia Group ECT Review (52) report the following subgroup analyses in their review of ECT in schizophrenia:

3.2.7.1 Diagnostic criteria

When studies that used diagnostic criteria to diagnose schizophrenia were evaluated separately, a modest but non-significant advantage of ECT over sham ECT in the numbers improved at the end of the course of treatment was maintained from heterogeneous data from five trials (n=165, RR random 0.72 CI 0.4 to 1.3). A significant advantage for ECT for this outcome was more evident when the three trials that did not use operational definitions of schizophrenia(114;120;122) were separately analysed (n=205, RR fixed 0.74 CI 0.6 to 0.98). The degree of overlap in the confidence intervals of these comparisons, however, indicates that the rigour with which the diagnosis of schizophrenia was made did not significantly affect the outcome with ECT.

3.2.7.2 Duration of illness

The Cochrane Schizophrenia Group ECT Review (52) acknowledge that the power of their review to detect a differential response to ECT for those with a short duration of illness (less than two years) as opposed to those with chronic schizophrenia was very limited. Six trials restricted inclusion to participants with durations of illness less than two years(111;112;116;119;128;130). Two of these(111;112) provided the data used in the comparison of mental state assessment. This demonstrated a significant advantage for an ECT/antipsychotic drug combination over sham ECT and antipsychotics in both the rate of clinical improvement and the degree of improvement at the end of the course and in the short term. The participants in the trial by Sarkar (119) were acutely ill with onset of symptoms less than two months before commencement of treatment. This trial found the combination of ECT and antipsychotics provided no additional benefit to treatment with antipsychotics (and sham ECT) in terms of the numbers improved at the end of the course of ECT, or in the short to medium term. The trials by Brill (114) and Miller (118) included people with chronic schizophrenia. ECT alone did not result in greater clinical improvement than sham ECT by the end of treatment in these trials. Chanpattana (132) and Chanpattana (129)included participants who had been ill from between 3 and 30 years and duration of illness did not significantly alter outcome. The remainder of the selected trials were heterogeneous for illness duration, thus preventing their inclusion in the evaluation of the effect of this variable on ECT response.

3.2.7.3 Catatonia

The Cochrane Schizophrenia Group ECT Review (52) found that ECT did not have significant beneficial effects in people with chronic catatonic schizophrenia who comprised the participants in the trial by Miller (118) although this finding could equally be attributed to chronicity rather than the subtype of schizophrenia. However, they found that ECT did significantly result in clinical improvement by the end of the course for those people diagnosed to have paranoid schizophrenia in the study by Taylor (121) (n=20, RR fixed 0.74, CI 0.6 to 0.91). It was not possible to separate the influence of the duration of illness from the symptom profile of the participants in the selected trials to assess whether ECT has differential effects on positive or negative symptoms. The trials that favoured ECT(111;113;120;121;127;129;132) reported a beneficial effect on positive symptoms. These trials included participants with varying durations of illness. The trial by Chanpattana (132)

on people with treatment resistant schizophrenia provided data on symptom clusters on BPRS, in those responding to ECT prior to randomisation to continuation treatments. These data indicate significant reductions in positive and negative symptoms, as well as depressive and aggressive symptoms.

We also identified one review (78) of 270 treatment episodes in 178 cases treated for catatonia of whom 55 episodes involved the use of ECT and 5 involved the use of ECT in combination with another drug. In the 55 episodes, 47 (85%) resulted in a complete resolution of symptoms in response to ECT, 73/104 (70%) episodes involving treatment with benzodazepines (70%) had a complete resolution, 57/72 (79%) treatment episodes demonstrated a complete resolution in response to lorazepam and 3/40 (7.5%) had a complete response to antipsychotics.

Since this review (78) was published in 1995 we identified 2 prospective case series studies(79;80) reporting on 8 cases who failed to respond to lorazepam and who were subsequently treated with ECT with varying lengths of treatment. One study did not provide details of ECT electrode placement(79) while the other used bilateral ECT(80). Both studies used the Bush-Francis Catatonia Rating Scale to evaluate outcomes. In Bush et al, 4/5 cases offered ECT showed a remission of symptoms while in Malur 2/3 cases showed a full remission of symptoms. Not data on adverse effects were recorded.

3.2.7.4 Children and adolescents

We identified 2 systematic reviews of non randomised evidence(1;71) and one case control study(72) published since the review evaluating the efficacy of ECT in children and adolescents. The cases included in the 1999 review had the following diagnoses major depression (n = 52), psychotic depression (n = 35), manic depression (n = 28), schizophrenia (n = 41), schizoaffective disorder (n =6), catatonia (n = 29), neuroleptic malignant syndrome (4) and other disorders (29).

Information on prior treatment was available for 57 patients, 20 had previously received a course of both antipsychotic and antidepressants; 5 had received antidepressants alone and 15 had received antipsychotics alone. 118 cases had information on gender and 55 (47%) were female. Information on age provided in 98 cases and the mean was 15.4 and the youngest was 7 years old.

Information on electrode placement in the systematic review was provided for 61 cases, 23 (38%) had unilateral ECT; 29 (48%) had bilateral ECT and 9 (15%) had both. Information on the number of ECTs administered was available for 95 cases and the mean was 9.6 with a range of 1-23. 38 cases had received EEG monitoring and no studies mentioned the use of stimulus dosing.

Efficacy

The systematic review presents data comparing the relative efficacy of ECT immediately post ECT and at 6 months follow up in adolescents with different diagnoses (see table 3 below), although no information is given regarding whether this analysis is on an intention to treat basis. It is therefore difficult to draw reliable conclusions from the review although the results suggest ECT is more effective in adolescents with depression, mania and catatonia than in schizophrenia.

Table 3: Summary of efficacy of ECT in children and adolescents from Rey and Walters(1;71)

Diagnosis	Responders immediately post ECT(1)	Responders 6 months post ECT(71)

	n	N	%	n	N	%
Depression total	58	87	67	13	18	72
Major depression	33	52	64	11	14	79
Psychotic depression	25	35	71	2	4	50
Manic episode	22	28	79	8	10	80
Bipolar disorder	54	70	71	17	24	71
Schizophrenia	17	41	42	1	10	10
Schizoaffective disorder	4	6	67	-	-	-
Catatonia	21	29	72	1	2	50

In the case control study, all participants receiving ECT showed recovery immediately after ECT although 6 had relapsed by the time of follow up (mean 5.2 years).

Adverse events: mortality

The 1997 review by Rey and Walters(71) included all 396 cases in their analysis of adverse events. They identified no deaths in adolescents with depression, schizophrenia, catatonia or mania who received ECT. One death occurred in a case with NMS due to cardiac failure.

One person from the case control(72) study had committed suicide since receiving ECT.

Adverse events: post ECT seizures

The review(71) reported post ECT seizures in 15 cases.

Adverse effects: cognitive functioning

The review(71) found few studies that assessed cognitive functioning systematically as children were "too sick" to undergo psychometric testing. Those studies that did formally assess cognitive functioning after ECT were conducted in the 1940's and 50's where the techniques used to administer ECT are not generalisable to current practice and results were not reported systematically.

Cohen(72) found no significant differences on the MMSE, the Weschler Memory Scale and the California verbal Learning test at a mean 5.2 years follow up.

Adverse effects: subjective side effects

The review (71) found that overall, the most common complaint was headaches reported in 16/396 cases. Subjective memory loss was described by nine cases, manic symptoms in seven, disinhibition in two and hemifacial flushing in one. The review found that more recent studies reported a higher percentage of side effects. One study reported mild side effects in 7/9 (78%) of patients while another reported headaches in the entire group (n = 11). Another study included in the review reported mild, transient side effects following 28% of ECTs including headache (15%), confusion (5%), agitation (3%), hypomac symptoms (2%) subjective memory loss (2%) and vomitting (1%).

Cohen (72)found 6 patients who received ECT reported having subjective memory impairments.

3.2.7.5 Older people

There was no randomised evidence of the efficacy of ECT in people older than 65. In searching for non randomised evidence we limited our inclusion criteria to studies whose populations were all aged 65 or over. We identified 1 prospective(73;74) and 3 retrospective case control studies(75-77) that compared older people who had been treated with ECT and those who had not.

Improvement at end of course of ECT

Three studies provided information on symptom improvement following treatment with ECT compared to pharmacotherapy(74;75;77).

Rubin et al(73) conducted an analysis of covariance using the Geriatric Depression Scale (GDS) scores at discharge from hospital as the dependent variable and ECT, gender, psychotic symptoms, cognitive dysfunction and baseline GDS scores as co-variates and found that the presence of absence of ECT had a statistically significant effect on GDS scores (F = 3.56, df 6,65, p = .004, r2 = .25) and that the other covariates with the exception of baseline GDS scores, did not. A similar result was obtained for the scores Beck Depression Inventory (BDI) at discharge. Admitting and discharge scores on the GDS were not statistically significantly different between the two groups. When changes in scores on the GDS from baseline to discharge were analysed, those treated with ECT (mean 10.8 SD 7.5) showed a statistically significantly greater improvement (p = 0.002) than those who did not receive ECT (mean 4.2 SD 6). A similar result was also obtained for change in BDI scores. Finally, 36/46 (75%) of patients treated with ECT showed major improvement as rated by a physician in comparison with baseline levels compared to 23/55 (42%) who did not receive ECT.

Phillibert(77) compared physician rated global improvement at discharge between those who had received ECT and those who had not. In the ECT group 43/108 (40%) made complete recovery, 60/108 (56%) had improved and 5/108 (5%) had not improved. In the non ECT group, 16/84 (19%) had made a complete recovery, 56/84 (66%) had improved and 12/84 (14%) had not improved. The differences in the numbers who completely recovered were statistically significant (p < 0.05).

Manly(75) also compared physician rated outcome although it is not clear when this outcome was measured. In the ECT group, 30/39 (77%) had a good outcome compared to 13/39 (33%) in the pharmacotherapy group (p = 0.001). In the ECT group, 9/39 (23%) had a moderate outcome compared with 22/39 (56%) in the pharmacotherapy group (p = 0.003). None of the ECT group had a poor outcome while 4/39 in the pharmacotherapy group had a good outcome (p = 0.06).

However, physician or patient rated outcomes were not made blind to treatment in any of the studies and results must be interpreted with caution. In two studies some effort was made to control for confounding variables.

Relapses and rehospitalisation

One study (76) provided data on relapses and rehospitalisation. At follow up, 29/37 (78%) of ECT had a reoccurrence compared to 8/28 (29%) in non ECT group and17/37 (46%) in ECT group were rehospitalised compared to 4/28 (14%) in non ECT group. Following treatment, 19/37 (51%) in ECT group were in a nursing home compared to 13/28 (46%) in non ECT group. The statistical

significance of these differences was not reported.

Adverse effects: mortality and survival

Two studies(76) provided data on mortality and survival and reported conflicting results. Kroessler and Fogel(76) followed up 65 participants for 3 years, of whom 37 received had ECT. They found 27/37 (73%) in the ECT group were living at 1 year compared to 27/28 (96%) in the non ECT group and 8/37 (22%) were living at the end point of the study compared to 17/28 (61%) for the non ECT group. In terms of mortality, 10/37 (27%) in the ECT group were dead at 1 year compared to 1/28 (4%) in the non ECT group. At 3 years follow up, 18/37 (49%) in the ECT group were dead at 3 years compared to 9/27 (33%) in the non ECT group. The statistical significance of these differences were not reported. In contrast, Philibert(77) reported that those who received ECT at some point during their care in hospital were statistically significantly more likely to be alive at follow up than those who received pharmacotherapy with only 45/84 (53%) in non ECT group and 68/108 (63%) in ECT group alive at follow up (p<0.05).

However, in the Kroessler and Fogel study(76), participants who received ECT were medically and mentally more ill than those who did not receive ECT. In the Phillibert study(77), the ECT group were more likely to be judged as suffering from psychomotor retardation and to have had prior course of ECT than the pharmacotherapy group.

Adverse effects: other

Two studies(74;75) reported data on a range of adverse effects following ECT. Manly(75) compared a number and types of complications reported in case notes between those who had received ECT (n = 39) and those who had not (n = 39), including CVD, confusion/neurological, gastrointestinal, pulmonary and metabolic complications and falls. The pharmacotherapy group experienced statistically significantly more CVD (p = 0.013) and gastro intestinal complications (0.027) but there were no other differences between the two groups.

Rubin et al (74) reported MMSE scores at admission and discharge for groups who did or did not receive ECT but results were not on an intention to treat basis. The results indicate similar scores between the two groups.

3.2.7.6 The use of ECT in pregnancy

We identified one review(81) of case reports and case series of the use of ECT during pregnancy and three further studies(82-84) reporting on four cases published since the review. In two cases ECT was administered during the third trimester, in one case during the second trimester and in one case during the first trimester. The review identified reports of 300 cases of the use of ECT during pregnancy published between 1942 and 1991. Of these cases, 14 (4.7%) used ECT during the first trimester, in 36 (12%) cases the used of ECT began in the second trimester and 31 (10.3%) in the third. In the remaining 219 (73%) of cases, the timing of ECT with respect stage of pregnancy was not reported. In 44 cases (14.7%) unmodified ECT was used and 21 (7%) reported that modified ECT was used. In the remaining 235 cases (78%) the method of ECT was not reported. The number of ECTs per patient ranged from 1 to 35. In 89 cases, (30%) there was some follow up of offspring after birth with the length of follow up ranging from two months to 19 years.

Efficacy

The review(81) provides no information on the efficacy of ECT during pregnancy. In the three out of four of the cases(82;83) reported subsequently, improvement in symptoms as judged by clinical opinion was observed which were still evident at 1 year follow up. All gave birth to healthy babies. In the remaining case(84), no clinical improvement was observed and no information is provided regarding the health of the baby.

Adverse effects

The review provides details of the prevalence of complications when ECT was used during pregnancy. Complications were noted in 28 (9.3%) cases and these are summarised below:

FOETAL CARDIAC ARRHYTHMIA

Five cases reported transient self limiting disturbances in foetal cardiac rhythm including irregular foetal heart rate post ictally (3 cases), foetal bradycardia during the tonic phase (1 case) or post ictally and reduced variability of foetal heart rate (1 case). In all cases the babies were born healthy.

VAGINAL BLEEDING

Five cases of known or suspected vaginal bleeding related to ECT were reported. In one case the bleeding was the result of mild abruptio placentae but in the other 4 the sources of bleeding was not identified. No adverse effects on the babies were reported in any of these cases. In the subsequent studies(83), one case of vaginal bleeding was reported which then lead to miscarriage (see below).

UTERINE CONTRACTIONS

In two cases uterine contractions began shortly after ECT but neither resulted in premature labour. In the subsequent reports(82), in one case uterine contractions were reported following 2nd, 3rd and 6th ECT treatments. Contractions following 2nd and 6th were self limiting, those following third required tocolytic therapy. In another case, premature labour was reported on day 6 post ECT which subsided following hydration and ritodrine hydrochloride tocolytic therapy.

ABDOMINAL PAIN

Three cases of abdominal pain were reported following ECT and of unknown aetiology and healthy babies were born in all cases.

PREMATURE LABOUR

Four cases of premature labour were reported after women had ECT. In subsequent reports(82;84), premature labour was reported in a further two cases. In one case (82), premature labour occurred 6 days post ECT which subsided following hydration and ritodrine hydrochloride tocolytic therapy. In the other case (84), premature labour occurred immediately after first ECT and was treated successfully with indomethacin and ritodrine.

MISCARRIAGE

Five cases of miscarriage were reported. In subsequent reports, one case of miscarriage was reported(83).

STILL BIRTH AND NEONATAL DEATH

Three cases of still birth or neonatal death were reported.

RESPIRATORY DISTRESS

One case of the baby having difficulty breathing at birth.

TERATOGENICITY

Five cases on congenital anomalies in offspring of mother who received ECT have been reported. The anomalies included hypertelorism, optic atrophy, anencephaly, club foot and pulmonary cysts. Four cases of developmental delay or mental retardation have been reported.

3.2.8 CONCLUSIONS AND DISCUSSION

The conclusions and a discussion of the effectiveness review are considered in the discussion section

4   ECONOMIC ANALYSIS

4.1   INTRODUCTION

There were no sponsor submissions to NICE to be evaluated. Therefore, economic models were constructed based on the review of published evidence to estimate whether ECT is a cost-effective treatment for depression and schizophrenia. No economic models were constructed for mania or catatonia due to the lack of published data on these specific depression subgroups. An attempt to estimate the cost per quality adjusted life year has been made using published data on health state utilities.

4.1.1   SEARCH STRATEGY

Searches were undertaken to identify any economic studies relating to ECT as reported in Section 3. No papers were identified in the economics search. The economic search was then extended to relate to any treatment undertaken in treating depression, schizophrenia, mania and catatonia and any data relating to ECT that could be used in an economic model was identified.

4.1.2   OVERVIEW OF ECONOMIC LITERATURE REVIEW AND ECONOMIC EVIDENCE

There was no literature concerned with cost-effectiveness of ECT to review.
This has therefore resulted in the need to build an economic model based on the author's perceived view of how ECT is used within the UK, through dialogue with advisors on what are the comparator treatments to ECT.

4.2   ECONOMIC MODELLING OF ELECTRO-CONVULSIVE THERAPY (ECT) FOR DEPRESSIVE ILLNESS, SCHIZOPHRENIA, CATATONIA AND MANIA

4.2.1   MODELLING DEPRESSIVE ILLNESS

4.2.2 INTRODUCTION

It is commonplace today to see cost-effective modelling techniques regularly used in deciding whether a treatment is deemed to be superior or otherwise to any other. Although not widespread, cost-effective modelling has been used in the area of depression, comparing one pharmacological treatment over another. However, no one to our knowledge has attempted to evaluate the cost-effectiveness of ECT treatment.

Electro-convulsive therapy (ECT) and antidepressant therapy are the primary treatments available to patients suffering from depressive illness. For mild/moderate depression drug therapy is usually the first line of treatment within the UK. ECT is primarily only administered for patients suffering from severe depression and is usually administered on an inpatient basis. Even for patients suffering from severe depression and requiring hospitalisation, antidepressant therapy is still seen as the first line treatment, with ECT only being administered to patients deemed as resistant to drug therapy or who have previously been successfully treated with ECT(133). However, some people (Fink(6)) support the view that ECT could be seen as a first line treatment for severe depression.

4.2.3   METHODOLOGY

As the literature search had produced no economic analysis on ECT treatment within depression a mathematical model was constructed using data from the clinical effectives evidence review and other relevant studies to derive clinical outcomes for ECT and its comparators. Health utility scores were adapted from relevant studies and incorporated into the model. As ECT is primarily provided on an inpatient basis for severely depressed patients the analysis concentrated on comparing inpatient ECT treatment with other inpatient treatments for severe depression. Input from Dr Paul Birkett, Clinical Lecturer, Honorary Consultant Psychiatrist University of Sheffield was sought for help in constructing the model. The pharmacoeconomic model used for the cost-effective analysis is based on a decision tree model incorporating Monte Carlo simulation techniques that determine the movement through the states depending on the treatment the patient receives. The model attempts to evaluate the cost-effectiveness of ECT treatment for adult patients suffering from a major depressive disorder (MDD) who require hospitalisation. The model attributes quality of life utility scores to each health state and determines the movement through the states

The health states in question are:

State 1: Severely depressed receiving inpatient treatment
State 2: Receiving maintenance/continuation therapy following successful antidepressant therapy.
State 3: Receiving longer-term psychotherapy having failed to respond to acute antidepressant therapy
State 4: Failing to respond to maintenance therapy and returning to a moderately depressed state.

Figure 1 shows the structure of the decision model

The model uses a 12-month time horizon, as valid data for longer time periods are not readily available and hence discounting has not been undertaken. The time unit used in this model is a week. For each week throughout the year the model determines whether the patient is severely depressed and receiving acute treatment, has successfully completed acute treatment and is no longer severely depressed and receiving maintenance/continuation therapy, receiving longer-term psychotherapy, or is in a relapsed state following successful treatment. Each state has a quality of life utility score attached to it and incorporates a relevant cost.

As opinion differs as to whether ECT treatment should be undertaken as a final option when all else has failed or that ECT should be provided higher up the treatment hierarchy, the model has been constructed to allow the evaluation of cost-effectiveness of ECT provided as either a 1st line, 2nd Line or 3rd line (defined as treatment resistant) treatment.

ECT treatment can either be provided using a bilateral or unilateral placement of electrodes on the head. Bilateral ECT therapy is generally more efficacious but also results in more side effects. A randomised trial by Sackheim (134) found that unilateral ECT delivered with high stimulus intensity relative to seizure threshold is equivalent in efficacy to a criterion standard form of bilateral ECT yet retains important advantages with respect to cognitive adverse effects. Patients who fail to respond to unilateral ECT treatment are frequently moved to bilateral treatment. Therefore, the approach that has been taken in the model is to group ECT as one treatment and by varying the efficacy, outcomes and cost in the sensitivity analysis incorporate the different approaches used in providing ECT therapy. The main comparative treatments to ECT analysed here are the three main classes of antidepressants used within the UK, Tricyclic antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Norepinephrine Reuptake

Inhibitors (SNRIs). Augmentation of a pharmacological intervention with Lithium is also considered in the analysis.

Following successful therapy, patients are usually treated on maintenance/continuation therapy to help prevent relapse. Following successful ECT therapy, maintenance ECT therapy can also be provided, normally on an outpatient basis. The comparative treatments that are used for maintenance/continuation therapy that the model addresses are TCA, Lithium, ECT and no therapy.

Figure 1
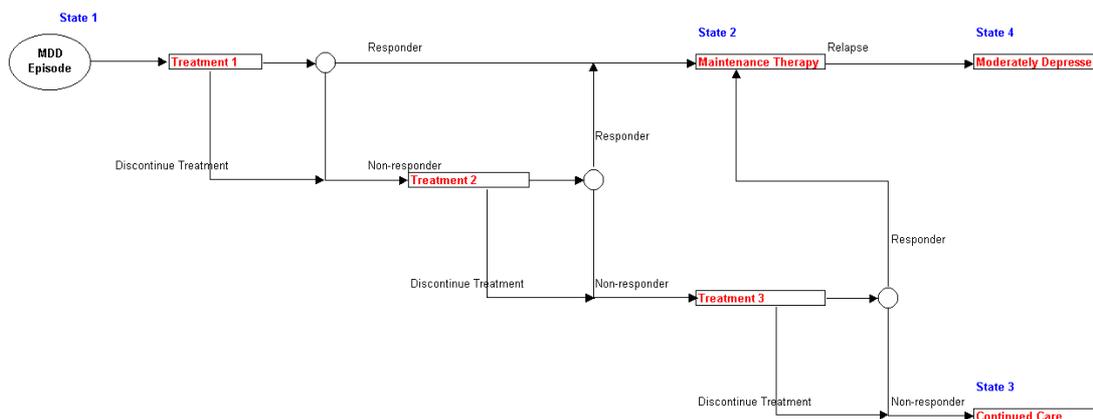
The model shows that three different phases of treatment are allowed before a final treatment of psychotherapy is used on non-responders. During each treatment episode there is a probability that the patient could have an adverse event/be deemed as not responding to the treatment and so move to the next treatment phase before completing the current treatment phase. After completion of a treatment phase there is a probability that the treatment is successful and the patient is discharged. Patients who are deemed not to have responded to treatment move to the next treatment phase. The probability of successful treatment and leaving the treatment early due to an adverse event/not responding to treatment is related to the type of treatment received and at which phase of the process the treatment was administered.

Following successful treatment the patients may be given continuation therapy to help prevent relapse.

Parameter values used in the model have been based on data from the clinical effectiveness element of the review for electro-convulsive therapy (ECT) for depressive illness, schizophrenia, catatonia and mania together with literature searches on economic evaluation of depression. Analysis of the literature produced different definitions of what constituted "successful treatment". For the model, therapeutic success has been quantified as a 50% decrease in the Hamilton Rating Scale for Depression (HAM-D) or other depression scoring system as used in other economic evaluations in depression. (135-137)

Caveat

The model has only used monotherapy pharmacological treatments as comparators to ECT although combination treatments are sometimes used in the treatment of depression. However, there is very little quality research on the success or otherwise of these treatments and combining drug therapies. The model makes no assumptions about previous depressive episodes and previous treatment received.

4.2.4 ASSUMPTIONS AND PROBABILITIES

4.2.4.1 Efficacy

A meta-analysis of ECT efficacy undertaken by Janicak (138) in 1985 showed that ECT was approximately 20% more effective than TCAs in the treatment of depressed patients. Although the analysis looked at studies from the 1960's, no comparative study has ever found a medication regimen to be more effective than ECT in the treatment of major depression (Sackeim, 1994) (139). A randomised controlled trial Prudic (140) in 1990 compared ECT treatment on patients who were defined as treatment resistant and those that were not. Prudic found that the success rate (>60% reduction on HAM-D score) was 86.2% and 50% for non treatment resistant and treatment resistant patients respectively. A randomised controlled trial by Folkerts (107) in 1997 comparing ECT with a SSRI in treatment resistant depression (defined as failing at least 2 previous antidepressant trials) showed that 71% of patients fulfilled the response criteria of a 50% decrease in the HAM-D score compared to 29% for the SSRI.

The clinical effectiveness review concludes that based on trials of ECT versus pharmacological treatment the people treated with ECT were 42% more likely to be defined as a responder than those treated with a TCA (RR 1.42 95% CI 1.17 to 1.72,p=0.0004). A meta-analysis of randomised trials by Einarson (141) found that the average successful treatment rate for TCA treatment was 58.2%. Applying a relative risk (RR) of 1.42 to this figure results in an expected success rate for ECT of 82.6%, which is very close to the success rate that Prudic (140) found for ECT treatment.

The model default assumption for clinical success for the treatment of major depressed patients undertaking ECT has been taken from the Prudic study, with 1st and 2nd line therapy for ECT having an 86.2% success rate and the 3rd line therapy rates having a 50% success rate.

The failure to complete treatment rates for ECT have been derived from Burke (142) which suggests that between 18% and 35% of ECT patients do not complete the treatment. For the model it has been assumed that these figures are the 95% confidence interval and the mean has been calculated as the mid-point.

The assumptions regarding the successful treatment rates and dropout/failure to complete treatment rates for the different classes of antidepressant drugs are taken from Doyle (143), Freeman (144) and Einarson (141) which are all in turn based on a meta-analysis of randomised trials comparing TCAs, SSRIs and SNRIs undertaken by Einarson (22). It has been assumed that each treatments failure to complete treatment rate is independent of the line of therapy. The efficacy rates for the pharmacological treatments are from trials undertaken within an inpatient setting on patients that had a HAM-D score ≥15 or a Montgomery Asberg Depression Rating Scale (MADRS) score ≥18. The measure of success is the percentage of patients that achieved a 50% reduction in their score. The failures to complete treatment rates are a combination of lack of efficacy and patients experiencing adverse events. For patients who are deemed as "treatment-resistant" lithium augmentation is seen as an effective pharmacological intervention. A meta-analysis by Bauer 1999(145) of placebo-controlled studies of lithium augmentation in treatment-resistant depression concluded that lithium augmentation, usually an SSRI with lithium, "should be the first choice treatment procedure for depressed patients who fail to respond to antidepressant monotherapy". The results of this paper have been used as the successful treatment rates for the 3rd line pharmacological therapy. The failure to complete treatment rates for this 3rd line therapy is assumed to be the same as those for a SSRI intervention.

The model assumes that when primary pharmacological treatment fails, a second line treatment would have the same success rate, as it would have been as the primary treatment. This assumption may not be true and it could be viewed as favouring the less effective treatments when the more effective treatments are given as backup. For a given population of depressed patients there would be a proportion that would respond well to treatment irrespective of whether that treatment was an SSRI or a TCA.

Consider the following simplified example in which we assume we have only two treatments, Treatment A with a success rate of 60% and Treatment B with a success rate of 50% and for simplicity both have a failure to complete treatment rate of zero. The overall successful treatment rate (after both treatments had been administered) could vary from 60% (success rate of treatment A) to 100% depending on the proportion of patients that would have responded to either treatment. Given that the sum of the success rates of treatment A and treatment B is greater than 100% implicitly there must be at least a 10% overlap in which patients would have responded to either treatment. If the overlap rate were only 10% then the overall treatment success following both treatments would be 100%. If the assumption is that the success rate is the same for the treatment regardless if it is given as a 1st or 2nd line therapy then with a population of 1000 people, 800 (80%) will be successfully treated after both treatments have been given (1000*0.6)+(1000-1000*0.6)*0.5.

Figure 2 shows a Venn diagram that represents the above example. The square box represents the population while the circles represent the success rates for treatments A & B. The area where the circles overlap represents the proportion of patients that would have responded to treatment A and also responded to treatment B. The area outside the circles represents the proportion of patients that would not respond to either treatment A nor B.

Figure 2
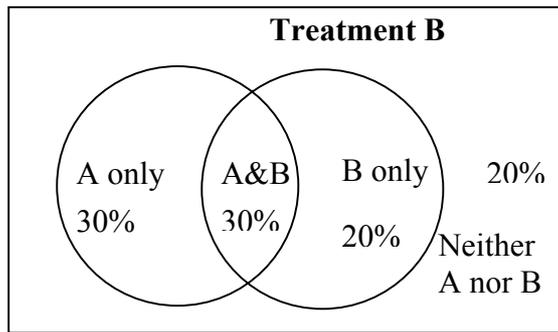
Successfully treated by Treatment A as a single therapy = A% =60%
Successfully treated by Treatment B as a single therapy = B% =50%
Successfully treated by A & B= X%   where $10\% \leq X \geq 50\%$
Successfully treated by A or B = A%+B%-X%

If we assumed that success rate for a 2nd line treatment is the same as for a 1st line treatment then in the above example X must equal 30% to give the overall success rate of both treatments as 80%. However, if the proportion of patients that would respond to both treatment A and B were 40% (X) then the overall success rate following both treatments would be 70%. This would be equivalent to assuming that the success rate for the 2nd line treatment B is half that if it was given as a 1st line treatment in the above example.

Therefore, the assumption in the model that treatments given as a 2nd line therapy have the same success rate as if it was given as a 1st line therapy has implications on the assumed proportion of patients that would have responded to either treatment.

Patients requiring 3rd line therapies are deemed as "treatment-resistant" and thus Lithium augmentation has been assumed as the preferred 3rd line pharmacological therapy.

Table 4 below summarises the models default values for clinical success for each treatment when used as a primary, 2nd or 3rd line therapy together with each treatments drop out rates.

Table 4: Clinical Success for Pharmacological and ECT Interventions in Major Depression

Treatment	Clinical Success	Mean	Lower 95% C.I.	Higher 95% C.I.
1st Line	TCA	58.2%	43.0%	73.5%
	SSRI	58.6%	48.2%	69.0%
	SNRI	62.3%	49.7%	74.9%
	ECT	82.6%	52.1%	98.8%
2nd Line	TCA	58.2%	43.0%	73.5%
	SSRI	58.6%	48.2%	69.0%
	SNRI	62.3%	49.7%	74.9%
	ECT	82.6%	52.1%	98.8%
3rd Line	Lithium Augmentation	27.0%	9.8%	44.2%
	ECT	50.0%	30.0%	70.0%

Table 5, below summarises the model default values for failure to complete treatment rates

Table 5: Failure to complete Treatment Rates

		95% Confidence Intervals	
Treatment	Average	LCI	UCI
TCA	29.9%	22.7%	37.1%
SSRI	25.8%	20.3%	31.3%
SNRI	20.7%	15.3%	26.1%
Lithium Augmentation	25.8%	20.3%	31.3%
ECT	26.5%	18.0%	35.0%

The final longer-term treatment of psychotherapy has been assumed to be an 8-week treatment in which patients are assumed to make a moderate improvement. More detailed assumptions about this treatment can be found in the quality of life and cost sections.

4.2.4.2 Duration of Treatment

Folkerts (107) found that ECT is considered as being quicker than pharmacological interventions in achieving a positive treatment response. Pharmacological treatments are usually continued for 6 weeks before the full effectiveness is achieved (146). Therefore, the model defaults for the duration of treatments within each phase of the model are:

6 weeks for pharmacological treatments, dropouts averaging 2 weeks of treatment
4 weeks for ECT treatment, dropouts averaging 1 week of treatment

4.2.4.3 Continuation/Maintenance Therapy

As relapse rates following successful treatment in major depression are high, up to 80% within a year (147) the common practice is to provide maintenance or continuation therapy to help prevent relapse. A study by Hirschfield (148) in 2001 showed that approximately one-third to half of all patients will relapse within a year following pharmacological therapy if medication is not continued. A randomised controlled trial by Sackheim (69) showed that a combination of Lithium and a TCA had the greatest effect in reducing the number of relapses following successful ECT therapy in medication resistant patients.

Continuation/Maintenance ECT (C/M-ECT) has been shown to be an effective treatment in preventing relapse in patients successfully treated with ECT. Swoboda (149) found that for patients with an affective disorder and schizoaffective disorder following successful ECT treatment 33% of patients who received C/M-ECT relapse (defined as being readmitted to hospital) while 67% patients who had not received C/M-ECT relapsed after 12 months. No studies were found that analysed maintenance ECT for non-schizoaffective patients therefore an assumption has been made that continuation ECT therapy is as effective for depressive patients as for patients with affective and schizoaffective disorders.

The Kaplan-Meier survival curves within these studies have been translated into the model to serve as default assumptions for relapse rates following successful depression treatment.

The model default values for relapse prevention for each type of maintenance/continuation therapy are shown in Table 6.

Table 6: Maintenance Therapy Relapse Assumptions

Following Pharmacological intervention	Maintenance Therapy	Relapse rate at 48th Week
	SSRI	13%
	No Therapy	46%
Following ECT Treatment	ECT	33%
	Lithium+TCA	32%
	TCA only	56%
	No Therapy	72%

Caveat

The survival rates from Sackheim 2001(69) were to 24 weeks only. In the model the survival times have been extended to 48 weeks. This assumption may not be valid. However, most relapses occur in the first 10 weeks of treatment.

4.2.4.4 Costs and Treatment Dosage

The cost for each pharmacological therapy has been extracted from the British National Formulary September 2001 42nd edition (BNF42) drug costs (274). The dosage of SSRIs and TCAs has been extracted form Hirschfield 1999 (150) study of clinical trials of SSRIs and TCAs conducted on severely depressed patients receiving inpatient treatment. The dosage for Venlafaxine (SNRI) was extracted from Einarson *et al(276)* pharmacoeconomic analysis of Venlafaxine.

The number of ECT treatments has been based on the UK practice of 2 treatments per week and with average treatment duration of 4 weeks; an average of 8 ECT treatments is given per therapy. The cost of ECT has been ascertained from Montgomery 1996 (151) which had a 1994 cost of £2,055 for 6 sessions. The estimated cost for ECT has been uplifted from 1994 to 2001 using the Hospital and Community Health Services inflation index from the Unit Cost for Health and Social Care (278). A pharmacoeconomic model by Hatziandreu (152) in 1994 looking at the maintenance treatment of recurrent depression listed the resource utilisation and costs of maintenance treatment for patients with major depression. This comprised of blood, thyroid and liver tests and visits to GP, psychiatrist and psychiatrist nurse. This resource pattern has been adopted for the maintenance resource use for this model with the costs uplifted to 2001.

Table 7 and Table 8 below summarise the default dosage and cost estimates for each acute treatment and maintenance therapy respectively.

Table 7: Cost of Acute Treatment for Major Depression

Acute Therapy	Drug	Dosage	Unit Cost	Hospital Costs	Cost/Week[#]
TCA	Clomipramine (non-proprietary)	150mg per day	£ 0.26	£171 per day	£ 1198.82
SSRI	Paroxetine (seroxat)	30mg per day	£ 1.04	£171 per day	£ 1204.27
SNRI	Venlafaxine (Efexor)	300mg per day	£ 2.86	£171 per day	£ 1216.99
ECT		2 sessions per week	£2,475 per 6 treats	£171 per day	£ 2022.00
Lithium-Augmentation	Lithium+SSRI	800mg Lith+30mg Paroxetine	£ 1.12	£171 per day	£ 1204.84

[#]Weekly cost equals 7 days at the inpatient costs per day of £171 plus 7 days at the unit treatment cost. ECT weekly dose is 2 treatments per week (£825).

Table 8: Cost of Continuation/Maintenance Therapy for Major Depression

Therapy	Drug	Dosage	Unit Cost	Hospital Costs	Cost/Week
TCA	Nortriptyline	50mg per day	£ 0.46	£ 260 /year	£ 5.24
SSRI	Nefazodone (Dutonin)	412mg per day	£ 0.62	£ 260 /year	£ 9.33
Lithium+TCA	Lithium+ Nortriptyline	600mg Lithium+ 50mg TCA /day	£ 0.54	£ 260 /year	£ 8.78
ECT		Average 2 per month	£2,475 per 6 treats	Included	£ 190.4

Hospital costs based on tests and visits to GP, psychiatrist and psychiatrist nurse as stated in Hatziandreu 1994 (152). ECT weekly cost based on 24 treatments per year divide by 52 weeks

Cost of continued care therapy (State 3) is based on the daily cost of maintaining a nursing home placement with psychiatric provision at a cost of £993 (278) per week for an average of 8 weeks. This cost averages out at £6,951 per patient who fails to respond to acute treatment.

For patients who relapse from maintenance therapy it has been assumed that they continue to take medication (equivalent of 20 mg of Fluoxetine per day) and an outpatient visit once per month (£131). This averages out at £32.05 per week.

Caveat

The costs for continued care therapy (State 3) and maintenance relapse (State 4) are not based on any research but are guesstimates made by the author. The model uses them as a cost offset in that the cost in treating patients in trying to prevent them reaching State 3 is offset by the savings in cost of not having to treat them in State 3. The higher the costs of treating patients in State 3 and State 4 the higher the potential savings will be.

4.2.4.5 Quality of Life Utility estimates

In order to estimate Quality of Life Years (QALYs), information is needed on the utility values that can be assigned to different health states. Utility values are defined along a 0-1 scale in which 1 represents perfect health while 0 represents death. Our sources for this information are primarily derived from two independent studies in which utility values for severe depression, moderate depression, mild depression and depression in remission were estimated (153;154). Other studies have derived utility values for depressed patients receiving different pharmacological treatments and their estimates have also been included in the modelling exercise where appropriate (137;152).

The utility values from the Bennett *et al.* 2000 study were elicited using the McSad health states classification system. Values were obtained from 105 patients who had experience at least one episode of major, unipolar depression in the previous two years but who were currently in remission. The health state descriptions referred to untreated depression. The mean utility values for each health state are as follows:

Mean   95% confidence interval

Severe depression	0.09	0.05 – 0.13
Moderate depression	0.32	0.29 – 0.34
Mild depression	0.59	0.55 – 0.62
Depression in remission	0.79	0.74 – 0.83

The utility values from the 1998 Revicki and Wood (153) study were elicited through the administration of standard gamble questions to 70 patients with major depressive disorder or dysthymia. Unlike the Bennett *et al* (154) study, the health state descriptions that were evaluated included descriptions of the side effects of drug treatment. Three different drugs were considered: nefazodone (SSRI), fluoxetine (SSRI) and imipramine (TCA). The mean utility values and standard deviations () for each health state are as follows:

Severe depression, untreated   0.30 (0.28)

Moderate depression
     nefazodone   0.63 (0.23)
     fluoxetine   0.63 (0.19)
     imipramine   0.55 (0.03)

Mild depression
     nefazodone   0.73 (0.21)
     fluoxetine   0.70 (0.20)
     imipramine   0.64 (0.20)

Depression remission
     nefazodone   0.83 (0.13)
     fluoxetine   0.80 (0.15)
     imipramine   0.72 (0.17)

The utility values from the Revicki study have very large standard deviations and thus reduce the confidence that there appears to be any significant difference both between the treatments within each level of severity of depression and also between the different severity levels. It was with this in mind that it was decided to use the Bennett *et al* utility values as the model defaults. Results of using the Revicki study utility values in the model are presented in the Sensitivity chapter.

In the model it is assumed that the patients admitted to hospital are classed as having severe depression. This would translate to a high HAM-D score, probably >20.

The default model parameter values for QALY utility estimates have been taken from Bennett *et al* and translate to the health states within the model and are shown in Table 9.

Table 9: QoL Utility assumptions

States	Definition	Mean Utility	95% confidence Intervals	
			LCL	UCL
State 1	Severely depressed receiving inpatient treatment	0.09	0.05	0.13
State 2	Responded to treatment, receiving maintenance therapy	0.79	0.74	0.83
State 3	Non-Responder	0.59	0.55	0.62
State 4	Relapsed from Maintenance therapy	0.32	0.29	0.34

Non-responders (State 3) receive intensive psychotherapy and on completion of treatment are deemed to have improved to a depression level similar to mild depression. Patients who relapse from maintenance therapy (State 4) do not revert to being severely depressed but require treatment to maintain a quality of life equivalent to moderate depression.

The default scenario is that the QALY utility scores are the same for all patients regardless of which treatment they have received. This assumption may not be true as side effects following treatments such as ECT may result in memory loss and hence a lower QALY utility score. Variation to the QALY assumptions is analysed in the sensitivity chapter.

Caveat

QALY utilities appear low for severely depressed, but reflect what a disabilitating illness depression can be. The assignment of QALYs to State 3 and State 4 is not based on any research but is the author's decision.

4.2.4.6 Suicide Risks

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED. A suicide rate of 0.85% per depressive episode is widely quoted and has been used in other economic evaluations (137). The assumption used in the model is that the longer the patient remains a non-responder the greater the chance of committing suicide. Once the patient has failed the 3rd line therapy they are assumed to receive psychotherapy (State 3). After this point is reached the chance of suicide is reduced to zero. Therefore the assumption is that patients who fail to respond to treatment or are not receiving treatment have a risk of suicide.

The 0.85% suicide rate per depressive episode has been converted into a weekly chance by assuming an arbitrary average duration per depressive episode (13 weeks). This assumption favours the treatments with higher efficacy and shorter duration to success. Sensitivity analysis performed on this variable is reported.

4.2.4.7 Summary of Scenarios

The following table (Table 10) shows a summary of the treatment therapies that have been combined to form the eight scenarios that have been analysed by the model.

Table 10: Summary of Model Scenarios

Strategy	**Scenario 1**	**Scenario 2**	SCENARIO 3	SCENARIO 4
1st Treatment	SNRI	ECT	ECT	SNRI
2nd Treatment	SSRI	SSRI	SSRI	ECT
3rd Treatment	Lithium Augmentation	Lithium Augmentation	Lithium Augmentation	Lithium Augmentation
Strategy	**Scenario 5**	**Scenario 6**	SCENARIO 7	SCENARIO 8
1st Treatment	ECT	SNRI	SNRI	SNRI
2nd Treatment	SSRI	SSRI	ECT	SSRI
3rd Treatment	Lithium Augmentation	ECT	Lithium Augmentation	ECT

4.2.5 RESULTS

A Monte-Carlo simulation approach was taken by varying the inputs for the successful treatment rates, the failure to complete therapy rates, the QoL utility values and the treatment costs. Values were selected randomly from within the 95% confidence interval, based on a normal distribution (Table 4 and Table 5).
For all costs, a pseudo-confidence interval was generated using a standard deviation of 15%. This generated a 60% range in cost that was considered suitable to reflect fluctuations in cost that may occur.

Combining the different treatments available into 1st, 2nd, and 3rd treatment therapies can generate a number of different treatment strategies. The following table (Table 11) shows the results from the 3000 Monte-Carlo simulation runs of different treatment strategies.

Table 11: Treatment Scenario Results

Strategy	**Scenario 1**	**Scenario 2**	SCENARIO 3	SCENARIO 4
1st Treatment	SNRI	ECT	ECT	SNRI
2nd Treatment	SSRI	SSRI	SSRI	ECT
3rd Treatment	Lithium Augmentation	Lithium Augmentation	Lithium Augmentation	Lithium Augmentation
Maintenance Therapy	SSRI following all 3 treatments.	SSRI following 2 treatments. Maintenance ECT following ECT	SSRI following 2 treatments. Lithium+TCA following ECT	SSRI following 2 treatments. Lithium+TCA following ECT
Average Total Cost / patient	£ 11,400 (£ 9,349 - £13,718)	£ 15,354 (£13,445 - £17,361)	£ 10,997 (£ 9,080 - £13,045)	£ 10,592 (£ 8,874 - £12,435)
QALYs	0.490 (0.453-0.526)	0.458 (0.422-0.493)	0.424 (0.389-0.459)	0.470 (0.431-0.508)
Average Cost per QALY	£ 23,246 (£18,682 - £28,487)	£ 33,530 (£28,886 - £38,646)	£ 25,923 (£21,165 - £31,324)	£ 22,557 (£18,381 - £27,279)
Strategy	**Scenario 5**	**Scenario 6**	SCENARIO 7	SCENARIO 8
1st Treatment	ECT	SNRI	SNRI	SNRI
2nd Treatment	SSRI	SSRI	ECT	SSRI
3rd Treatment	Lithium Augmentation	ECT	Lithium Augmentation	ECT
Maintenance Therapy	SSRI following all 3 treatments.	SSRI following 2 treatments. Lithium+TCA following ECT	SSRI following 2 treatments. Maintenance ECT following ECT	SSRI following 2 treatments. Maintenance ECT following ECT
Average Total Cost / patient	£ 11,022 (£ 9,016 - £13,069)	£ 13,939 (£ 11,161- £17,049)	£ 12,591 (£ 10,678- £14,497)	£ 14,548 (£ 11,680 - £17,717)
QALYs	0.539 (0.498-0.579)	0.489 (0.452-0.524)	0.486 (0.449-0.522)	0.494 (0.459-0.529)
Average Cost per QALY	£ 20,463 (£16,420 - £24,788)	£ 28,518 (£22,349 - £35,630)	£ 25,934 (£21,459 - £30,656)	£ 29,426 (£23,112 - £36,529)

Scenario 1 is the best pharmacological treatment in terms of cost per QALY. This is mainly due to both the SNRI success and SNRI failure to complete treatment rates, which have the highest and lowest mean value respectively. However, it should be noted that due to the range of values the parameters can take, the 95% confidence intervals do overlap (not shown).

Scenario 2, scenario 3 and scenario 5 represent the results of having ECT as the primary strategy. The only difference between the strategies is the maintenance therapy provided to the patients treated with ECT. Scenario 2 provides maintenance ECT while scenario 3 provides Lithium + TCA

combination as the maintenance therapy and scenario 5 assumes an SSRI is an effective maintenance treatment to prevent relapse.

Scenario 4 and scenario 7 show results of having ECT as the 2nd line therapy. The only difference between the strategies is the maintenance therapy provided to the patients treated with ECT. Scenario 4 has Lithium & TCA as the maintenance therapy for patients successfully treated with ECT while scenario 7 provides maintenance ECT.

Scenario 6 and scenario 8 show results of having ECT as the 3rd line therapy. Again the only difference between the strategies is the maintenance therapy provided to the patients treated with ECT. Scenario 6 has Lithium & TCA as the maintenance therapy for patients successfully treated with ECT while scenario 8 provides maintenance ECT.

Table 11 shows that no one scenario "dominates" all the others, in that the scenario that generates the highest number of QALYs is not also the cheapest. There are scenarios that "dominate" other scenarios however, it should be noted that the 95% confidence intervals of most of the results presented here do overlap. Scenario 5 has the overall lowest cost per QALY ratio at £20,463.The main reason for this is that scenario 5 assumes that the relapse rate for patients following acute ECT treatment is the same as for those following pharmacological treatment. Although no studies have been found that suggest a relapse rate of only 13% after 48 weeks can be achieved by providing an SSRI as the maintenance therapy following ECT treatment, scenario 5 shows that if a therapy could be introduced that maintains a high level of success following acute ECT treatment then ECT could be seen as the preferred primary treatment. However, to establish the preferred strategy from these scenarios we must look at the incremental net benefit.

It should be noted that the 95% confidence intervals of most of the costs and QALY results presented here do overlap.

4.2.5.1 Incremental net Benefit

The comparison of the cost-effectiveness of two or more treatments a consideration of the incremental net benefit of one treatment over the other is required. The net benefit of the treatments combines the health gain and financial consequences together. If the societal value of a QALY (the amount that one is prepared to pay to gain 1 QALY) is £30,000 then for a treatment that provides 2.0 QALYs for a cost of £15,000 the net benefit is:

$$£ 30,000*2.0 - £ 15,000 = £ 45,000$$

£45,000 is the net benefit of introducing this treatment.

The incremental net benefit of one treatment (T1) over another (T0) is represented by the formula:

$\lambda*(QALYsT1 - QALYsT0)-(CostT1 – CostT0)$

where λ is the societal value of a QALY

The traditional decision rule on whether to fund one treatment over another is when the Incremental Cost Effective Ratio (ICER) is better than the societal value of a QALY (λ).

The following paragraphs illustrate the process of undertaking an ICER analysis between the scenarios to help identify a preferred strategy. In this study only the average QALY and average

cost have been analysed and it has been assumed that even the worst scenario is cost-effective in the treatment of hospitalised severely depressed patients versus no treatment and the societal value of a QALY is £30,000(155).

Scenario 5 "dominates" all the other strategies except scenario 3 and scenario 4. Scenario 5 has an ICER of £217 versus scenario 3 and an ICER of £6,232 versus scenario 4. As both these ICERs are well below our £30,000 assumed threshold scenario 5 would be the preferred strategy.

If scenario 5 didn't exist as a realistic treatment then we need to establish which treatment would be our preferred strategy. Scenario 4 would be the preferred strategy. This is because scenario 4 dominates both scenario 2 and scenario 3 (greater QALYs for a lower cost) while scenario 6 has an ICER of £ 176,158 versus scenario 4, scenario 7 has an ICER of £124,938 versus scenario 4, scenario 8 has an ICER of £164,833 versus scenario 4 and scenario 1 has an ICER of £ 40,400 versus scenario 4. All these ICERs are outside our £30,000 assumed threshold although scenario 1 is fairly close.

If scenarios 4&5 didn't exist then scenario 1 would be the preferred strategy. This is because scenario 1 dominates all the remaining scenarios except scenario 3. Against scenario 3, scenario 1 has an ICER of £6,106, which is well inside our £30,000 assumed threshold.

If scenarios 4,5 & 1 didn't exist then scenario 7 would be the preferred strategy. This is because scenario 2 is dominated by scenario 7 while scenarios 6 & 8 have an ICER versus scenario 7 of £449,333 and £244,625 respectively, which are both outside our £30,000 assumed threshold. Scenario 7 versus scenario 3 has an ICER of £25,710, which is within our £30,000 assumed threshold.

If scenarios 4,5,1 & 7 didn't exist then scenario 3 would be the preferred strategy. This is because scenarios 2,6 & 8 have an ICER versus scenario 3 of £128,147, £45,262 and £50,729 respectively, which are all outside our £30,000 assumed threshold.

The order of the final three scenarios with respect to the ICER analysis would be scenario 6 followed by scenario 8 and finally scenario 2. This is due to scenarios 6&8 dominating scenario 2 while scenario 8 has an ICER of £121,800 versus scenario 6, which is outside the £30,000 assumed threshold.

The results of the analysis are summarised in Table 12 with the order of preferred strategies shown in the left-hand side column. Reading along each row provides the information on why that scenario is superior to the scenarios that follow it. The information in each cell states that either the following scenario is dominated or gives the ICER of the superior scenario (in bold) or gives the inferior strategy's ICER. For example scenario 7 precedes scenarios 3, as its ICER versus scenario 3 is less than £30,000 Scenario 7 precedes scenarios 6 and 8, as their ICERs versus scenario 7 are greater than the £30,000 threshold. Finally scenario 7 precedes scenario 2 in the hierarchy as it dominates scenario 2.

Table 12: Analysis of the Incremental Net Benefit

Preferred Strategy Order	.1.1 Scenario						
	4	1	7	3	6	8	2
5	**£ 6,232**	dominates	dominates	**£ 217**	dominates	dominates	dominates
4		£40,400	£124,938	dominates	£176,158	£164,833	dominates
1			dominates	**£ 6,106**	dominates	dominates	dominates
7				**£25,270**	£449,333	£244,625	dominates

			£45,262	£50,729	£128,147
3					
6				£121,800	dominates
8					dominates

Caveat

The ICER analyses have been undertaken on the mean cost and mean QALYs of each scenario only. Table 11 shows that there is a high level of overlap in the confidence intervals of the costs and QALYs.

The ICER analysis shown here has tried to identify a preferred strategy in the treatment of severely hospitalised depressed patients. As stated in the caveat the analysis has been performed on the mean costs and QALYs only. However, from the modelling exercise we have 3000 iterations of each scenario and hence 3000 possible ICERs. Thus by using these 3000 potential ICERs we can analyse the proportion of these that are less than the willingness to pay threshold value. Indeed by altering the threshold value we can see how the relative cost-effectiveness of one scenario compares to another through a range of threshold values. The resulting set of calculations can then be used to describe a 'cost effectiveness acceptability curve' or CEAC. The cost effectiveness acceptability curve plots the proportion of cost-effect pairs generated by the stochastic process that indicates when one scenario is optimal relative to the threshold. Figure 3 below shows the CEAC for all the given scenarios compared to scenario 3. Scenario 3 has been chosen as the comparator treatment as on average it is the scenario that generates the least number of QALYs.

Figure 3

Cost Effectiveness Acceptability Curves
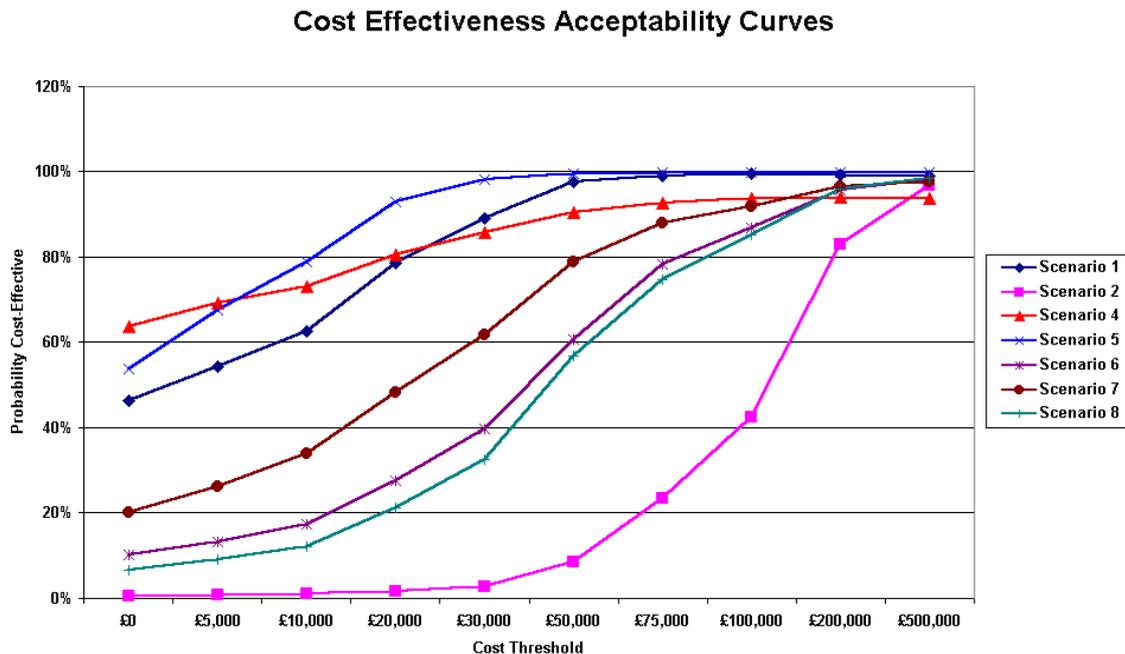
Figure 3 shows that as the willingness to pay for a gain in a QALY increases the probability that the scenarios are cost-effective compared to scenario 3 also increases. At the 30,000 threshold level Scenarios 1,4,5 and 7 have a higher than 50% probability of being a cost-effective intervention compared to scenario 3. Scenarios 1 and 4 are very close at this threshold value and although direct comparisons between these two treatments should not be made on this particular CEAC, nevertheless it does reflect the fact that the ICER between these two treatments is close to £30,000. Figure 4 below shows a direct CEAC between scenario 1, the pharmacological only scenario, and scenario 4, ECT provided as a 2nd line therapy.

Figure 4

Cost Effectiveness Acceptability Curve
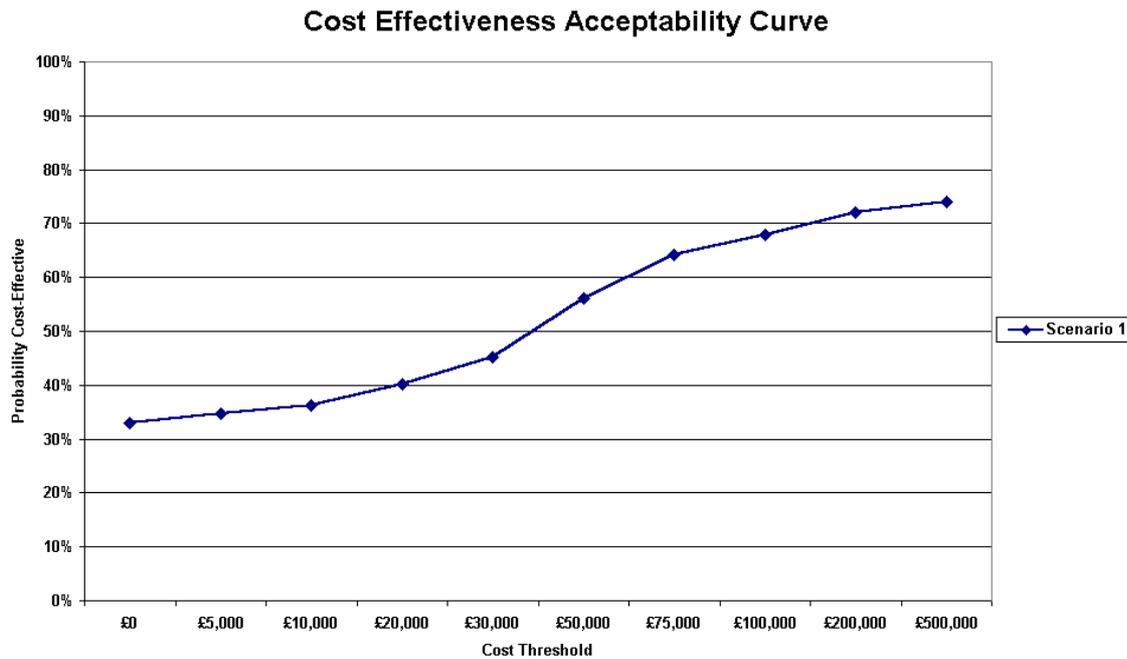
Figure 4 shows that at the £30,000 cost threshold there is a 46% probability that scenario 1 is cost effective compared to scenario 4. This highlights the uncertainty that scenario 4 would be the preferred strategy compared to scenario 1.

4.2.6 SENSITIVITY ANALYSIS

This section of the report attempts to evaluate the robustness of the model assumptions and show which variables require further information to enable us to be more confident about the results.

4.2.6.1 QALY Sensitivity analysis

The default quality of life utility scores used in the model were derived from the Bennett *at al* (154) study. However, another study by Revicki(153) presented significantly different QALY scores especially for severely depressed patients. The following table, Table 13 shows the results of the costs and QALYs for each scenario based on the Revicki QALY utility estimates following 3000 runs of the model. The costs should be very similar to the results in Table 11, as these assumptions have not altered. The QALYs gained by each scenario have decreased due to the reduction in QALY utility between severely depressed and the other depression levels. As with the scenarios based on the default assumptions there is a high degree of overlap between each scenarios cost and QALY results.

An ICER analysis between each of the eight scenarios using the Revicki QALY assumptions is shown in Table 14. Again it has been assumed that the willingness to pay for one QALY is £30,000.

Table 13: Scenario Results based on Revicki QALYs

Scenario	Cost (CI)	QALY (CI)	Cost/QALY
1	£ 11,325 (£ 9,204 - £ 13,647)	0.346 (0.311 – 0.381)	£ 32,709 (£ 26,076-£ 40,909)
2	£ 15,329 (£ 13,452 - £ 17,291)	0.297 (0.261 – 0.333)	£ 51,566 (£ 43,178-£ 61,684)
3	£ 11,205 (£ 9,206 - £ 13,405)	0.261 (0.225 – 0.296)	£ 40,893 (£ 31,854-£ 52,302)
4	£ 10,613 (£ 8,913 - £ 12,450)	0.314 (0.278 – 0.353)	£ 33,751 (£ 27,208-£ 41,558)
5	£ 10,965 (£ 8,978 - £ 13,065)	0.378 (0.338 – 0.419)	£ 28,998 (£ 22,888-£ 35,948)
6	£ 13,946 (£ 11,201 - £ 17,061)	0.341 (0.305 – 0.377)	£ 40,893 (£ 31,854-£ 52,302)
7	£ 12,597 (£ 10,751-£ 14,587)	0.329 (0.293 – 0.365)	£ 38,422 (£ 31,356-£ 46,498)
8	£ 14,550 (£ 11,736-£ 17,704)	0.344 (0.309 – 0.381)	£ 42,453 (£ 32,885-£ 53,850)

Table 14: ICER Analysis using scenarios based on Revicki QALYs

Preferred Strategy Order	.1.2 Scenario						
	1	4	7	3	6	8	2
5	dominates	£ 5,500	dominates	dominates	dominates	dominates	dominates
1		£22,250	dominates	£ 1,412	dominates	dominates	dominates
4			£132,267	dominates	£123,444	£131,233	dominates
7				£20,470	£112,417	£130,200	dominates
3					£34,263	£40,301	£114,556
6						£201,333	dominates
8							dominates

Table 14 shows that the preferred strategy order has changed with scenario 1 becoming the 2nd placed scenario at the expense of scenario 4 due to the ICER of scenario 1 over scenario 4 reducing to below the assumed £30,000 threshold.

4.2.6.2 Sensitivity of the cost of ECT

The assumption for the cost of ECT is based on a paper from 1994 and uplifted for inflation. The following analysis reports on the affect on the eight scenario results of decreasing the average cost of ECT by 25% while keeping all the other assumptions at their default values. Table 15 show the cost and QALYs for each of the eight scenarios. All the scenarios that have ECT therapy included as a treatment have reduced their average cost. This reduction in cost varies between the scenarios depending on whether ECT is prescribed as a 1st line therapy and whether maintenance ECT therapy is also given. The confidence intervals of the cost and QALYs still have a high level of overlap between the scenarios.

Table 15: Scenario Results based on reduction of 25% in ECT Cost

Scenario	Cost (CI)	QALY (CI)	Cost/QALY
1	£ 11,349 (£ 9,191 - £ 13,699)	0.490 (0.453 – 0.525)	£ 23,246 (£ 18,682-£ 28,487)
2	£ 12,747 (£ 11,104 - £ 14,552)	0.458 (0.424 – 0.492)	£ 27,822 (£ 23,861-£ 32,342)
3	£ 9,739 (£ 7,962 - £ 11,710)	0.421 (0.388 – 0.456)	£ 23,108 (£ 18,627-£ 28,142)
4	£ 9,871 (£ 8,184 - £ 11,684)	0.470 (0.432 – 0.509)	£ 21,016 (£ 16,990-£ 25,298)
5	£ 9,518 (£ 7,661 - £ 11,485)	0.538 (0.499 – 0.580)	£ 17,675 (£ 13,989-£ 21,817)
6	£ 13,568 (£ 10,876 - £ 16,760)	0.490 (0.453 – 0.526)	£ 27,704 (£ 21,808-£ 35,283)
7	£ 11,296 (£ 9,595-£ 13,063)	0.486 (0.449 – 0.523)	£ 23,253 (£ 19,318-£ 27,689)
8	£ 13,990 (£ 11,167-£ 17,169)	0.494 (0.457 – 0.531)	£ 28,341 (£ 22,256-£ 35,743)

Analysis of the incremental cost-effective ratios ICERs does not produce anything surprising. Table 16 shows that although the actual ICERs have changed from the scenarios with the default ECT costs the preferred strategy order remains the same with the exception of scenario 2 changing places with scenario 8.

Table16: ICER Analysis using scenarios based on a 25% reduction in ECT Cost

Preferred Strategy Order	.1.3 Scenario						
	4	1	7	3	6	2	8
5	dominates	dominates	dominates	dominates	dominates	dominates	dominates
4		£73,900	dominates	£ 1,412	dominates	dominates	dominates
1			£13,250	£23,333	dominates	dominates	£660,250
7				£23,954	£568,000	dominates	£336,750
3					£55,492	£81,293	£58,233
6						£25,656	£105,500
2							£34,528

Sensitivity analysis has also been performed on the cost assumptions of treatment for Continued Care (State 3) and cost of patients who fail to respond to maintenance therapy (State 4) but this had little difference in the overall scenario results.

Sensitivity analysis has also been performed on the model assumptions of suicide rates. The average duration per depressive episode has been altered to increase and decrease the suicide rate. These changes had little effect on the overall results.

4.2.7 CONCLUSIONS

The model described here is the first known attempt at modelling the cost-effectiveness of ECT treatment in a depressed population. Evidence from published trials has been used where possible but it is accepted that there are a few assumptions made that are based on the authors' limited knowledge of the area due to lack of available data. The model appears to suggest that ECT treatment provided as a 2nd line therapy as the pharmacological only treatment (scenario 1) has an ICER versus scenario 4 greater than the assumed £30,000 willingness to pay threshold (£40,400). However, this cannot be stated with any great confidence. The main drawbacks in terms of cost effectiveness of using ECT as a therapy are its higher costs and its higher rate of relapse than the pharmacological treatments. However, on the plus side there is evidence that ECT has a high success rate of treatment both for treatment resistant and non-treatment resistant patients alike.

The economic modelling does not demonstrate that any of the available scenarios have a clear economic benefit over the other available options. Specifically if ECT should be used whether it should be a 1st, 2nd, or 3rd line treatment. The main reason for this is that there is so much uncertainty around the values of the main parameters, efficacy, and failure to complete treatment and quality of life measures. This may be due in part to the lack of randomised controlled trials concerned with ECT treatment in the severely depressed. However, it could also be the nature of depressive illness. The clinical evidence produced by this review suggests ECT is an effective treatment for depression for some people while for others it could even have a detrimental effect.

4.2.8   FURTHER RESEARCH

The economic modelling undertaken for depression has shown a need for more robust information on the effectiveness of treatment for depressed patients. There is a lack of studies that have attempted to estimate the quality of life of patients suffering from depression and there are currently no studies that have tried to estimate the quality of life of depressed patients who have been treated with ECT.

Further economic analysis, such as Expected Value of Perfect Information (EVPI), may be useful in identifying key parameters where further research would reduce the uncertainty of the cost-effectiveness estimate.

4.3   MODELLING SCHIZOPHRENIA

4.3.1 INTRODUCTION

The main schizophrenic population for which ECT is indicated in the APA and RCP guidelines is patients resistant to pharmacotherapy(3;4). Therefore, the model structure has concentrated on the use of ECT in treatment resistant schizophrenia. All the economic analysis concentrated on pharmacological intervention in the treatment of schizophrenia. One cost-utility study was identified that analysed treatment resistant schizophrenia. This was a Canadian study by Oh 2001(5) that centred on treating treatment resistant schizophrenia with clozapine. This was a decision tree model that compared clozapine to a standard treatment with chlorpromazine or haloperidol. Oh obtained clinical outcomes from a random effect, single arm meta-analysis and utility weights were evaluated in a cohort of patients by using a standard gamble technique. As no cost effective study incorporating ECT in the treatment of schizophrenia existed and this was the only cost-utility study

that analysed treatment resistant schizophrenia it was decided to use the framework of Oh's model and incorporate an ECT arm to the decision tree by acquiring clinical outcomes and other information on ECT treatment in TRS from other appropriate studies. This would allow analysis of whether ECT was a cost-effective treatment compared to both clozapine, which is the standard treatment for patients who are treatment resistant, and chlorpromazine which is a neuroleptic which as stated by Thornly B *et al* (30) "remains the benchmark treatment for patients with schizophrenia".

4.3.2 METHODOLOGY

Ohs model is a cost-utility analysis that compares the costs and quality adjusted outcomes of hospitalised treatment resistant schizophrenia with moderate symptomatology. Costs and outcomes were evaluated over a time frame of one-year. Figure 5 shows the decision tree framework with the added treatment arm of ECT.

The clinical outcomes for the pharmacological interventions were obtained from the meta-analysis within Oh. This meta-analysis was conducted in 1995 and the search concentrated on all randomised controlled trials involving clozapine, haloperidol and chlorpromazine compared to placebo or active therapy in treatment resistant schizophrenia. For ECT the clinical success outcome was based on a study by Chanpattana 1999(132), which was the only study in the clinical effectiveness review that had both clinical outcomes and a treatment resistant population. Chanpattana states that research on the use of ECT in TRS has been characterised by a variety of methodological limitations. There have been no randomised single-blind studies contrasting the efficacy of ECT and neuroleptic treatment with neuroleptic treatment alone in TRS patients. However, he concludes that the literature does suggest that ECT is effective in the treatment of schizophrenia and that ECT with a neuroleptic appears to be more effective than either ECT alone or neuroleptic treatment alone. In his study Chanpattana concludes that combined ECT and neuroleptic therapy effectively reduced psychotic symptoms in 57% of treatment resistant patients with schizophrenia.

The failure to complete treatment rates for ECT have been derived from Burke (142) which suggests that between 18% and 35% of ECT patients do not complete the treatment. For the model it has been assumed that these figures are the 95% confidence interval and the mean has been calculated as the mid-point.

Figure 5 One-year Treatment Resistant Schizophrenic Treatment Model
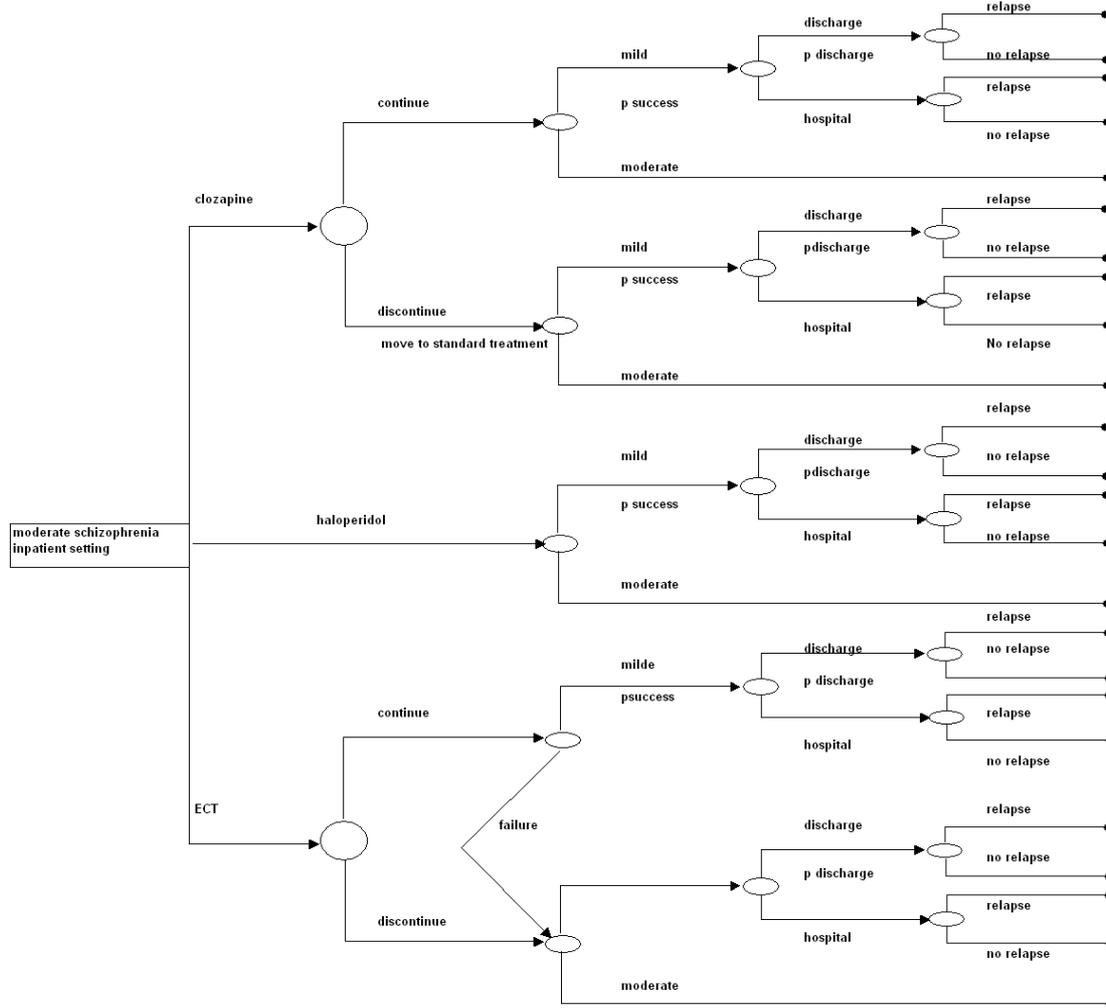
Table 17 below shows the event rates for the three comparators in the treatment of treatment resistant schizophrenia.

Table 17: Event Probabilities

Variable	Estimate
Success Rates	
Clozapine	0.65 (0.04 to 1.0)
ECT + neuroleptic	0.57 (0.48 to 0.67)
Clorpromazine/haloperidol	0.04 (0.01 to 0.08)
Discontinue rate	
Clozapine	0.05 (0.02 to 0.09)
ECT + neuroleptic	0.26 (0.18 to 0.35)
Clorpromazine/haloperidol	0.05 (0.02 to 0.09)
Discharge If symptoms improve	0.81 (0 to 1)
Relapse within one year	
Clozapine	0.16 (0 to 1) within 48 weeks
ECT + neuroleptic	0.40 within 10 weeks
Clorpromazine/haloperidol	0.16 (0 to 1) within 48 weeks

Quality of life utility scores in the Oh study were obtained through interviews with seven patients with schizophrenia using the Standard Gamble technique and a rating scale. Standardised patient profiles were developed based on the average Positive and Negative Symptoms Scale (PANSS) score in each of three PANSS subscales (positive, negative and general psychopathology) from clinical trials used in his meta-analysis. It should be noted that with only seven patients in the study the confidence intervals for each estimate of quality of life in each "state" overlap. Therefore, it could be argued that there is no difference in quality of life between the "states". The robustness of these assumptions is examined in the sensitivity analysis.

Caveat

The Oh paper was the only study that incorporated utility scores for patients suffering from treatment resistant schizophrenia. These patients were described as having only moderate symptomatology. These utility scores are higher than those used in the depression illness model and the variation between severities of illness is smaller. It is unknown to the author whether this is a real reflection of the difference in quality of life between patients with depression and schizophrenia.

The resultant utility scores from Oh are shown in Table 18.

Table 18: Quality of Life Utility Estimates

Description	Average Utility rating	95% CI
Moderate symptoms- hospitalised patient	0.82	0.76 to 0.88
Mild symptoms – community Clozapine Chlorpromazine	0.91 0.86	0.86 to 0.96 0.77 to 0.95
Mild symptoms-hospitalised patient Clozapine Chlorpromazine	0.87 0.84	0.82 to 0.92 0.75 to 0.93

It has been assumed that the utility scores of patients on clozapine are applicable to patients following ECT therapy. The robustness of all the assumptions used in the model has been investigated in the sensitivity chapter.

The following table, Table 19, shows the dosage and cost assumptions for each of the comparable treatments for TRS.

The pharmacological treatment costs have been taken from the BNF42 (274)and dosages from Oh. The ECT treatment cost is based on the Montgomery paper (151) which estimated the cost of ECT in 1994 was £2,055 for six sessions. The estimated cost for ECT has been uplifted from 1994 to 2001 using the Hospital and Community Health Services inflation index from the Unit Cost for Health and Social Care 2001(278). ECT treatment incorporates a neuroleptic, as combined ECT and neuroleptic treatment appears to be more effective than either ECT alone or neuroleptic alone (156) (157). The neuroleptic chosen is flupenthixol as this was the neuroleptic of choice in the Chanpattana study.

Table 19: Dosage and Cost Estimates

Treatment	Dose	Cost
Clozapine	500 mg/day	£ 9.78 per dose
Blood Test	1 per week (18 weeks) 1 per fortnight thereafter	£25 per test
ECT Acute Flupenthixol	Two sessions /week for 4 weeks 12 mg/day	£2,475 per 6 sessions £ 0.60 per dose
ECT maintenance Flupenthixol	One session fortnightly 12 mg/day	£ 212.12 per session £ 0.60 per dose
Haloperidol	20 mg/day	£ 0.43 per dose
Hospital Costs		£171 per day
At Home Costs		£275 per year

4.3.3 RESULTS

Table 20: shows the results from the decision model assuming the central values for each parameter.

Table 20: Cost-Effectiveness Results

Treatment	Average Cost	QALYs	Cost/QALY
Clozapine	£ 34,787	0.863	£ 40,319
ECT	£ 55,267	0.842	£ 65,672
Clorpromazine/haloperidol	£58,265	0.820	£ 71, 034

The results suggest that clozapine is the most cost-effect treatment for patients with TRS with a cost per QALY of £40,319. Clozapine dominates the other two strategies as it is both cheaper and generates more QALYs. ECT dominates the chlorpromazine /haloperidol strategy.

The results do show that ECT is cost-effective when compared to the "standard" treatment of chlorpromazine /haloperidol.

These results would suggest that ECT treatment of TRS is a cost-effective treatment for patients who do not respond to clozapine.

4.3.4 SENSITIVITY ANALYSIS

Sensitivity of the model assumptions have been examined by undertaking a threshold analysis to determine:

- The parameter values for which ECT would be the preferred strategy in the treatment of treatment resistant schizophrenia.

- The parameter values for which ECT would not be the least preferred strategy in the treatment of treatment resistant schizophrenia.

Threshold analysis showed that ECT could not become the cheapest treatment per QALY by just altering any one of the ECT variable assumptions. Even reducing the cost of ECT to £ 0.00 on its own would not alter the results sufficiently without also reducing the cost of inpatient care from £171 down to £42. Altering the quality of life utility estimates do not change the results sufficiently to make ECT treatment the preferred option even if we assumed that the QALYs of patients following ECT treatment are higher than that of clozapine. For ECT treatment to become the preferred treatment strategy then the one variable that could realistically vary sufficiently to change the results would be the probability of clozapine success. The central default value is 0.65, or 65%. If this value were to fall below 21% then ECT would become the preferred option, as the cost per QALY of clozapine would increase beyond £65,672. The 95% confidence intervals for the probability of clozapine success vary from 4% to 100% based on the meta-analysis undertaken by Oh (5) and so 21% lies within its limits.

Table 21: Threshold Analysis for Treatment-Resistant Schizophrenia

Variable	Baseline Value	Threshold Value	Direction of Effect

	(95% CI)		
Cost of clozapine	£ 9.78	£ 72.80	If the cost of clozapine rises above £72.80 then ECT would be the preferred strategy. This would require over a 7-fold increase in cost.
Adverse Events for clozapine	0.5 (0.02-0.09)	0.837	If the adverse events rate for Clozapine rises above 83.7% then ECT would be the preferred strategy. This is well above its 95% CI
Probability of clozapine success	0.65 (0.04-1.0)	0.21	If the probability of clozapine success falls below 21% then ECT would be the preferred strategy. The 95% CIs for this variable are large although 0.21 is towards the lower end.

4.3.5 CONCLUSIONS AND RECOMMENDATIONS

The cost-effective analysis using the model present here shows that ECT treatment for treatment resistant schizophrenia is cost-effective alternative compared to chlorpromazine /haloperidol treatment. However, the model showed that based on the assumptions clozapine is the preferred strategy of the three for the treatment of treatment resistant schizophrenia. These results would suggest that ECT treatment of treatment resistant schizophrenia is a cost-effective treatment for patients who do not respond well to clozapine.

5 IMPLICATIONS FOR OTHER PARTIES

These are discussed in secton 7.1

6 FACTORS RELEVANT TO THE NHS

ECT is an intervention that is has been used since the NHS was formed since 1948. Since 1985, the use of ECT in England has been decreasing (12). The estimated 65,930 administrations in 1999 compares with 105,466 reported administrations in 1990-91 and 137,940 in 1985 (12). Most administrations of ECT are provided on an inpatient basis. In contrast, current government policies such as the NSF on mental health (43) advise that the care and treatment of people with psychiatric illness should be provided in community settings.

7   DISCUSSION

7.1   SUMMARY OF MAIN RESULTS AND DISCUSSION

7.1.1   *DEPRESSIVE ILLNESS*

7.1.1.1   Real vs sham ECT

The efficacy of real vs sham ECT is unclear.

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Our analysis of limited data from one trial suggests that unilateral ECT is not more effective than sham ECT (RR = 1 (95% CI = 0.54 to 1.84)). Heterogeneous, dichotomous data from 3 trials suggested that real bilateral ECT was also not more effective than sham ECT (RR = 1.21 (95% CI = 0.61 to 2.40) and homogenous data from two trials also suggested that real bilateral ECT was not more effective than sham ECT (RR of 1.51 (95% CI = .94 to 2.49). However, removal of the trial (54)that included 1 real ECT treatment in the control group, leaving one trial (90), suggests that real bilateral ECT is more effective than sham ECT (RR = 1.98, 95% CI = 1.05 to 3.73).

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

These trials also varied in other aspects of the stimulus parameters used such as machine used to administer the stimulus, the number of ECT administered, the dosage and waveform of the stimulus. Most of the trials were conducted during the 1970's and 1980's, and in all cases, the methods used to administer ECT do not conform to current guidelines set by the RCP (18) or the APA (17). Five trials specified the machine used to deliver ECT and none are of the type recommended by current guidelines (17;18). Two used Duopulse MKIV machines (87;90), two used Ectron MkIV machines (91;92) and one used a Transycon machine (94). Of the 7 trials that specified the dosage and wave form of ECT, none used stimulus dosing but gave a fixed dose. Two used sine wave at 150v (54;90), 1 used sine wave but did not specify the dosage (87), 1 used chopped sine wave (dosage not specified) (89), 1 used 60% sine wave at 400v (92), 1 used a double sided unrectifed wave at 40J (94) and only 1 used brief pulse at 10J. (91). Seizure threshold has been shown to vary 40-fold between individuals, and to increase over the course of ECT (16). Thus it is possible that the dosages used in these trials were below the minimum necessary to induce a seizure of therapeutic efficacy, which is likely to explain why unilateral ECT was not found to be more effective than sham ECT (91). It has subsequently been shown that the stimulus dose needs to be increased to between 5-6 times higher than seizure threshold for unilateral ECT to equal bilateral ECT in efficacy (134).

7.1.1.2   ECT vs antidepressant pharmacotherapy

Overall, the data suggests that ECT is more effective than pharmacotherapy in the short term but the data on which this assertion is based is subject to important flaws. ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.
Our analysis of limited data from 1 trial suggests that ECT is more effective than SSRIs in the short term (RR = 3.41 95% CI = 1.39 to 7.11). Our pooled analysis of data from 6 trials suggest ECT was also more effective than TCAs in the short term (RR = 1.42, 95% CI = 1.17 to 1.72).

However, the results of our own analysis need to be interpreted with some degree of caution. Only 1 trial (107) compared right unilateral ECT with an SSRI (paroxetine). It was unclear how participants were randomised or whether the outcomes were rated blindly but in other respects the trial was of a reasonable quality. The criteria for a response was defined apriori (reduction of 50% on HRSD) and is similar to that used to define response in trials of antidepressants. Stimulus dosing was used and the dosage of paroxetine (50mg) was therapeutically adequate.

The quality of reporting in the 14 trials was largely inadequate and only 6 trials (43%) provided data for analysis. Thus a large amount of data was unusable with consequent loss of power in the analyses. Overall, the trials that did provide data for analysis were low quality. Only one (110) of the 6 trials that contributed data for analysis used blinded clinicians to rate outcomes, the remaining 5 (97-99;102;108) were either not blind or the blinding was not clear. This is of particular importance when the method of judging responders is considered. Two trials (102) defined responders using different criteria specified apriori based on scores from quantitative outcome measures while the remaining 4 were based on clinical opinion of improvement. Analysing the two trials based on a quantitative assessment of improvement separately results in no difference in the likelihood of being defined as a responder between ECT and TCAs (RR = 1.23, 95%CI = 0.90 to 1.67, p = 0.58, n = 38). However, the number of people included in this analysis is very small and thus there is a low power to detect any differences between ECT and TCAs. Analysis of heterogeneous data from the four trials based on clinical opinion gives a RR of 1.63 (95% CI = 1.21 to 2.20, p = 0.001, n = 346) in favour of ECT. This suggests that the method used to define responders may have an important influence on judgements of the efficacy of ECT relative to antidepressant medication.

A further issue that may influence the relative efficacy of ECT in comparison to pharmacotherapy is the dosage of drugs used. Of the 15 trials that compared ECT with either TCAs or SSRIs, one (107) used a fully adequate therapeutic dose of SSRI (50mg paroxetine) but none used a fully adequate dose up 300mg or equivalent of imipramine. Two trials used 250 mg(101;108), one used 220g(93)one used 200mg (98)and 4 used 150mg (97;100;102;105). One trial (96) used 100mg, the minimum therapeutic dose shown to be therapeutically effective while two trials used dosages below this levels (88;99). Two trials did not state the dosage of TCA used (95;110). Although most trials used a dosage of TCA above the minimally therapeutic dosage, none compared ECT to a dosage of TCAs that would normally be administered before ECT would be considered in the case of treatment resistance.

It is also important to consider the extent to which trial findings can be generalised to usual clinical practice in terms of the characteristics of participants included in the study and the ways in which the interventions are delivered. In 15 studies the dosage of the ECT stimulus was not specified and in 17 studies the type of ECT machine used was not specified. It is therefore very difficult to assess the extent to which the administration of ECT used in these trials is similar to current clinical practice. Of three trials that did specify the stimulus dose used, one (100) used a fixed dose of 110 V of alternating current while the other two used stimulus dosing at 2.5 times (107) or 60mc (97) above seizure threshold. One trial (107) used an ECT machine that is in line with current standards (17;18).

Trials examining the efficacy of ECT have been criticised for rarely reporting the number of people who were initially screened prior to inclusion in the trial, making it impossible to assess whether the results apply to all or only a fraction of patients seen in usual clinical practice (158). A recent study has shown the ECT was less effective in a "real life" heterogeneous patient sample compared to homogenous patient samples used in RCTs (159). None of the trials comparing ECT with pharmacotherapy provided any information regarding the number of people initially screened prior

to entry into the trial. Important parameters that influence current clinical decisions regarding the use of ECT are the severity of depression and treatment resistance. Treatment resistance has been shown to have an important impact on the efficacy of ECT. Those who received an adequate dose of antidepressant medication were less likely to respond to ECT than those who had not received an adequate dose of antidepressants (27).

In terms of inclusion criteria, 3 trials did not specify inclusion criteria and 8 did not use explicit diagnostic criteria to diagnoses or assess the severity of depression (88;93;95;98;99;104;108;109). Of these, 5 stated that the severity of depression was severe enough to indicate the use of ECT (88;99;104;108;109). The remaining 3 did not state the severity of depression (93;95;98). Six trials used explicit diagnostic criteria. Two used ICD-10 (9) criteria for major depression (105;107), one (106) used DSM-III (160), one used DSM-IV (97), one used the Feighner (161) criteria (96) and one (102) used the criteria specified by Klein (162). Four trials specified the severity of depression for inclusion according to the HRSD with two (97;100) specify scores on the 17 item HRSD of less than 17, one (106) specifying a score of less than 20 and one specifying scores of less than 22 on the 21 item HRSD (107).

Four trials explicitly included people who were treatment resistant to antidepressants (96;102;106;107). Two did not define treatment resistance (96;102).One (106) defined treatment resistance as failure to respond to a full course of TCAs defined as at least 150mg of anitryptaline for at least 4 weeks and failure of HRSD to drop by 40% or at least to fall by 20. The other (107) defined treatment resistance as failure to respond to at least two different antidepressants (including at least one TCA) at a dosage of at least 100g imipramine or equiv. and no improvement for a total period of 8 weeks. These definitions are both different, and are different to that proposed by Neirenberg defined as failure to respond to a trial of more than one antidepressant drug in a dose equivalent to 250-300mg of imipramine given for a duration of 6-8 weeks each (25). A further five trials (88;97;98;100;105) indicated that a certain percentage of participants in the trial had been treated with antidepressants during the current episode but did not state the dosages or type of drugs used, nor how long the drugs had been administered for. None of the trials included people for whom ECT was indicated as an emergency.

This suggests that in 9 trials included participants had severe depression and 4 included people who were treatment resistant, though none of the participants met the criteria for treatment resistance specified by Neirenberg (25). None of the trials reported data separately for older people.

Only one trial (100) out of 18 administered ECT on an outpatient basis, in the rest ECT was administered on an inpatient basis. This is similar to current clinical practice where the majority of ECTs are administered on an inpatient basis (2). In contrast, current government policies such as the NSF on mental health (43) advise that the care and treatment of people with psychiatric illness should be provided in community settings.

7.1.1.3 ECT vs rTMS

Limited data from one trial including 40 participants indicated that ECT is significantly more effective than rTMS in the short term. The weighted mean difference was 6.8 points (95%CI = 1.41 to12.19) on the HRSD in favour of ECT.

This treatment is not currently used in routine clinical practice.

7.1.1.4 Adjunctive therapy

Limited data suggests that the efficacy of ECT may be improved by the concomitant use of TCAs during ECT course (WMD = –2.80 (95% CI = -5.63 to 0.03; n = 52) and that the addition of pindol may increase the speed but not the extent of response to ECT.

None of the participants in the 9 trials included (58-66) were specifically selected because they had treatment resistant depression. However, many of the participants in the trials had previously been treated with pharmacotherapy for the current episode and had received ECT in the past. In the Shiah (59) trial (59) 9/35 (26%) were treatment resistant. In Arfiwidsson (60), 42% of participants had received antidepressant medication during the current episode, in D'Elia (62) 39% had received antidepressants and in Lauritzen (66) 90% in the paroxetine group and 76% in the placebo group had received antidepressants during the current episode. The inferior response of paroxetine treated patients in Group A and imipramine patient in group B in this trial (66) could reflect the fact that participants had failed to response to the same class of antidepressent medication prior to ECT. Mayur (58) reports that only half of the participants in either group had received an adequate drug trial prior to participation in the study. Depression was diagnosed according to standardised criteria in 3 trials with Lauritzen using DSM-IIIR (66) and Shiah (59) and Mayur (58) using DSM-IV. The remaining 6 trials did not use standardised criteria to diagnose depression in their inclusion criteria.

7.1.1.5 Continuation pharmacotherapy

Limited data suggests that continuation pharmacotherapy with tricyclic antidepressants reduces the risk of a relapses during the six months following a course of ECT (RR = 0.78, 95% CI = 0.61 to 0.99).

In only 3 of the 7 trials, participants were randomised following a positive response to ECT (67-69). In one trial (64) in which respondent were initially randomised to ECT + drug, all participants were said to have responded to treatment. In the remaining 3 there was not a uniformly positive response to ECT (63;65;66). Thus only 3 trials can be said to match current clinical practice.

7.1.1.6 Electrode placement
ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

7.1.1.7 Dosage and frequency of administration

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

7.1.2 SCHIZOPHRENIA

7.1.2.1 Real vs sham ECT

The Cochrane Schizophrenia Group ECT Review (52) found a non significant trend that real ECT was more effective than sham ECT. There was considerable heterogeneity in the trials and removal of one outlying trial resulted in no difference between the two interventions on their primary outcome measure of global improvement.

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

7.1.2.2 ECT vs antipsychotic drugs

The Cochrane Schizophrenia Group ECT Review (52) found that ECT alone was less effective than

antipsychotic medication. When ECT was added to antipsychotic medication, there was no clear difference between those treated with ECT in addition to antipsychotic and those treated with antipsychotics alone. Limited data from one trial suggest an advantage of ECT antipsychotic combination but only in relation to mental state as measured by the BPRS.

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

7.1.2.3 ECT vs Psychotherapy

The Cochrane Schizophrenia Group ECT Review (52) found limited evidence from one trial that ECT is more effective than psychotherapy both in the short and longer term, but adding medication to psychotherapy reverses the trend. There were no trials comparing ECT with family therapy or other psychosocial interventions.

7.1.2.4 Continuation ECT

The Cochrane Schizophrenia Group ECT Review (52;53) found limited evidence from one trial to support the efficacy of maintenance ECT added to antipsychotic medication in a population who were medication resistant but who had response to a course of ECT by strict criteria. They (52) suggest the number needed to treat to prevent a relapse in this population was 2 (95% CI 1.5 to 2.5).

7.1.2.5 Electrode placement

The Cochrane Schizophrenia Group ECT Review (52;53) found no evidence for a difference between unilateral and bilateral ECT. **ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.**

7.1.2.6 Dosage and frequency

The Cochrane Schizophrenia Group ECT Review (52) found limited data from one trial that suggested higher doses resulted in a faster rate of improvement but had no impact on the extent of improvement compared to lower doses. No conclusions can be drawn from the limited evidence on the impact of the frequency of ECT.

7.1.2.6 Generalisability of the trial evidence in schizophrenia

The Cochrane Schizophrenia Group ECT Review (52) reported that there was considerable variation between trials in the clinical and demographic profile of the participants, criteria used to establish the diagnosis of schizophrenia and methods of administering ECT. The APA (3) recommend that ECT could be used when patients are treatment resistant or in a catatonic state and when the psychotic symptoms in the current episode have an abrupt or recent onset (17). Similarly, the RCP (4) advise the practical usefulness of ECT in schizophrenia is limited to acute catatonic states, schizo-affective disorders, acute paranoid syndromes and people with type I schizophrenia who are either intolerant or unresponsive to a dose of a neuroleptic equivalent to 500mg of chlorpromazine daily.

The Cochrane Schizophrenia Group ECT Review (52) found that the diagnosis of schizophrenia was established using operationally defined criteria in 13 of the 24 trials while the remainder diagnosed the disorder by clinical consensus. Diagnostic criteria used included ICD 9, ICD 10, DSM III R, DSM IV, Feighners' criteria, Present State Examination and CATEGO Research Diagnostic Criteria, and the Chinese Medical Council Clinical Diagnostic Criteria. Ungvaria (126) classified participants based on the classification of Lenohard (163) into systematic and

unsystematic schizophrenia, a classification similar to the process and reactive or non-process classification of Langfeldt (164). Two trials included people with homogenous clinical subtypes of schizophrenia, namely chronic catatonic schizophrenia (118)and paranoid schizophrenia (121). One trial (119), included only young males with schizophreniform disorder (a diagnosis made when the symptoms of schizophrenia have been present for less than the six months required for the diagnosis of schizophrenia. If the symptoms persist beyond six months this provisional diagnosis is changed to schizophrenia). One trial (127) included 12 people with unspecified psychosis among the 40 participants in the trial. None of the included trials studied people with schizoaffective disorder which is one of the few indications for the which clinicians currently use of ECT according to a recent survey(19).

The Cochrane Schizophrenia Group ECT Review (52) found little homogeneity between trials in the duration of the disorder, with seven trials stipulating a duration of less than two years, of which Abrams (130) included participants with onset of disorder less than three months and Sarkar (119)less than two months. Seven trials included participants who had been ill for more than two years and two of these trials (118;122) included individuals with chronic illness hospitalised for ten years or more, with the former including some individuals who had been treated with leucotomy as well. Seven trials included people with varying duration of the disorder ranging from one month to thirty-two years. From the reports of Bagadia (100) and Baker (131), it was unclear how long the participants had been ill.

In terms of past history of response to antipsychotic drugs, Cochrane Schizophrenia Group ECT Review (52) found 3 trials (115;132;165) that specifically included people with treatment resistant schizophrenia that fulfilled modified criteria for treatment resistant schizophrenia (166). A further three trials (112;121;131), also included participants who had failed to respond to antipsychotics, though it is uncertain how many would meet stringent criteria for treatment resistance. They (52) also report that other trials included people with varying degrees of non-response to conventional antipsychotics, though Abrams (130), Sarkar (119) and possibly Ungvari (126) included people who were acutely ill and hence unlikely to be resistant to treatment. One trial (118) predominantly included people with catatonia and one included only people with paranoid schizophrenia (121).

The Cochrane Schizophrenia Group ECT Review (52) also found considerable variation in the quality of reporting of details of the administration of ECT. Thirteen of the trials described that ECT was modified, while seven appear to have used unmodified ECT. It was unclear from three reports whether ECT was modified.

The Cochrane Schizophrenia Group ECT Review (52) report that five trials (115;121;124;132;165) stated that brief pulse ECT devices were used; the remainder appear to have used sine wave machines. The Cochrane Schizophrenia Group ECT Review (52) found that the quality of reporting on electrode placement, frequency and duration of ECT administration was generally adequate in the selected trials. With the exception of five studies out of the 24, little information was provided in the trial reports on methods used to ensure adequacy of treatments with ECT. Two studies (132;165) titrated individual thresholds for participants and monitored seizures with the cuff method and EEG recordings. Two studies (115;124) used suprathreshold stimuli and monitored motor and electrical seizure activity as above. One study (119) used sine wave stimuli at settings sufficient to ensure seizures of 25 seconds or more, monitored by the cuff method.

Thus it appears that many of the included trials did not deliver ECT in line with currently recommended standards (17;18) with reference to the use of stimulus dosing and brief pulse stimuli.

7.1.3 MANIA

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

7.1.4 CATATONIA

Limited subgroup analyses by The Cochrane Schizophrenia Group ECT Review (52) suggested that ECT had no significant benefits in people with catatonia. Poor quality on randomised evidence does not allow firm conclusions to be drawn regarding the relative efficacy of ECT in this group.

7.1.5 CHILDREN AND ADOLESCENTS

The use of ECT in adolescents and children is rare. This explains, in part, why there are no randomised controlled trials of the efficacy of ECT in this group. The non randomised evidence did not allow firm conclusions to be made regarding the efficacy of ECT compared to other treatments. It suggests that ECT is probably more effective in adolescents or children with depression, mania or catatonia than in schizophrenia. Studies rarely studied or reported information on adverse events.

7.1.6 OLDER PEOPLE

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.
The trials that we reviewed comparing real vs sham ECT and ECT vs antidepressant medication did not report results separately for older people. Non randomised evidence of the use of ECT in older people with depression was subject to difficulties with confounding variables and information bias. It did not provide consistent results making it difficult to draw any firm conclusions regarding the efficacy of ECT in this group.

7.1.7 PREGNANCY

There was no randomised evidence relating to the use of ECT in during or after pregnancy. At the time of writing non randomised evidence provides limited information on the rate of complications only and suggests that the rate of complications tends to be relatively low at around 1%. However, these figures should be interpreted with caution due to the poor reporting in the studies.

7.1.8 LONG TERM EFFICACY OF ECT

ACADEMIC IN CONFIDENCE UK ECT GROUP AND SURE GROUP DATA REMOVED.

7.1.9 ADVERSE EVENTS: MORTALITY

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED. During the trials included by The Cochrane Schizophrenia Group ECT Review (52), none of the 779 participants died during or immediately after a course of ECT. **ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.**

7.1.10 ADVERSE EVENTS: COGNITIVE FUNCTIONING

The Cochrane Schizophrenia Group ECT Review (52) report finding limited evidence to suggest that greater cognitive impairment occur at the end of a course of ECT than for antipsychotics in people with schizophrenia.
ACADEMIC IN CONFIDENCE UK ECT GROUP AND SURE GROUP DATA REMOVED.

7.1.11 ADVERSE EFFECTS: BRAIN DAMAGE

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

7.1.12 PATIENT ACCEPTABILITY IN CHOICE

ACADEMIC IN CONFIDENCE UK ECT GROUP AND SURE GROUP DATA REMOVED.

7.1.13 PATIENT INFORMATION AND CONSENT

ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.

Limited data from one small (70) and one larger trial (86) suggested that patient information videos do not improve patient knowledge of ECT. In both trials, there were no statistically significant differences between the two groups in either the number of questions correctly answered (70) or mean knowledge score following the intervention. However, the results of these trial should be interpreted with caution. The sample size in one trial was small (70) and included no baseline assessment of knowledge and in both trials (70;86), the instrument used to measure knowledge had not been psychometrically tested.

7.2 ASSUMPTIONS, LIMITATIONS AND UNCERTAINTIES

7.2.1 COMPREHENSIVENESS OF THE REVIEW

Our own searches of the randomised evidence and those included in the 3 good systematic reviews were exhaustive and we are confident that we have not missed any important randomised controlled trials of ECT. We cannot be certain that our searches of the non-randomised literature were as comprehensive. We did not review evidence concerning the different types of anaesthesia or the impact of pretreatment with caffeine on the efficacy of ECT. We also did not examine adjunctive or post treatments that aimed to reduce the cognitive side effects of ECT.

7.3 NEED FOR FURTHER RESEARCH

7.3.1 CLINICAL EFFECTIVENESS

This review highlighted many areas where there is a need for further research into the effectiveness and cost effectiveness of ECT.

There is no good quality randomised evidence of the effectiveness of ECT in specific subgroups that are most likely to received ECT. These included older people, women with post partum exacerbations of depression or schizophrenia and people with catatonia. There is also a lack of good quality randomised evidence of the effectiveness of ECT in people with mania and people who are treatment resistant to pharmacotherapy in schizophrenia and depression.

There is currently no randomised evidence comparing ECT with, or in addition to newer antipsychotic drugs (for example clozapine and risperidone) and antidepressants (for example venlafaxine) that are currently used in clinical practice. Further work is needed in these areas. More research is also needed to compare ECT with repetitive transcranial magnetic resonance imagine, especially in people with schizophrenia.

More research is needed to examine the long term efficacy of ECT and the effectiveness of post ECT pharmacotherapy. In most trials, the after care of people receiving ECT was not randomised and people were rarely followed up beyond the course of ECT. Future work in the area requires longer follow up periods. Further work is also needed to develop ways of incorporating consumer's perspectives on the impact of ECT into future randomised controlled trials. Consideration should be given to the use of both quantitative and qualitative methods. The outcome measures used should reflect both clinical and consumer perspectives on the impact of ECT.

There is also little, good quality of quantitative evidence of the short term and longer term cognitive side effects of ECT. Cognitive functioning should be measured using well validated instruments and methods need to be developed that also reflect consumer's concerns regarding personal memory loss. These instruments should be incorporated into trial design at the outset and hypotheses set and results interpreted using a well developed theory or set of theories from cognitive psychology. Again, longer term follow up is needed as memory losses may only become apparent in the longer term. There is also a need for longer term follow within RCTs to explore the impact of RCT on suicide and all cause mortality.

Further work is needed to examine the information needs of people deciding whether to accept ECT and how their decision making can be facilitated. The influence of these choices on the perceived efficacy of ECT also requires further exploration.

Despite over 50 years of research ECT, there is still no agreement on the mechanism of action of ECT. More research is needed in this area.

Finally, the quality of reporting of trials in this area would be vastly improved by strict adherence to the CONSORT recommendations.

7.3.2   COST EFFECTIVENESS

Further economic analysis, such as Expected Value of Perfect Information (EVPI), may be able to identify areas in which research would be best targeted by identifying parameters where reducing the level of uncertainty would have the most effect in helping make the decision on whether ECT is a cost-effective treatment.

8. CONCULSIONS

8.1   CLINICAL EFFECTIVESS

In people with depression, real ECT is probably more effective than sham ECT but stimulus parameters have an important influence on efficacy; low dose unilateral ECT is no more effective than sham ECT. ECT is probably more effective than pharmacotherapy in the short term but the evidence on which this assertion is based was of variable quality and inadequate doses of pharmacotherapy were used. Limited evidence suggests ECT is more effective than rTMS. Limited data suggests that continuation pharmacotherapy with TCAs in people who have responded to ECT reduces the rate of relapses. **ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.**   There was much less evidence regarding the efficacy of ECT in schizophrenia and no randomised evidence of the effectiveness of ECT in catatonia. ECT either combined with antipsychotic medication or as a monotherapy is not more effective than antipsychotic medication in people with schizophrenia. The evidence did not allow any firm conclusions to be drawn regarding the efficacy of ECT in people with catatonia, older people, younger people and women with psychiatric illness. **ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.**

8.2 COST EFFECTIVENESS

8.2.1 DEPRESSION

No previous analysis has been undertaken on the cost-effectiveness of ECT treatment in depression. The model described here has attempted to reflect the possible treatment protocols that could be employed in treating severely depressed patients who require hospitalisation through devising different treatment scenarios. Different treatment scenarios, which are based on ECT being provided as a 1st, 2nd, or 3rd line therapy, have been compared to a pharmacological only therapy.

The results from the model are not conclusive as to the cost-effectiveness of ECT. Based on the default assumptions the economic modelling results suggest that ECT provided as a 2nd line therapy is the preferred treatment strategy. However, the confidence intervals around the results are large primarily due to the large confidence intervals around the inputs due to lack of quality clinical evidence. The clinical evidence seems to suggest that ECT is an effective treatment although there is no evidence of ongoing antidepressant action beyond the duration of the course of treatment itself. ECT treatment needs to be followed by pharmacological treatment or maintenance ECT in order to maintain improvement and the limited evidence seems to suggest that the relapse rates of patients following ECT even with maintenance therapy are higher than the relapse rates of patients who have received pharmacological therapy. This is reflected in the model, which suggests if an effective treatment that reduces the relapse of patients following ECT can be found, ECT treatment would become a cost-effective treatment in the hospitalised severely depressed.

8.2.2 SCHIZOPHRENIA

No previous analysis has been undertaken on the cost-effectiveness of ECT treatment in schizophrenia. The economic model constructed for schizophrenia was based on a pharmacological model constructed by Oh (5) which was the only cost-utility study identified in the treatment of

schizophrenia. This model analysed the cost-effectiveness of clozapine compared to haloperidol/chlorpromazine treatment in treatment resistant schizophrenia. The results of the adapted model including ECT suggest that clozapine is a cost-effective treatment compared to ECT. However, for patients who fail to respond to clozapine ECT treatment would be the preferred therapy to the comparative treatment of haloperidol/chlorpromazine. Although it should be stated that the clinical evidence underpinning the ECT assumptions in the model is weak.

Appendix 1 **Electronic Bibliographic Databases Searched**

1.   Biological Abstracts
2.   Cinahl
3.   Cochrane Controlled Trials Register (CCTR)
4.   Cochrane Database of Systematic Reviews (CDSR)
5.   Cochrane Schizophrenia Group Trials Register
6.   Database of Abstracts of Reviews of Effectiveness (DARE)
7.   EBM Reviews
8.   Embase
9.   Health Management Information Consortium (HMIC)
10.   Health Technology Assessment (HTA) Database
11.   Medline
12.   NHS Economic Evaluations Database (NHS EED)
13.   OHE Health Economic Evaluations Database (HEED)
14.   PreMedline
15.   PsycINFO
16.   Science Citation Index
17.   Social Sciences Citation Index

<u>Appendix 2</u> Other Sources Consulted

1. Agency for Healthcare Research and Quality (AHRQ)
2. AltaVista
3. ARIF (Aggressive Research Intelligence Facility)
4. Association of British Health Care Industries
5. Bandolier
6. Canadian Co-ordinating Centre for Health Technology Assessment (CCOHTA)
7. CenterWatch Trials Register
8. Centre for Health Economics, University of York
9. Copernic
10. Current Controlled Trials (CCT)
11. Current Research in Britain (CRiB)
12. Dantec Electronics Ltd.
13. Department of Health
14. Ectron Ltd.
15. eGuidelines
16. Health Evidence Bulletins, Wales
17. INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
18. Index to Theses
19. Mental Health Foundation
20. MIND
21. MRC (Medical Research Council) Funded Projects Database
22. National Assembly for Wales
23. National Guideline Clearinghouse (NGC)
24. National Research Register (NRR)
25. NCCHTA (National Co-ordinating Centre for Health Technology Assessment)
26. Organising Medical Networked Information (OMNI)
27. Research Findings Register (ReFeR)
28. Royal College of Anaesthetists
29. Royal College of Nursing
30. Royal College of Psychiatrists
31. ScHARR Library Catalogue
32. Schizophrenia Association of Great Britain
33. Scottish InterCollegiate Guideline Network (SIGN)
34. The Association of Anaesthetists of Great Britain and Ireland
35. The Mental Health Act Commission
36. Trent Working Group on Acute Purchasing
37. Turning Research into Practice (TRIP) Database
38. Wessex DEC (Development and Evaluation Committee) Reports
39. West Midlands DES (Development and Evaluation Services) Reports
40. World Health Organisation (WHO)

Appendix 3 Search Strategies Used in the Major Electronic Bibliographic Databases

Biological Abstracts
1985-2001
SilverPlatter WebSPIRS
Search undertaken December 2001

#1   electroconvulsive therap* or electro convulsive therap* or electroshock therap* or electro shock therap* or ect

#2   depression or schizophreni* or catatoni* or bipolar disorder* or mania or manic or mood disorder* or mental disorder*

#3   #1 and #2

#1   ELECTROCONVULSIVE-THERAPY*:ME
#2   ELECTRIC-STIMULATION*:ME
#3   ELECTRIC-STIMULATION-THERAPY*:ME
#4   ((ELECTRO NEXT CONVULSIVE) NEXT THERAP*)
#5   (ELECTROCONVULSIVE THERAP*)
#6   (ELECTRO NEXT SHOCK) NEXT THERAP*)
#7   (ELECTROSHOCK NEXT THERAP*)
#8   (ELECTRIC* NEXT STIMULATION)
#9   #1 OR '2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10   DEPRESSION*:ME
#11   SCHIZOPHRENIA*:ME
#12   SCHIZOPHRENI*
#13   CATATONIA*:ME
#14   CATATONI*
#15   BIPOLAR-DISORDER*:ME
#16   (MANIA OR MANIC)
#17   MOOD-DISORDERS*:ME
#18   ADJUSTMENT-DISORDERS*:ME
#19   PSYCHOTIC-DISORDERS*:ME
#20   AFFECTIVE-SYMPTOMS*:ME
#21   MENTAL-DISORDERS:ME
#22   #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR
        #20 OR #21
#23   #9 AND #22

Cinahl
1982-2001
Ovid Biomed
Search undertaken December 2001

1   electroconvulsive therapy/
2   electro convulsive therap$.tw
3   electroconvulsive therap$.tw
4   electro shock therap$.tw
5   electroshock therap$.tw
6   ect.tw
7   or/1-6
8   exp depression/
9   exp schizohrenia/
10   schizophreni$.tw
11   catatoni$.tw
12   exp affective disorders, psychotic/
13   (mania or manic).tw
14   exp affective disorders/
15   exp adjustment disorders/
16   exp mental disorders/
17   or/8-16
18   7 and 17

CRD Databases (NHS DARE, EED, HTA)
CRD Web site - complete databases
Search undertaken December 2001

(electro convulsive therapy or electroconvulsive therapy or electroshock therapy or electro shock therapy or electrical stimulation)/All fields AND (depression or schizophrenia or catatonia or bipolar disorder or mania or manic or mood disorders or mental disorders)/All fields

Embase
1980-2001
SilverPlatter WebSPIRS
Search undertaken December 2001

#1   'electroconvulsive-therapy' / all subheadings
#2   electroconvulsive therap* or electro convulsive therap*
#3   electroshock therap* or electro shock therap*
#4   ect
#5   #1 or #2 or #3 or #4
#6   explode 'affective-neurosis' / all subheadings
#7   depression
#8   schizophreni*
#9   explode 'schizophrenia-' / all subheadings
#10   catatoni*
#11   'catatonia-' / all subheadings
#12   explode 'manic-depressive-psychosis' / all subheadings
#13   mania or manic
#14   #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15   #5 and #14

HEED (Office of Health Economics Health Economic Evaluation Database)
CD ROM version
Search undertaken December 2001

<u>Search terms:</u>
- ect or electroconvulsive or electro convulsive or electroshock or electro shock

<u>Fields searched:</u>
- Abstract
- All data
- Article title
- Book title
- Keywords
- Technology assessed

HMIC (Health Management Information Consortium)
1980-2001
SilverPlatter WinSPIRS
Search undertaken December 2001

#1   ect
#2   electroconvulsive therap*
#3   electro convulsive therap*
#4   #1 or #2 or #3

Medline
1966-2001
Ovid Biomed
Search undertaken December 2001

1	electroconvulsive therapy/
2	electro convulsive therap$.tw
3	electroconvulsive therap$.tw
4	electro shock therap$.tw
5	electroshock therap$.tw
6	exp electric stimulation/
7	electric$ stimulation.tw
8	or/1-7
9	depression/
10	exp schizophrenia/
11	schizophreni$.tw
12	catatonia/
13	catatoni$.tw
14	exp bipolar disorder/
15	(mania or manic).tw
16	exp mood disorders/
17	adjustment disorders/
18	psychotic disorders/
19	affective symptoms/
20	mental disorders/
21	or/9-20
22	8 and 21

PsycINFO
1967-2001
SilverPlatter WebSPIRS
Search undertaken December 2001

#1   'electroconvulsive-shock-therapy' in de
#2   electroconvulsive therap* or electro convulsive therap*
#3   electroshock therap* or electro shock therap*
#4   ect
#5   #1 or #2 or #3 or #4
#6   explode 'mental-disorders' in de
#7   schizophreni* or catatoni* or bipolar disorder* or mania or manic or depression
#8   #6 or #7
#9   #5 and #8

Science and Social Sciences Citation Index
1981-2001
Web of Science
Search undertaken December 2001

Title=(ect or electroconvulsive therapy or electro convulsive therapy or electroshock therapy or electro shock therapy) and (depression or schizophreni* or catatoni* or bipolar disorder* or mania or manic or mood disorder* or mental disorder*); DocType=All document types; Languages=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=All Years

Appendix 4 Methodological Search Filters Used in Ovid Medline

Guidelines
1   guideline.pt
2   practice guideline.pt
3   exp guidelines/
4   health planning guidelines/
5   or/1-4

Systematic reviews
1   meta-analysis/
2   exp review literature/
3   (meta-analy$ or meta analy$ or metaanaly$).tw
4   meta analysis.pt
5   review academic.pt
6   review literature.pt
7   letter.pt
8   review of reported cases.pt
9   historical article.pt
10   review multicase.pt
11   or/1-6
12   or/7-10
13   11 not 12

Randomized controlled trials
1   randomized controlled trial.pt
2   controlled clinical trial.pt
3   randomized controlled trials/
4   random allocation/
5   double blind method/
6   or/1-5
7   clinical trial.pt
8   exp clinical trials/
9   ((clin$ adj25 trial$)).ti, ab
10   ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti, ab
11   placebos/
12   placebos.ti, ab
13   random.ti, ab
14   research design/
15   or/7-14
16   comparative study/
17   exp evaluation studies/
18   follow up studies/
19   (control$ or prospectiv$ or volunteer$)).ti, ab
20   prospective studies/
21   or/16-20
22   6 or 15 or 21

Economic evaluations
1   economics/
2   exp "costs and cost analysis"/
3   economic value of life/
4   exp economics, hospital/
5   exp economics, medical/
6   economics, nursing/
7   economics, pharmaceutical/
8   exp models, economic/
9   exp "fees and charges"/
10   exp budgets/
11   ec.fs
12   (cost or costs or costed or costly or costing$).tw
13   (economic$ or pharmacoeconomic$ or price$ or pricing).tw
14   or/1-13

Quality of life
1   exp quality of life/
2   quality of life.tw
3   life quality.tw
4   hql.tw
5   (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw
6   qol.tw
7   (euroqol or eq5d or eq 5d).tw
8   qaly$.tw
9   quality adjusted life year$.tw
10   hye$.tw
11   health$ year$ equivalent$.tw
12   health utilit$.tw
13   hui.tw
14   quality of wellbeing$.tw
15   quality of well being.tw
16   qwb.tw
17   (qald$ or qale$ or qtime$).tw
18   disability adjusted life year$.tw
19   daly$.tw
20   (hamilton depression rating scale or hdrs-17 or ham-d).tw
21   hopkin$ symptom checklist score$.tw
22   chronic disease score4.tw
23   (montgomery asberg depression rating scale or madrs).tw
24   brief psychiatric rating scale.tw
25   "kiddie schedule for affective disorders and schizophrenia".tw
26   clinical global impression.tw
27   (symptom free days or sfd).tw
28   social functioning scale.tw
29   depression recurrence rate$.tw
30   mini-mental state examination.tw
31   retrograde memory test$.tw
32   anterograde memory test$.tw
33   or/1-32

Patient acceptability
1   exp patient acceptance of health care/
2   patient$ acceptabil$.tw
3   patient$ complian$.tw
4   patient$ choice$.tw
5   patient$ preference$.tw
6   patient$ knowledge$.tw
7   or/1-6

Side effects
1   ae.fs
2   ct.fs
3   co.fs
4   ((side or adverse or unintended or unwanted) adj2 (effect$ or event$)).tw
5   harm$.tw
6   complication$.tw
7   contraindication$.tw
8   exp suicide/
9   exp memory disorders/
10   exp cognition disorders/
11   memory loss$.tw
12   cognitive$ impairment$.tw
13   or/1-12

Staff training
1   (staff adj3 train$).tw
2   (staff adj3 supervision$).tw
3   exp inservice training/
4   audit$.tw
5   exp medical audit/
6   nursing audit/
7   exp management audit/
8   or/1-7

Appendix 5: Descriptions of included studies

Table A5.1 Systematic reviews of the clinical effectiveness and safety of ECT in depression, schizophrenia and mania

ACADEMIC IN CONFIDENCE UK ECT GROUP DATA REMOVED.

Table A5.1 cont'd

Authors	Inclusion/exclusion criteria	Search strategies	Data quality	Data synthesis methods
Tharyan P and Adams CE (52)	**Interventions**: ECT (modified or unmodified) electrode placement (bilateral vs unilateral), dosage, wave form, frequency of administration, number of ECT sessions. **Comparators:** placebo, sham ECT, pharmacological interventions, non-pharmacological interventions. **Populations**: people with schizophrenia, schizo-affective disorder or chronic mental disorder (non-affective) **Outcomes**: *Primary*: clinically meaningful benefits in overall functioning, hospitalisation status, changes in mental state, behaviour, social and occupational functioning, remission of symptoms in short term (less than 6 weeks), medium term (6 weeks to 6 months) and long term (over 6 months). *Secondary:* premature withdrawal from trial by decision of either research or investigators and adverse events such as cognitive side effects and mortality. Continuous data excluded if more than 50% of people were lost to follow up or if the instrument had not been published in a peer reviewed journal. Also excluded from analysis if did not report means and standard deviations, or did not meet a priori criteria for normal distribution. **Studies**: all relevant randomised controlled trials with quality rating A or B according to Cochrane Handbook.	**Electronic databases**: Biological abstracts (1966-1996), EMBASE (1980-1996), MEDLINE (1966-2001), Psyclit (1974-1996), Cochrane Schizophrenia Group Register up till 2001. **Other**: Citations of included studies were checked for additional trials and first author of each trial published since 1980 contacted for additional references and unpublished trials, manufacturers of ECT and editorial board of journal "Convulsive Therapy" were contacted for additional studies.	**Blinded assessment**: not reported **Study quality rating**: Cochrane Collaboration Handbook categories A and B **Method**: two independent reviewers	**Meta-analysis method**: fixed then random effects **Heterogenity**: Mantel-Haenszel test, significance level of less than 0.10 evidence of heterogeneity. If remained following use of random effects model results not pooled and sensitivity analysis undertaken. **Sensitivity analysis**: conducted where evidence of heterogeneity and to test effect of including studies with high attrition rates. **Subgroup analyses**: Defined a priori and tested for method of schizophrenia diagnosis, symptom profile, duration of illness, trial size. **Publication bias**: funnel plot **Continuous data**: pooled weighted mean difference **Dichotomous data**: relative risk, number needed to treat, number needed to harm **Confidence intervals**: yes

TABLE A5.2 SYSTEMATIC REVIEWS OF NON RANDOMISED EVIDENCE: PATIENT ACCEPTABILITY AND CHOICE

ACADEMIC IN CONFIDENCE SURE GROUP DATA REMOVED.

Authors	Inclusion/exclusion criteria	Search strategies	Data quality	Data synthesis methods
SURE, 2002 (55)				

TABLE A5.3: SYSTEMATIC REVIEWS OF NON-RANDOMISED EVIDENCE: CHILDREN AND ADOLESCENTS

Authors	Inclusion/exclusion criteria	Search strategies	Data quality	Data synthesis methods
Walter and Rey, 1997, 1999(1;71)	**Interventions**: ECT **Populations**: People 18 or under who received ECT. **Outcomes**: Response to treatment defined by reviewers as those who showed marked improvement or recovery both immediately after ECT and 6 months post ECT as defined by the study authors, adverse events including cognitive functioning, seizures and subjective side effects Study type: Included if data on diagnosis and individual outcomes was provided, in all languages, all study types.	**Electronic databases**: Medical and psychological database (names not stated) up to March 1996. **Other**: Manual searches to identify studies that assessed the effectiveness of ECT in people under the age of 18.	**Blinded assessment**: no **Study quality rating**: Yes **Methods**: Two independent raters rated study quality on several variables to obtain a quality score.	**Meta – analysis**: no **Other methods**: Data on outcome summarised by adding case series and reports together to produce an overall percentage of these with a good outcome after ECT (intention to treat) and at 6 months (not intention to treat) by diagnosis. Qualitative overview of data on adverse effects.

Table A5.4 Systematic reviews of non-randomised evidence: Catatonia

Authors	Inclusion/exclusion criteria	Search strategies	Data quality	Data synthesis methods
Hawkins et al (78)	**Interventions**: Any intervention to treat catatonia, including ECT combined with pharmacotherapy and ECT alone **Populations**: Provide sufficient detail to determine whether cases met DSM-IV criteria for catatonia. Papers were excluded if clinical descriptions were likely to be due to NMS or if the treatment and response were not clearly described. **Outcomes**: Response to treatment based on original authors' clinical description of change in catatonic symptoms after treatment. Response was then retrospectively rated by reviewers on a 3 point scale – none, partial and complete. **Study type**: All study types, written in English.	**Electronic databases**: Paperchase medical literature search system between 1985 and 1994 **Other**: Citation tracking from included studied	**Blinded assessment**: No **Study quality rating**: No **Methods**:	**Meta – analysis**: no **Other methods**: Descriptive statistics of percentage of cases with each outhcome by treatment type

Table A5.5: Systematic review of non randomised evidence: Use of ECT in pregnancy

Authors	Inclusion/exclusion criteria	Search strategies	Data quality	Data synthesis methods
Miller (81)	**Interventions**: ECT **Populations**: Pregnant women **Outcomes**: physiological effects of ECT during pregnancy, risk of ECT **Study type**: all	**Electronic databases**: Medline dates not reported **Other**: Not reported	**Blinded assessment**: No **Study quality rating**: No **Methods**:	**Meta – analysis**: No **Other methods**: Results are summarised in terms of the percentage of cases reporting each complication

Table A5.6 Randomised controlled trials comparing real vs sham ECT: depression

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Gregory et al(87)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Met MRC (1965) criteria for depression of greater than one month duration and were right handed **Exclusion:** Severe physcial illness or had laready received ECT for current episode of illness **Age**: Not specified **Gender**: Not specified **History**: Not specified	**Comparison**: Real ECT vs Sham ECT **ECT**: ECT: Either unilateral or bilateral ECT at waveform 1 of the duopulse Mark IV machine tiwce weekly, no of treatmend determined by clinical team in charge of the patient's care. Right unilateral ECT in the tempoparietal position (Lancaster et al, 1965); bilateral in the bifrontotemporal position. Monitored using the cuff method and length of fits timed with a stopwatch. **Comparator**: Sham ECT twice weekly as treatment group but with no electricity, no ECTs determined by clinical team in charge of patients care	Continuous: MADRS, HDRS, PIRS, PSE (unusable, graph or mean change scores only no mean or SD) Dichtomous: none	**N randomised:** 69 **n completed:** 48 **Length of follow up**: Till end of ECT treatment	Information on numbers who improved in eac group not provided.

121

Table A5.6 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
West (94)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Met Feighner criteria for primary affective disorders (Feighner et al, 1972) **Exclusion**: **Age**: Real ECT mean, (SD), range: 52(11.1) 35-78; Sham ECT mean (sd) range: 53.3 (22.9) 26-82 **Gender**: 13 men (6 real, 7 sham); 9 women (5 real, 4 sham) **History**: All patients given 50mg amitryptaline at night during the study. All had depression severe enough to warrant ECT and all had suicdal ideas. 16 had previously had unipolar illness and two had bipolar illness. No info on previous ECTs	**Comparison**: Real ECT vs Sham ECT **ECT**: Real ECT: Bilateral anterior placement ECT using double sided unrectified waveform of 40joules from a Transycon machine twice weekly for 3 weeks, receiving a total of 6 treatments. **Comparator**: Sham ECT: received anaesthesia as treatment group but no electricity twice a week for 3 weeks.	Continuous: BDI, Nurses rating scale, Psychiatrists rating Dichotmous: none	**N randomised:** 25 **n completed:** 22 **Length of follow up**: 3 weeks - till end of treatment	No information on no's in each group who improved.

Table A5.6 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Jagadeesh et al(54) (1992)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Aged between 20 and 60, diagnosis of major depression endogenous subtype on Research Diagnosistic criteria (Spitzer et al, 1978) Present depressive episode untreated with ECT, antidepressants or antipsychotics,informed consent **Exclusion:** Organic factors contraindicating ECT, current suicide attempt or suicide score of greater than 3 on HRSD. **Age**: 6 Real mean (sd): 39.92(8.39), 5 Sham ECT mean(sd): 31.92 (6.34) range 22-52 **Gender**: 14 women (7 in each group) , 10 men (5 in each group) **History**: First episode for 5/12 in real ECT and 2/12 in single ECT. Mean duration of current episode was 2.91 months in real ECT and 1.92 months in single ECT. Mean initial HRSD score: Real ECT 26.83; single ECT 26.17.	**Comparison**: 6 real vs 1 real +5 sham ECT **ECT**: 6 real ECT: Bifrontotemporal bilateral ECT, sine wave 120-150 volts for .5-.8 seconds 3 times per week for 2 weeks. Seizure monitored using the cuff method. **Comparator**: 1 real + 5 sham received initial real ECT as treatment group plus 5 sham ECT where received anaesthesia but no electricity	Continuous: HRSD, GRSD Dichotmous: Responder: a score of 2 or less on global rating for depression at end of treatment	**N randomised:** 24 **n completed:** 23 **Length of follow up**: 2 weeks	No real control group - no group receiving sham ECT only.

Table A5.6 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Lambourn and Gill (91)	**Allocation**: c quasi-randomised **Blinding**: double-blind	**Inclusion**: Right handed, diagnosis of depressive illness referred for ECT **Exclusion:** Another psychiatric of organic disorder or received ECT within the previous 3 months **Age**: Real ECT mean 54.4 (36-69); sham ECT mean 53.4 (37-66) **Gender**: 18 women and 14 men, evenly distibuted acorss groups **History**: All ECT group inpatients, 2 sham ECT group outpatients. 8 real ECT and 6 sham ECT had previous failed courses of antidepressants. 11/16 in the real ECT and 10/16 in the sham ECT group had previously received at least 1 course of ECT in the past. Mean Hamilton score was 25 for real ECT and 27 for sham ECT.	**Comparison**: Real ECT vs Sham ECT **ECT**: Real ECT: Unilateral right temporietal (Lancster 1958) brief pulse ECT at 10J from Ectron Duopulse Mk4 3 times a week for two weeks **Comparator**: Sham ECT 3 times a week for two weeks, received anaesthesia but no electricity.	Continuous: HRSD (15 item) (unsable mean change only reported) Dichtomous: individual data presented, a priori decsion by reviewer of a 50% reduction on HRSD	**N randomised:** 32 **n completed:** 26 **Length of follow up**: 2 weeks	The authors note that only 5 people failed to make any improvement at all - 1 in the real ECT group and 5 in the simulated ECT group based on those who failed even to make a 1-33% improvement on the HRSD.

Table A5.6 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Freeman et al (92)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: In patients, aged 20-780 years, clinical diagnosis of depression and a minimum score of 15 on both the Beck and HRSD **Exclusion:** Depression secondary to other psychiatric illnesses such as schizophrenia, major or proggressive physcial illness, organis brain disease or received ECT in last 6 months **Age**: Real ECT mean age 51; sham ECT mean age 50.5 **Gender**: 11 men (6 real, 5 sham); 29 women (14 real 15 sham) **History**: 50% of real ECT and 60% of sham ECT had received ECT before and 14 real and 14 sham had one or more previous episodes of depression. 7 real and 11 sham ECT were taking some sort of anitdepressant medication. 25% in each group had had previous manic illness	**Comparison**: Real ECT vs Sham ECT **ECT**: Bilateral ECT twice weekly with bidirectionla 60% sine wave current of 400v for a peak of 1.5s from Ectron MkIV machine. Number of ECTs titrated against treatment outcome and no ranged from 3-12 ECTs **Comparator**: Sham ECT: Initial two treatments were sham ECTs where patients received anaesthesia but no electric current but remaining ECTs were real as above	Continuous: HRSD, Wakefield Scale, BDI, VAS (unusable, graph only) Dichtomous: clinical judgement of a "satisfactory response"	**N randomised:** 40 **n completed:** 38 **Length of follow up**: Not specified but outcome measurement occurred after last ECT treatment	

Table A5.6 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Johnstone et al (90)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Aged 30-69, met MRC criteria for depressive illness, Feighner criteria for primary depressive illness, Newcastlecriteria for endogenous depressive illness, Newcastle criteria for predicting a good outcome to ECT, **Exclusion:** Poor anaesthetic risk. **Age**: Mean age 49.4 years **Gender**: 52 women, 18 men **History**: 46 had definite previous episodes of depressive illness and 7 had definite previous episodes of mania. 15 patients received ECT for a previous epidosde (21%). 49 patients had had antidepressant prescribed for the index episode pror to the trial.	**Comparison**: Real ECT vs Sham ECT **ECT**: ECT: 8 treatments of twice weekly bi frontal ECT using Duopulse wave form 1 at 150 volts for 3 seconds over 4 weeks. Confirmation that a convulsion had taken place was measured using the cuff method. **Comparator**: Sham ECT: Received anaesthesia and muscle relaxants but no electrcity was passed.	Continuous: HRSD, HAD (then the "Leeds Scale"), memory tests, Bunney and Hamburg nurses Rating scale (unsuable, graph only) Dichotmous: Hamilton score below or above median of 17 for final rating - above is a "good outcome" and below is a "poor outcome"	**N randomised:** 70 **n completed:** 62 **Length of follow up**: 4 weeks, 1 month and 6 months - but after the end of ECT care was not randomised.	

Table A5.6 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Brandon et al(89)	**Allocation**: a concealed **Blinding**: double-blind	**Inclusion**: All patients prescribed for inpatient ECT (n = 219). 186 interviewed and 48 refused treatment, of remaining 95 had depression and 43 had no depressive diagnoses. Total of 138 entered trial. **Exclusion**: **Age**: Real ECT mean 55.4; sham ECT mean: 53 **Gender**: Real ECT M/F: 21/32; Sham ECT M/F: 13/29 **History**: The mean no of previous admission was 2.6 in the real ECT group and 2.5 in the sham ECT group. 36% in the real and 48% in the sham ECT group were judged to have received an adequate course of antidepressants prior to the trial. 55% in the real and 65% in the sham had received ECT before	**Comparison**: Real ECT vs Sham ECT **ECT**: ECT: Bilateral ECT using chopped sine wave current from Ectron Mark IV machine on setting one twice a week for 4 weeks. Received a maximum of 8 but clinician could withdraw patient if deteriotation occurred. Patient carefully observed to ensure fit took place. **Comparator**: Sham ECT - received ECT procedure as for control gorup but without electricity	Continuous: HRSD (unsable, graphs only)	**N randomised:** 95 **n completed:** 77 **Length of follow up**: Till end of treatment	Not really a criteria that says whether patients improved or not by the end of 8 treatments?

Table A5.7: Randomised controlled trials comparing ECT with phamacotherapy: depression

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Dinan and Barry (106)	**Allocation**: b unclear **Blinding**: clinician	**Inclusion**: 1. Fulfilled DSM-II for major depression; 2. Score on HDRS of greater than 20; 3. Newcastle endogenicity score greater than 5. **Exclusion:** 1. Not on any other medication **Age**: 29-77 years **Gender**: 10 men, 20 women **History**: All had failed to respond to a full course of TCAs defined asat least 150mg of anitryptaline for at least 4 weeks and failure of HRSD to drop by 40% or at least to fall by 20. 11 had previously received ECT and 28 had a previous history of depression. Mean duration of current episide was 6.1 months in lithium group and 7.7 in ECT group.	**Comparison**: ECT vs TCA+Li **ECT**: 1. ECT (n = 15): Bilateral, 6 treatments over 3 weeks, other stimulus parameters not speciifed. **Comparator**: 2. Lithium + TCA: remained on prestudy dose of TCA with lithium added initially at a dose of 600mg or 800mg and dose adjusted to obtain serum Li between 0.5-0.7mEq/1.	Continuous: HRSD (unusable, graph only) Dichotomous: unclear, no aprior defn, independent clinician unclear	**N randomised:** 30 **n completed:** 30 **Length of follow up**: 3 weeks	

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Folkerts et al (107)	**Allocation**: b unclear **Blinding**: Unclear	**Inclusion**: 1. Fulfil ICD-10 criteria for major depression; 2. Score of at least 22 on the HDRS 21 item version; 3. relative therapy resistance defined as at least two different antidepressants (including at least one TCA) at a dosage of at least 100g imipramine or equiv and no improvement for a total period of 8 weeks. **Exclusion:** 1. Major depressive disorder with psychotic features, pronounced suicidal tendencies, severe physical illness or histroy of substance abuse; 2. Previous paroxetine or ECT fir current episode; 3. Age over 80. **Age**: ECT group mean (sd) 47.6 (14.7); Paroxetine group mean (sd) 52.3 (15.7). **Gender**: 18 men, 21 women, gender of drop out not specified **History**: All treatment resistant with a mean of 4-5 previous antidepressant trials. Baseline HDRS 31.1 in ECT group and 32.6 in paroxetine group. Current episode lasted a mean of 59.8 weeks in ECT group and 75.2 in the paroxetine group.	**Comparison**: ECT vs SSRI **ECT**: 1: ECT (n=21) right unilateral ECT at 2.5 supra threshold, brief pulse (1ms, 0.9A) performed with a THYMATRON-DGx 3 times per week. Mean no of ECTs received was 7.2. **Comparator**: 2: Paroxetine (SSRI): Starting dose 20mg daily, 40mg within 7 days with a maximum of 50mg. Mean end dose 44mg daily.	Continuous (HRSD 21 item) Dichotomous: Responder defined as reduction of at least 50% on HDRS 21 item version	**N randomised:** 43 **n completed:** 39 **Length of follow up**: Till end of ECT or 4 weeks	Those showing no improvement: ECT: 6/21, Paroxetine 17/22

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Herrington (104)	**Allocation**: b unclear **Blinding**: none	**Inclusion**: Physically health adults aged 25-69 with a primary diagnosis of depression. The severity of their illness was such that immediate admission to hospital and ECT were considered appropriate. **Exclusion**: **Age**: ECT 54.8 years; L-Tryptophan 52.7 years **Gender**: ECT M6 F15; L-Tryptophan M7 F15. **History**: Duration of current episode: ECT 4.1 months; L-Tryptophan	**Comparison**: ECT vs L-tryptophan **ECT**: ECT administered twice weekly, a total of 6-8 treatments. Option for crossover if no success after two weeks **Comparator**: L-tryptophan, 6g daily for first two weeks and 8 g daily for the second two weeks. Option for crossover if no success after two weeks.	Continuous: MRC depression scale, HRSD, BDI, Taylor manifest anxiety scale (unusable, grpahs only) Dichotomous: clinical opinion of response, not defined	**N randomised:** 40 **n completed:** 38 **Length of follow up**: Six Months	All patients in both groups were given a supplement of 100 mg pyridoxine daily (Vitamin B6). 5 ECT patients and 6 tryptophan patients required diazepam: nitrazepam was necessary for 4 tryptophan patients only.
Bruce (99)	**Allocation**: b unclear **Blinding**: Not blind	**Inclusion**: Suffering from depression, considered to be suffieciently ill to require ECT. 49/50 endogenous depression (no details as to the remainder). **Exclusion:** None recorded. **Age**: No data **Gender**: No data **History**: No data	**Comparison**: ECT vs TCA **ECT**: Average 6.1 treatments in the first month. **Comparator**: Tofranil (Tricyclic antidepressant) rising to 75 mg tds or less if they were responding well.	Continuous: none Dichotomous: clinical opinion as responder (not defined)	**N randomised:** 50 **n completed:** 49 **Length of follow up**: 1 month and 3 months	"Barbiturate sedation" used in both groups.

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Steiner et al (102)	**Allocation**: a concealed **Blinding**: Not blind	**Inclusion**: Met criterial for endogenomorphic depression as defined by Klein (1974) **Exclusion:** Known endocrine or cardiovascular disorders, central nervous system disorders including brain trauma or convulsive disorders, drug addiction or mental deficiency and treated with ECT at any time in the last 6 months **Age**: 30-60 mean 55.5 **Gender**: all female **History**: Mean number of previous episodes of depression 2.4 and a family history of depression in 4 patients. All were currently depressed for 6 weeks and had been unsuccessfully treated in an outpatient treatment trial (definition not specified)	**Comparison**: ECT vs TCA+placebo vs TCA+L-trodothyronine **ECT**: ECT: Bilateral ECT twice a week until improvement was noticed but no more than 10 treatment allowed. Wave form, dosage and machine not specified **Comparator**: (1) Imipramine 150g plus placebo for 5 weeks; (2) Imipramine 150mg plus L-triodothyronine (T3)	Continuous: Personal Data inventory, CGI, HRSD, Side Effect Symptom Scale Dichotmous: Responder defined as moderate or marked improvement on the CGI and a total score on the HRSD of 10 or less (50% reduction in HRSD also gives same result)	**N randomised:** 12 **n completed:** 12 **Length of follow up**: 5 weeks	Using the criteria of at least a 50% reduction in HDRS scores also produced the same result (pretreatment and final HRDS are given for each patient in the trial). 1 in each group showed no improvement.

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Greenblatt (108)	**Allocation**: b unclear **Blinding**: Unclear	**Inclusion**: All patients admitted with a symptomatology of severe depression, regardless of dynamics or specifi diagnostic category. The major diagnostic categories thus comprised: psychoneurotics, manic-depressives, involutionals, schizophrenic reactions, schizo-affective type, and a mixed category of character. **Exclusion:** Patients with severe organic brain syndromes, chronic alcoholism or drug addiction. **Age**: Males 46.8 Females 45.4 **Gender**: M 32% F 68% **History**: not recorded	**Comparison**: ECT vs TCA vs MAOI **ECT**: ECT Three times per week. **Comparator**: Imipramine (Tofranil - tricyclic antidepressant) 200 mg + optional 50 mg; Phenelzine (Nardil - Monoamine-oxidase inhibitors or MAOI) 60 mg + optionsl 15 mg; or Isocarboxazid (Marplan - also a MAOI) 40 mg + optional 10 mg.	Continuous: none Dichotmous: Clinician opinion of 'marked improvement': the patient is practically symptom-free and capable of functioning in the community.	**N randomised:** 281 **n completed:** 281 **Length of follow up**: End of treatment	Not stated how many participants were initially randomised or if there were any dropouts, only N for results given

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Gangadhar (105)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Fulfilled criteria for for major depressive episode according to ICD-10 as judged independently by two psychiatrtists. Two had bipolar depresion, the others had either single or recurrent major depression - F31.31, F 31.4, F32.11, F32.2, F33.11, F33.2. **Exclusion:** Patients treated with any psycho-pharmacological agents except benzodiazepines in the past one month, those who had received ECT for the current depressive episode and patients who had major physical illnesses, **Age**: ECT: 46.06 ± 11.80; Impramine 42.19 ± 12.66 **Gender**: ECT M9 F7; Impramine M5 F11 **History**: Past history of affective illness - ECT: depression 3, mania 3, both 1; Impramine Depression 2, mania 1. Family history of affective illness - ECT 0; Impramine 3. Duration of illness - ECT <3 mth 10, >3 month 6; Impramine <3 mth 7, >3 month 9.	**Comparison**: ECT vs TCA **ECT**: Modified bilateral ECT using 150-250 mg of thiopentone, 20-30 mg of succinylcholine and 0.65 mg of atropine was employed. Six ECTs on alternate days for the first two weeks and one ECT each week in the next two weeks. Three 'maintenance' ECTs were administered in the next eight weeks during the 6th, 8th and 12th weeks of the trial period. **Comparator**: Imipramine (tricyclic antidepressant) (25 mg) 3 per day 1st week, 6 per day 2nd - 11th week and 3 per day during 12th week.	Continuous: HRSD, social dysfunction and organic brain dysfunction battery, side effects checklist (unsable, medians, no sd) Dichotomous: none	**N randomised:** 32 **n completed:** 24 **Length of follow up**: 6-12 months	Included, but data unusable: results presented as medians without ranges.

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
McDonald (88)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: All new admissions eligible **Exclusion:** Organic complications to contraindicate drugs or ECT, antipepressants last 2 weeks, unable to speak English. **Age**: 20-65 **Gender**: M 11; F 19 **History**: None - new admissions.	**Comparison**: ECT vs TCA vs sham ECT **ECT**: ECT; electrode placement unclear; minimum number of treatements = 8; three times weekly. **Comparator**: Amitriptyline; tricyclic anti-depressant; 20mg intramuscular for 3 days; 50 mg orally for the remainder of the one month trial period. Sham ECT was delivered while patient was unconscious through injection of thiopental sodium (Pentothal - a barbiturate).	Continuous: MMPI, WBIS, BGT, unvalidated depression scale (unusable, no sd) Dichotomous: none	**N randomised:** 30 **n completed:** 30 **Length of follow up**: End of treatment	Control group: 4 received sham ECT and 4 received placebo

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Janakiramaiah (97)	**Allocation**: b unclear **Blinding**: Not blind	**Inclusion**: DSM-IV melancholic depression who were never treated for the current episode. Medically fit. HSRD 17+. **Exclusion:** **Age**: ECT 36.7 ± 2.5; IMN 43.4 ± 11.9; SKY 36.0 ± 7.8 **Gender**: ECT M6 F9; IMN M10 F5; SKY M9 F6 **History**: Duration of current episode (months): ECT 4.8 ± 3.3; IMN 5.4 ± 3.5; SKY 3.8 ± 2.8. Recurrent: ECT 3; IMN 2; SKY 4.	**Comparison**: ECT vs TCA vs Yoga **ECT**: ECT with bilateral electrode placement three time weekly. The stimulus was set 60 mC above threshold (determined on the first and seventh ECT). Mean number of ECT sessions 8.9 ± 3.3. Seizures of 25 s on EEG or 15 s on motor were ensured in all sessions. **Comparator**: Imipramine (Tofranil - tricyclic antidepressant) 150 mg once daily for four weeks. No other psychotrpoic drugs; or Yoga 45 minutes six days per week. Mean number of SKY sessions 20.3 ± 2.8.	Continuous: BDI, HRSD (17 item) Dichotomous: remitters defined as HRSD 17-item score <8	**N randomised:** 45 **n completed:** 45 **Length of follow up**: 4 weeks	None recorded.

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Wilson et al (93)	**Allocation**: b unclear **Blinding**: unclear	**Inclusion**: All women aged 40-59 admitted to psychiatric hospital with depressive symptoms **Exclusion:** Schiophrenia and organic brain disorder **Age**: 40-59 **Gender**: all women **History**: Not specified	**Comparison**: ECT+ TCA vs ECT+placebo vs Sham ECT+imipramine **ECT**: two treatments per week for a total of 6 treatments, electrode placement, dosage wave form and machine not specified **Comparator**: Imipramine: mean dose 150g in the first and last two thirds of the study 220g in the middle third of the study	Continuous: HRSD, MMPI"D" (unusable, graph or mean change only reported) Dichotmous: none	**N randomised:** 24 **n completed:** 22 **Length of follow up**: 5 weeks	Two sections of this study - one comparing ECT with imipramine and one comparing real ECT with sham ECT

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Shepherd.M RC trial (98)	**Allocation**: b unclear **Blinding**: unclear	**Inclusion**: Aged 40-69 years, previous duration of illness under 18 months, depressive illness **Exclusion:** Treatment during last 6 months with either ECT or adequate trial of pharmacotherapy, depression secondary to other psychiatric illness siuch as schizophrenia or an obsessional state, physical disease such as malignancy, organic cerebral disease. **Age**: Mean age in years in 4 groups: ECT: 55.4, Imipramine 54.8, Phenelzine: 54.7, Placeob: 56.3 **Gender**: M/F in 4 groups: ECT: 24/42, Imipramine: 22/41, Phenelzine: 18/43, Placebo: 17/44 (this is in completer) **History**: Number rated severely ill in 4 groups: ECT: 35/65, imipramine: 27/63, phenelzine, 20/61 placebo.	**Comparison**: ECT vs TCA vs MAOI vs placebo **ECT**: 4-8 treatments within first 3 and half weeks of trial, according to physicians judgement.. **Comparator**: Either 50mg of imipramine or 15mg of phenelzine or 15 mg of placebo with 2 tablets on the first day, 3 on the second, 4 between days 3-28, 4 between days 29 and 56, 2 between days 57-84 and 1 between days 85 and 112.	Continuous: Physicans rating on 15 symptoms (unvalidated) (unusable, no sd) Dichtomous: clinical opinion of wholly or almost without symptoms	**N randomised:** 269 **n completed:** 250 **Length of follow up**: 4 weeks and 8. 12 and 24 weeks and immediately post dischrge.	

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Stanley and Fleming (109)	**Allocation**: b unclear **Blinding**: clinician	**Inclusion**: Patient suffering depression and ECT was normally indicated. **Exclusion:** Not reported **Age**: Mean ECT 43.8; mean Phenelzine 51.3 **Gender**: All female **History**: Acute admissions	**Comparison**: ECT vs MAOI **ECT**: Given 3 times per week and total number of treatments determined by response, usually 6-8. **Comparator**: Phenelzine (MAOI)	Continuous: nine "depressive scales" found to be valid by Foulds and Caine (1959) (unusable no sds)	**N randomised:** 47 **n completed:** 38 **Length of follow up**: 1 month	
MacSweeney, (103)	**Allocation**: b unclear **Blinding**: not blind	**Inclusion**: Not reported **Exclusion:** Not reported **Age**: Average age of completers in ECT group 57.2; average age of completers in drug group 54.8 **Gender**: M:F ECT group: 3:11; Drug group: 3:10 **History**: Not reported	**Comparison**: ECT vs Ltryptophane **ECT**: Unilateral ECT administered twice weekly **Comparator**: 3g of L-tryptophan and 1g of nicotinamide daily	Continuous: BDI (unusable, no sd) Dichotomous: none	**N randomised:** 27 **n completed:** 25 **Length of follow up**: 28 days	
Kendrick et al(95)	**Allocation**: b unclear **Blinding**: unclear	**Inclusion**: Elderly patients admitted to Bethem Royal Hospital suffering from affective disorder **Exclusion:** Not reported **Age**: Elderly but age not reported **Gender**: 32 men, 34 women **History**: Not reported	**Comparison**: ECT vs TCA+TCA **ECT**: Not reported **Comparator**: Imipramine and Trofranil	Continuous: Mill Hill vocabulary Scale, Raven's Coloured Progressive Mstrices, WAIS, Synonym Learning Test, Ing's Paired Associate Leanring Test, Digit Copying Test (unusable, no symptom scales reported)	**N randomised:** 69 **n completed:** 68 **Length of follow up**: Not reported	No data on depression symptoms, only on testing a new instrument to measure memory - no before after data presented.

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Davidson et al (96)	**Allocation**: a concealed **Blinding**: clinician	**Inclusion**: Unipolar depression or depression secondary to anxiety or character disorder as defined by the Feighner et al (1972) criteria and therapy resistant (no definition given). **Exclusion**: **Age**: ECT mean 40.7, Pharmacotherapy mean 41.5 **Gender**: ECT M/F: 2/7; Pharmacotherapy: M/F: 3/5 **History**: All were treatment resistant to conventional psychotropic drugs in clinically adequate doses. Baseline mean Hamiltonscores were 26.5 in ECT group and 22.8 in pharmacotherapy group. The pharmacotherapy group has a greater mean number of previous illnesses (2.5) than the ECT group (1.1).	**Comparison**: ECT vs TCA+MAOI **ECT**: ECT: bilateral ECT minimum of 4 and a maximum of 10 3 times per week with the mean number of ECTs received 5.4. Dosage, wave form and machine not specified **Comparator**: Combinaton of MAOI(phenelzine) and TCA (amitryptaline): Initiated with amitryptaline up to 100mg for 5-7 days with addition of 15mg of phenelzine up to a mximum of 45mg for mimimum of 3 weeks. Mean daily does of MAOI was 34mg and 71 mg of TCA.	Continuous: HRSD, BDI, Stait Trait Anxiety (mean and SE) Dichtomous: none	**N randomised:** 19 **n completed:** 17 **Length of follow up**: Unclear - 3-5 weeks	Unclear how many people were actually randomised to each group - 19 were randomised and 17 completed the study but no information is given regarding dropouts in each treatment.

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Bagadia et al (100)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Aged 18 to 65, clear depression of non organic cause, score of at least 16 on Hamilton Rating Scale for Depression (17item version), score of at least 12 on Beck Depression Inventory **Exclusion:** Treatment within the previous three weeeks with antidepressant or antipstychotic drugs, within the previous 8 weeks with ECT or insulin therapy, organic brain syndrome, convulsive disorder and physical illness. **Age**: Actual age of participants not reported **Gender**: Both, numbers not reported **History**: Not reported	**Comparison**: ECT + placebo vs TCA + sham ECT **ECT**: Bilateral ECT with stimulus of 110volts AC for approximatelly 0.5 seconds. One person received 8 ECTs the others received 6 ECTs. Three ECTs were given in the first week, 2 the week after. **Comparator**: Imipramine 25mg with an initial does of 2 tablets a day increased to 6 tablets a day, up to 150mg. Placebo was calcium lactate 300mg.	Continuous:HRSC, BDI, BPRS, Clinical Global Assessment, Cognitive test battery (unusable, HRSD not reported)	**N randomised:** 35 **n completed:** 20 **Length of follow up**: Till end of ECT course	2 people receiving ECT and 4 receiving simulated ECT required chlordiazepoxide (20-40mg) to control their anxiety or agitation. No data on depression scores are provided, only memory scores.

Table A5.7 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Hutchinson and Smedberg (101)	**Allocation**: a concealed **Blinding**: patient	**Inclusion**: Not specified **Exclusion:** Not specified **Age**: Not specified **Gender**: All female **History**: Not specified	**Comparison**: ECT vs TCA vs MAOI **ECT**: 1: ECT (no description given); **Comparator**: 2: Imipramine up to 250mg daily; 3: Parstelin 1 tablet t.d.s.; 4: amitryptaline up to 75mg t.d.s; 5: Pheniprazine 12 mg daily; Phenelzine 15mg t.d.s.; Chorloprothixene 120mg daily up to 180mg daily. 25 people in each group apart from imipramine n = 50	Continuous: unvalidated depression scale (unsable, no sd) Dichotmous: none	**N randomised:** 200 **n completed:** 0 **Length of follow up**: 3 weeks	No information on numbers who dropped out, if any.
Robin and Harris (110)	**Allocation**: b unclear **Blinding**: clinician	**Inclusion**: Not specified **Exclusion:** Not specified **Age**: Not specified **Gender**: Not specified **History**: Not specified	**Comparison**: ECT+ placebo vs TCA + sham ECT **ECT**: Bi weekly ECT plus placebo **Comparator**: TCA (imipramine) + biweekly anaesthesia	Continuous: Immobility index, Clinical Item score, HRSD, Behaviour Score (unusable: not reported) Dichotomous: clinical opinion of marked or moderate improvement	**N randomised:** 31 **n completed:** 31 **Length of follow up**: 3 weeks	No continuous data provided.

Table A5.8: Randomised controlled trials of ECT compared with rTMS in depression

Trial ID	Methods	Participants	Interventions	Outcomes	N	Follow up
Pridmore (57)	Allocation:a concealed Blinding: clinician	Inclusion: 'Medication-resistance' MDE; diagnosis of major depressive disorder (DSM-IV) Exclusion: None recorded. Age: ECT Alone median 48 (25-70); ECT + rTMS median 46 (26-58) Gender: ECT Alone M5 F6; ECT + rTMS M6 F5 History: None recorded.	Comparison:ECT vs ECT + RTMS ECT: Non-dominant hemisphere unilateral; 3 times per week for 2 weeks; number of treatmentsdosage according to age-based protocol in instruction manual (Percentage of 504 mC equivalent to the patient's age; RTMS: rTMSW (Magstim Super Rapid stimulator) ada Magstim 70 mm double coil; intensity 100%; frequency 20Hz; train length, 2 sec; number of trains, 30, intertrain interval 20 sec.	Clinical Response defined as MADRS of 12 or less and HRDS of 8 or less; VAS one-item scale, Global Assessment of Functioning (GAF), Side-effects: 6-item subjective side-effects questionnaire derived from Gomez 1975.	23	None recorded.
Grunhaus (56)	Allocation:b unclear Blinding: patient	Inclusion: Aged 18+; DSM-IV diagnosis of MDD; 17-item HRSD (HAM-D) score of 18 or greater; no personal or first-degree relativfe history of seizure; no medical, neurological or neurosurgical disorder that would preclude the administration of ECT or rTMS. Exclusion: Additional axis-I diagnoses. Age: ECT 63.6 ± 15.0; ECT + rTMS 58.4 ± 15.7 Gender: ECT 63.6 ± 15.0; ECT + rTMS 58.4 ± 15.7 History: Duration of episode ECT 6.9 ± 7.9 months, rTMS 8.3 ± 7.4; Previous episodes ECT 2.4 ± 3.05 months, rTMS 2.3 ± 2.85; Previous ECT - ECT 9/20, rTMS 14/20.	Comparison:ECT vs RTMS ECT: Non-dominant unilateral, switched to bilateral electrode placement if no improvement Wave form brief pulse bidirectional current. Mean number of treatments 9.6 (range 7-14) RTMS: Motor threshold determined daily by electromyographic method, placement of the electrode over the left dorsolateral prefrontal cortex. During stimulation the coil was held with the handle towards the back of the head. Administered five times a week for 4 weeks (for a total of 20 stimulations).	Hamilton (HRSD), Brief Psychiatric Rating Scale (BPRS), Global Assessment of Function Scale (GAS), Global Depression Scale (GDR), Pittsburgh Sleep Quality Index (PSQI).	40	No follow-up.

Table A5.9: Randomised controlled trials of ECT plus pharmacotherapy vs ECT plus placebo/pharmacotherapy only 2: Depression

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Mayur (58)	**Allocation**: b unclear **Blinding**: unclear	**Inclusion**: DSM-IV major depression **Exclusion:** Neurological and cardiological disorders. **Age**: Group 1 33.8 ± 8.0; Group 2 34.6 ± 11.9. **Gender**: Group 1 M6 F9; Group 2 M8 F7. **History**: Previously on antidepressant drugs with or without psychotropics; previous ECT use unclear. Group 1 episode number 2.7 ± 1.2, mean episode duration 4.3 ± 2.5 months. Group 2 episode number 3.1 ± 1.5, mean episode duration 5.3 ± 3.4 months. 17/30 had adequate drug trial (56%)	**Comparison**: ECT + TCA/SSRI vs ECT + Placebo **ECT**: Non-dominant D'Elia Unilateral ECT (ULECT); thrice weekly; machine wave form; dosage 30 mC upwards in steps to threshold stimulus dose (at least 25 s of EEG seizure). N=15 **Comparator**: TCAs (n = 26),SSRI (fluoxetine, n = 4)	Continuous: HRSD (17 item), MADRS, UKU subscales 1-3. Dichtomous: relapses defined as HRSD > 7	**N randomised:** 30 **n completed:** 30 **Length of follow up**: Two weeks.	Baseline scores are based on all participants but follow up scores are only based on completer samples

Table A5.9 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Shiah et al (59)	**Allocation**: b unclear **Blinding**: unclear	**Inclusion**: People routinely referred for ECT because treatment resistant depression, depression characteristed by psychotic features or acute suicidaility **Exclusion:** Other DSM-IV axis I diagnoses, past alcohol or cubstance abusecontraindications to the use of beta blockers, received fluoxetine within 5 weeks or MAOIs within 2 weeks **Age**: Completers: ECT plus Pindol: 50(9.3) ECT plus placebo: 45.8 (6.3) **Gender**: Completers: Men: 5; Women: 10 **History**: 5 in Pindol and 4 in placebo were treatment resistant	**Comparison**: ECT+pindol vs ECT+ placebo **ECT**: Stimulus delivered at just supra threshold for bilateral ECT and 3 times suprathreshold for unilateral ECT, 3 times per week for 2 weeks. **Comparator**: Pindol: 2.5mg orally, 3 times per day Placebo: 2.5mg orally, 3 times perday	Continuous: HRSD (29 item), CGI Dichtomous: Responder defined as score of 12 or less on the 29 item Hamilton Depression Scale after 6th treatment	**N randomised:** 20 **n completed:** 15 **Length of follow up**: 2 weeks	

Table A5.9 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
D'Elia (62)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Symptomatically, all syndromes with a global, pervasive depression of mood as central symptom, with one or more concomitant symptoms, such as psychomotor retardation, anxiety, sleep disturbance, depressive ideas, suicidal tendancies, and diurnal rhythm with amelioration of symptoms in the evening. Etiologically, endogenous symptoms. Severity severe enough that ECT considered the treatment of choice by doctor responsible. **Exclusion:** Patients over the age of 65, somatic disease which could have a relation to the depressive period, pregnant patients, or patients given ECT in the last 3 months. **Age**: ECT + Placebo 46.1 ± 12.7; ECT + L-tryptophan 48.3 ± 12.4. **Gender**: ECT + Placebo M12 F18; ECT + L-tryptophan M11 F20. **History**: Previous treatment: 40/61 anti-depressants in previous periods; 24/61 anti-depressants in present period. 24/61 had previous ECT courses. Duration of present period 0.5 to 6.5 months.	**Comparison**: ECT+ L-tryptophan vs ECT + Placebo **ECT**: Unilateral stimulation on the non-dominant hemisphere. Number of treatments: individual - ECT+ Placebo 6.1 ± 2.1; ECT+ L-tryptophan 6.3 ± 2.5. Frequency not clear - may be available from d'Elia 1970. Machine wave form not clear; n=30. **Comparator**: ECT as above plus: L-tryptophan; class ?; dosage 6 g daily; initiated at least 1 day before first ECT and terminated 4 days after the last ECT.	Continuous: Cronholm and Ottoson Rating scale (CODS) Nurses Rating Scale (NRS), HAD (not usable, no sd) Dichotmous:Clinical opinion of recovered and much improved (responders) and slight improvement and unchanged (non responders)	**N randomised:** 61 **n completed:** 57 **Length of follow up**: 1 month	

Table A5.9 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Arfwidsson (60)	**Allocation**: b unclear **Blinding**: patient	**Inclusion**: Endogenous or mixed-endogenous depression. **Exclusion:** Age 65+ **Age**: Chloropromazone 45.7 (19-64); Placebo 47.5 (22-63). **Gender**: Chloropromazone M11, F 17; Placebo M14, F14. **History**: 24/57 had received ECT previously, 31/57 had received anti-depressant medication during the current episode.	**Comparison**: ECT + C.ATP vs ECT + C. Placebo **ECT**: Bifrontotemproal electrodes, threshold stimulation with unidirectional stimuli. Initially 3 X per week, later 2 or 1 of treatments determined by clinical effect. **Comparator**: Chlorpromazine 50 -150 mg for 32 days with aug daily dose 106 mg	Continuous: Cronholm and Ottoson Depression scale (unsable, no sd) Dichotmous: clinical opinion of recovered or much improved(responder) or slightly improved or resistant (non responder)	**N randomised:** 57 **n completed:** 57 **Length of follow up**: 4-5 days after end of treatment	Hypnotics restricted to pentobarbital, chloral hydrate and diazepam. Diazepam 2-5 mg X 3 as day sedative. Cronholm & Ottoson rating unusable because they do not give data for the whole group, only thise who complete ratings.

Table A5.9 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Kirkegaard (61)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: None recorded. **Exclusion:** None recorded. **Age**: Both groups mean 63 years. **Gender**: Both groups M3; F7 **History**: Previous treatment not recorded. ECT use in the past not recorded. Duration of illness not recorded. Prognostic factors: at least two of the following four criteria: a phastic course; changes in psychomotor activity; exacerbation of the symptoms during morning hours; unfounded changes in self-esteem. Treatment resistance not recorded.	**Comparison**: ECT + L-tryptophan vs ECT+placebo **ECT**: ECT: unilateral (side unclear, but see Kirkegaard 1975); number of treatments unclear; frequency 2 times per week; machine wave form unclear; dosage unclear; number of particpants see below **Comparator**: L-tryptophan in isotonic saline; class unknown; dosage 1.ml/kg bodyweight of a 10 mg/ml solution; length of time taken unknown; change in dosage unknown.	Continuous: HRSD 17 item (not usable, graph only) Dichotomous: none	**N randomised:** 20 **n completed:** 20 **Length of follow up**: End of ECT course	Included, but data unusable: HAM-D scores only presented on graph not in text of table form.

Table A5.10: Randomised controlled trials comparing ECT+ pharmacotherapy/placebo + continuation pharmacotherapy: Depression

Author	Methods	Participants	Interventions	Outcomes	N and follow up	Notes
Imlah et al (64)	**Allocation**: b unclear **Blinding**: unclear	**Inclusion**: Suffering from depressive illness of sufficient degree to warrant use of ECT **Exclusion:** **Age**: 32% were under the age of 40, 63% between 40-60 and 5% over 60 **Gender**: 53 men and 97 women **History**: 54% had duration of illness under 6 months, 26% 6-12 months and 20% over 12 months.	**Comparison**: ECT +C. MAOI vs ECT+ C.TCA vs ECT+C.placebo **ECT**: ECT given twice weekly and discontinued when two observers agreed that the patient had reached a mximal response and discontinued after 12 in those who had residual symptoms **Comparator**: placebo 1 tabImipramine: 25mg t.d.s phenelzine: 15mg t.d.s	Continuous: none Dichotmous: Clinical opinion of relapse (not defined).	**N randomised:** 150 **n completed:** 111 **Length of follow up**: 6 months	No continuous data immediately post ECT, only average number of ECT's per patient in each groupl 1: 6.9, 2: 7.15, 3: 7.9s, differences not significant.
Kay (65)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Affective disorders. **Exclusion:** Organic brain disease, schizophrenia or subnormality. **Age**: Overall Age range 20-75 years with >50% 40-59. Age differences between groups were "non-significant". **Gender**: Male 48; Female 84. Gender differences between groups were "non-significant". **History**: Mostly in-patients. None with ECT over the last 6 months, no restriction on prior drug therapy.	**Comparison**: ECT + TCA vs ECT + Diazepam **ECT**: ECT: no details of ECT. One month trial. **Comparator**: Amitriptyline (Tricyclic antidepressant) 25mg 3 tablets at start (2-6 tablets) daily at doctor's discretion. One month trial. Diazepam (Benzodiazepine) 2 mg 3 tablets at start (2-6 tablets) daily at doctor's discretion. One month trial.	Continuous: Mood rating, HRSD, BDI, Lubin (unusable, no sd) Dichotomous: clinical failure defined as removal from trial due to relapse, unsatisfactor progress, side effects, taking an overdose.	**N randomised:** 132 **n completed:** 53 **Length of follow up**: Three months.	Method of randomisation not centraly organised, leading to problems in baseline comparability; post ECT no sd's available for HRSD and at 6 month follow up, greater than 50% of each arm of their trial were lost to follow up.

Table A5.10 cont'd

Author	Methods	Participants	Interventions	Outcomes	N and follow up	Notes
Seager and Bird (63)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: In patients suffering from a depressive illness of moderate to severe intensity, with retardation or agitation, feelings of hopelessness and pessimism, warranting electrical treatment **Exclusion:** **Age**: ECT+imipramine: 47.9 (28-71) ECT+ placebo: 49 (30-70) **Gender**: **History**:	**Comparison**: ECT+ C.TCA vs ECT+ C.placebo **ECT**: Modified ECT twice weekly using an Ecton machine (1 second duration shock), number of treatments based on clinical opinion. No information on electrode placement **Comparator**: Imipramine: 25mg t.d.s for 3 days increased to 50mg for hospital and first month after then reduced to 25mg Placebo: indentical in appearance	Continuous: None Dichtomous: Clinical opinion of a satisfactor response or a relapse (not defined)	**N randomised:** 43 **n completed:** 28 **Length of follow up**: 6 months	Data difficult to analyse. In patient treatment randomised to ECT+imipramine (19) vs ECT + placebo (24). On discharge patients had their tablets changed to either placebo or imipramine, conducted randomly by the pharmacist. Eight patients dropped out and it is not known to which group they belonged. Not possible therefore to analyse results on an intention to treat basis.

Table A5.10 cont'd

Author	Methods	Participants	Interventions	Outcomes	N and follow up	Notes
Lauritzen (66)	**Allocation**: b unclear **Blinding**: patient	**Inclusion**: Major depressive episode in accordance with DSM-III-R; HRSD score of 18+; age 18+; ability to understand oral and written information about the trial and giving informed consent. **Exclusion:** Severe cardiovascular disease within the preceding 6 months, in cluding intraventricular conduction abnormalities; severed unstabilized somatic diseases; untreated glaucoma; dementia; schizophrenia; chronic alcohol/drug abuse; treatment with irreversible MAO inhibitors within the preceding 14 days; pregnancy/nursing mothers; epilepsy; prophylactic lithium treatment. **Group A**: **Age**: Paroxetine 71.4 ± 8.5; Placebo 73.0 ± 8.5 **Gender**: Paroxetine M7 F11; Placebo M4 F13 **History**: Number of previous depressive episodes - Paroxetine 2.1; Placebo 3.8. Bipolar/Unipolar - Paroxetine 7/11; Placebo 4/13. Mean duration of current episode Paroxetine 19.1 ± 9.5 weeks; Placebo 22.4 ± 24.9 weeks. Received treatment for current episode - Paroxetine 90%; Placebo 76%. **Group B**: **Age**: Paroxetine 55.9 ± 12.7;	**Comparison**: Group A: ECT + C.SSRI vs ECT + C. Placebo Group B: : ECT + C.SSRI vs ECT + C.TCA **ECT**: EEG-monitored ECT was applied, three sessions per week, total number of sessions decided by the treating clinician. Bilateral placement for the first three sessions; thereafter, nondominant ECT. Stimulation levels adjusted by patient over sessions. **Comparator**: Group A: Paroxetine (30 mg daily) or placebo Group B: Paroxetine (30 mg daily) or Imipramine (150 mg daily).	Continuous: HRSD, Newcastle scale, Melancholia scale Dichotomous: no data	**Group A:** **N randomised:** 35 **n completed:** 33 **Group B:** **N randomised:** 52 **n completed:** 45 **All: Length of follow up**: 6 Months	Imipramine associated with side effects of constipation. Data for follow up period unusable, only presented in graphical form, no means or Sds

		Imipramine 63.3 ± 11.5 **Gender**: Paroxetine M3 F24; Imipramine M9 F 16 **History**: Number of previous depressive episodes - Paroxetine 2.9; Imipramine 2.4. Bipolar/Unipolar - Paroxetine 7/20; Imipramine 2/23. Mean duration of current episode Paroxetine 17.2 ± 13.5 weeks; Imipramine 12.8 ± 8.3 weeks. Received treatment for current episode - Paroxetine 92%; Imipramine 84%.				

Table A5.11: : Randomised controlled trials comparing continuation pharmacotherapy only.

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Coppen (67)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Major Depressive Disorder with scores of 16+ in the HRSD **Exclusion:** None recorded. **Age**: Placebo 54.0 ± 2.8; Lithium 56.2 ± 3.0 **Gender**: Placebo M8 F12; Lithium M6 F12 **History**: For 12 patients this was the first episode of depression. No history of mania. Number of previous spisodes Placebo 2.2 ± 0.5; Lithium 1.6 ± 0.4.	**Comparison**: Continuation Li vs Continuation Placebo **ECT**: Not described **Comparator**: Lithium carbonate (Priadel, Delandale - Antimanic drugs). Lithium plasma maintained through out between 0.8 and 1.2 mmol/l.	Continuous: HRSD (unusable graph only), no weeks with depression Dichotomous: none	**N randomised:** 38 **n completed:** 38 **Length of follow up**: One year.	Nitrazepam (Benzodiazepine hypnotic) or triazolam were the only other drugs administered during the trial.

Table A5.11 cont'd

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Grunhaus et al (68)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: Successfully responde to a course of ECT (post HRSD 17 item less than or equal to 10 maintained for 1 week). **Exclusion:** **Age**: Fluoxetine+ Melatonin: 61.1 (10.7) Fluoxetine+ placeob: 59.6 (14.1) **Gender:** **History**: Duration of illness was mean (sd) of 6.6 (8.3) in FM group and 8.7 (7.6) in FP group. Were referred to Ect because of medication resistance, presence of delusions or hallucinations and/or very severe depressive illness.	**Comparison**: C.SSRI vs C.SSRI+melatonin **ECT**: Started on unilateral but switched to bilareral if not achieved decrease of 30% in baseline HRSD scores by 6th treatment. Seizure threshold determined by method of limites and second treatment delived at 2.5 time threshold and at following sessions electrical parameters were set to deliver seizures of > 25s **Comparator**: FM: 7 days post ECT 20mg fluoxetine daily plus 5mg slow release melatonin 3 hours before bedtime. Following 3 months received 20-40mg fluoxetine plus 5 or 10mg melatonin FP: 7 days post ECT 20mg fluoxetine daily plus 5mg placeob 3 hours before bedtime.Following 3 months received 20-40mg fluoxetine plus 5 or 10mg placebo.	Continuous: HRSD, BPRS, GDR, MMSE, PSQI Dichtomous: Relapse defined as return of 5 or more DSM-IV symptoms of major depression and an HRSD of greater than or equal to 16	**N randomised:** 39 **n completed:** 35 **Length of follow up**: 3 months	

Author	Methods	Participants	Interventions	OUTCOMES	N and follow up	Notes
Sackeim (69)	**Allocation**: b unclear **Blinding**: double-blind	**Inclusion**: ECT remitters (improvement of greater than 60% reduction in HRSD score) randomized to 3 continuation pharmacotherapy groups, stratified by classification of the index episode as psychotic depression; medication-resistant nonpsychotic depression; and nonpsychotic depression depression without medication resistance. **Exclusion:** History of bipolar disorder, schizophrenia, schizoaffective disorder, nonmood disorder psychosis, neurological illness, alcohol or drug abuse within the past year, ECT within the past 6 months, or severe medical illness that markedly increased the risks of ECT. Patients with medical contraindications to Nortriptyline or Lithium.**Age**: Placebo 55.8 $\pm$ 13.6; Nortriptyline and Placebo 57.2 $\pm$ 19.8; Nortriptyline and Lithium 59.2 $\pm$ 18.3. **Gender**: Placebo M31.0% F69.0%; Nortriptyline and Placebo M29.5% F70.4%; Nortriptyline and Lithium M39.3% F60.7%. **History**: Psychotic: Placebo 44.8%; Nortriptyline and Placebo 37.0%; Nortriptyline and Lithium 42.9%. Medication resistant: Placebo 48.3%; Nortriptyline and Placebo 44.4%; Nortriptyline and Lithium 50.0%.	**Comparison**: C.TCA vs CTCA+Li vs C. Placebo **ECT**: Based on clinical judgement - either unilateral or bilateral ECT using the d'Elia or bifrontotemporal placements respectively. 3X weekly. Seizure threshold calculated at first treatment using empirical titration; minimal duration 20 seconds of motor/25 seconds EEG. Length of ECT course determined on clinical grounds. **Comparator**: Nortriptyline (TCA) 25 mg; Lithium (antimanic) 300 mg; oral doses adjusted to maintain plasma levels at 17-125 ng/mL (Nortriptyline) and 0.7 mEq/L (lithium).	Continuous: HRSD, Clinical Global impression, Global Assessment Scale Dichtomous: relapse defined as mean HRSD (continuous rater and study psychiatrist(of at least 16 that was maintained for at least 1 week.	**N randomised:** 84 **n completed:** 73 **Length of follow up**: 24 weeks	290 patients completed the ECT phase. 159 (54.8%) were remitters. 84 (52.8% entered the continuation phase). 11 patients (13.1%) dropped out of the trial before completing 24 weeks or meeting relapse criteria: 4 placebo; 2 nortriptyline; 4 nortriptyline-lithium).

Table A5.12: RCTS of patient information videos

Author	Methods	Participants	Interventions	OUTCOMES
Battersby et al (86)	**Allocation**: b unclear **Blinding**: not blind	**Inclusion**: Not reported **Exclusion**:Acute or chronic brain disorder, dysfunction or distress to limit participation. Patients about to have ECT were excluded. **Age**: Not reported **Gender**: Not reported **History**: Out patients and admission to psychiatric ward with spectrum of diagnoses of psychotic, neurotic and personality disorders.	**Comparison**: **ECT**: Not ECT involved **Other**: Video: watched a video of a psychiatrist interviewing a depressed elderly inpatient prior to receiving ECT. Interpspersed were segments of her receiving ECT, a post ECT interview, and her leaving hospital well, psychiatrists discussed ECT itself, its indications and side effects. No person was interviewed who expressed disatisfaction with ECT or had a negative outcome with ECT. No video: usual care, did not watch a video.	Continuous: knowledge, behavioural intent, fear Dichtomous: none
Westreich et al (70)	**Allocation**: a concealed **Blinding**: not blind	**Inclusion**: Drawn from geropsychiatry in patient unit and two general psychiatry in patient units, English speaking **Exclusion**:Non English speaking **Age**: Median age video group: 63; no video group: 65 **Gender**: Not reported **History**: Mean (sd) number of past ECT course in video group: 2.57(3.95), no video group: 1.00 (1.34). Mean (sd) score on BPRS video group: 34.71 (7.32), no video group: 40.00 (5.04)	**Comparison**: Video vs no video **ECT**: No ECT **Video+ Written consent:** Received information video on ECT and written consent form prior to giving consent to ECT **Written consent alone**: Received written consent form only prior to giving consent to ECT	Continuous: MMSE BPRS as measures of illness severity, 8 item knowledge questionnaire Dichotomous: none

Table A5.13: Non randomised evidence of efficacy of ECT in older people with depression

Study ID	Method	Participants	Interventions	Outcomes	N/LTF	Follow up
Manly et al (75)	**Design**:cohort (retrospective) **Quality assessment**: Some control of confounding by matching, blinding, comparison treatments and length of follow up not reported	**ECT**: patients aged 75 years or older who were diagnosed with major depressions and who had received ECT between 1987, 36 women, 3 men. **Comparison**: People over 75 treated pharmacologically computer matched by age, gender and discharge diagnosis.	**ECT**: Administered 2 or 3 times per week using brief pulse dvice (Mecta SRI). 19 patients received bilaterla ECT, 9 right unilateral, both bilaterla and unilateral in 9 and not noted in 2 patients. **Pharmacotherapy**: No information provided on drugs received by the pharmacology group.	Response to treatment (good, moderate, poor) complications including falls, CVD, confusion, gastrointestinal, pilmonary, metabolic and total complications.	78 Loss TF: unclear	Not specified
Kroessler and Fogel (76)	**Design**:cohort (retrospective) **Quality assessment**: No control of confounding factors, unblinded outcome assessment	All patients who received ECT at Rhode Island hospital between 1974 and 1983 who were over the age of 80 when admitted and who had a discharge diagnosis of major depressive disorder according to wither DSM-II or ICD 9 or 8 and were treated with ECT or pharmacotherapy. Some patients from the pharmacotherapy group recruited from another hospital	**ECT**: Mean number of ECTs received was 7.9 (2.9). No information on electrode placement, dosage or wave form used. Two patients had only 2 ECTS, one patient withdrew consent and one developed CHF and died before treatment could be continueed. **Pharmacotherapy**: TCAs (n = 20), bezodiazepines (n=15), trazodone (n = 6), neuroleptics (n = 5), chloral hydrate (n = 2), lithium carbonate (n = 2), maprotiline (n = 1), carbamazepine (n = 1) and nomifensine (n = 1).	Mortality, survival, recurrence of depression, rehospitalisationa dditional ECT and residence following hospitalisation	65 Loss TF: 3 in ECT group	3 years

Table A5.13 cont'd

Study ID	Method	Participants	Interventions	Outcomes	N/LTF	Follow up
Philibert et al (77)	**Design**:cohort (retrospective) **Quality assessment**: No control of confounding factors, unblinded outcome assessment	All patients who were older than 65 years and admitted to hospital meeting the DSM-III criteria for unipolar depression between 1980 and 1987, identified by computerised search.	**ECT**: Mean (SD) number of ECTs 10.7 (4.1). ECT administered 3 times per week and both unilaterla and bilateral ECT was used but no information is provided on the numbers receiving either. **Pharmacotherapy**: No information provided on treatment received by those not receiving ECT.	Global improvement and all cause mortality	192 unclear	Until 1992, between 5 and 12 years
Rubin et al (73;74)	**Design**:cohort (prospective) **Quality assessment**: Some control over confounding variables using statistical analyses and exclusions, unblinded outcome assessment but loss to follow up reported.	All patients with a major affective disorder (either unipolar or bipolar), without other psychiatric diagnoses and without possible or probable dementia admitted to an inpatient unit for people over the age of 65.	**ECT**: 3 times per week at a moderately suprathreshold dose using a Mecta SRI brief pulse device. 36 received bilateral ECT, 6 received unilateral ECT using the D'Elia placement and 6 received both. Seizures were monitored using EEG. The mean (SD) number of treatments was 9.3 (3). **Pharmacotherapy**: Both the non ECT group and the ECT group received pharmacotherapy and the type and dose of treatment was derermined by the treating physician, including TCAs, antipsychotics, lithium and antianxiety agents.	Geriatric depression scale, Beck Depression Inventory, Minimental state examination and length of stay.	103 Loss TF: 7/48 ECT group; 8/55 in control	Until discharge

157

Table A5.14: Non randomised evidence: Children and adolescents

Study ID	Method	Participants	Interventions	Outcomes	N/LTF	Follow up
Cohen et al (72) (	Design:case control (retrospective) Quality assessment: Large loss to follow up, no control of confounding variables, unblinded outcome assessment	20 adolescents treated with ECT for a mood disorder prior to the age of 19 in 3 adolescent units and 2 adult clinics in Paris between 1987 and 1996, but only 10 were included in the study (6 women, 4 men). .5 had major depression with psychotic features, 3 had manic depression with psychotic features and 2 had mixed depression with psychotic features. 10 matched controls who had never received ECT.	ECT: ECT:Bilateral ECT between 2 and 9 years previous to interviews. Received a mean of 9.8 ECTs. Comparison: No information on treatment received	Clinical judgement of improvement, relapses and various cognitive test including MMSE, Weschler Memeort test, California Verbal Learning Tests. Perceptions of the adequacy of ECT information and perceptions of the perceived benefit of ECT.	30 10	mean 5.2 years post ECT

Table A5.15: Non randomised evidence: Catatonia

Study ID	Method	Participants	Interventions	Outcomes	N/LTF	Follow up
Bush et al (79)	Design:case series (prospective) Quality assessment: No control group, unblinded assessment of outcome, loss to follow up	Those treated with ECT were those who failed to respond to lorazepam 5/28. 3/5 had mania, 3 women, 2 men and the duation of catatonia was 11 days (SD 12.1).	ECT: in 5 patients the sysmptoms of catatonia resolved 2 days before treatment. 2 patients were withdrawn. 21 patients received a full trial of lorazepam for up to 5 days. 16/21 had signs of catatonia relieved and 11 of these had a full resoluation of catatonic symptoms. The 5 nonresponders were treated with ECT, one refused consent. Comparison: None	BFCRS scores	1	End of treatment
Malur et al (80)	Design:case series (prospective) Quality assessment:	Case 1: Age 24, female, no known medical or psychiatric history, 7 catatonic signs with a duration of 14 weeks prior to ECT, BFCRS score of 19, probable NMS, respiratory acidosis and carida asystole. Case 2: Age 26, female, systemic lupus erythematosus, 4 signs of catatonia with a duration of 14 weeks, BFCRS score 14, respiratory acidosis. Case 3: Aged 39, male, hypertension, Schizo-affective disorder and mild mental retardation, 4 signs of catatonia with a duration of 10 weeks, BFCRS score 16, definite NMS, acute respiratory insufficiency.	ECT: Case 1: Max 12md/D Lorazepam for 5.5 weeks resulting in BFCRS score of 15 then follwed by 15 bilateral ECTs over a 6 week period. Case 2: Max of Lorazepam 4mg/d for 10 weeks resulting in BFCRS score of 10, followed by 14 bilateral ECTs over 5 weeks Case 3: Max of Lorazepam 16mg/day for 3 weeks resulting in BFCRS score of 10 followed by 22 bilateral ECTs over 3 months. All ECTs were administered using a Thymatron DG device with bi-directional brief pulse sqaure current 3 times per week. Initial stimulus intensisty was 50% in Case !, 20% in Case 2 and 40% in Case 3.	Bush Francis Catatonia Rating Scale (BFCRS)		Variable

Table A5.16: non randomised evidence: pregnancy

Study ID	Method	Participants	Interventions	Outcomes	N/LTF	Follow up
Bhatia et al (82) 1999	Design:Case series (prospective) Quality assessment:	Case 1: Age 26, white primagravida at 35 weeks gestation, uncomplicated pregancy. Current episode treated with desipramine (150g per day) and lorazepam (0.5mg t.I.d. Case 2: Age 23 white gravida at 27 weeks gestation. Pregnancy complicated by generalised anxity disorderwith panic attacks and depression resulting in wieght loss and an episode of threatened abortion. Failed to respon to desipramine 400mg/day, oxazepam 15mg q.I.d and tryptopham 1g qhs	ECT: Case 1: Bilateral ECT 3 times per week for 6 treatments in delivery room Case 2: Bilateral ECT 5 treatments, one on day 1 two on day 2 and two on day 3 Comparison:	Clinical opinion on efficacy, complications	2	
Moreno et al (83)	Design:case report (prospective) Quality assessment:	Aged 25, 8 weeks gestation. Diagnosed with severe depression with psychotic symptoms. Initally treated with levopromazine (25mg intramuscularly) and haloperidol (5mg) then changed to amitryptaline (75)mg), haloperidol (10mg) and carbemazepine (1,200mg). Treatment with amitryptaline and carbemazepine was stopped when a second pregnancy test was positive.	ECT: Bilateral ECT with sine wave of 2.5s duration at an intenstity of 0.7A for 9 treatments Comparison:	Clinical opinion of efficact, adverse events		

Table A5.16 cont'd

ID	Method	Participants	Interventions	Outcomes	N/LTF	Follow up
Polster and Wisner (84)	Design:case report Quality assessment:	Aged 29 white in week 23 of pregnancy. History of paranoid schizophrenia and depression. Current episode became catatonic and suicidal. Did not respond to Resperidone (3mg b.I.d.), loxapine (75mg b.I.d.), lorazepam (1mg t.i.d.) and noritriptyline (50mg).	ECT: Unilateral ECT, pulse width 1.2ms, frequency 50hz current 0.6A and seizure length 89s for 8 treatments followed by bilateral ECT 3 times per week for 3 and a half weeks. Comparison:	Clinical improvement, adverse events	1	

Reference List

(1) Walter G, Rey JM, Mitchell PB. Practitioner review: electroconvulsive therapy in adolescents. [Review] [67 refs]. Journal of Child Psychology & Psychiatry & Allied Disciplines 1999; 40(3):325-334.

(2) Department of health. Electro-convulsive therapy:survey covering the period January 1999 to March 1999, England. -. 2002.
Ref Type: Generic

(3) American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. American Journal of Psychiatriy 1997; 154(4 Suppl):1-63.

(4) Freeman CP. The ECT handbook : the second report of the Royal College of Psychiatrists' Special Committee on ECT. London: - 17 Belgrave Square, London SW1X 8PG : Royal College of Psychiatrists, 1995, 1995.

(5) Oh PI, Iskedjian M, Addis A. Pharmacoeconomic evaluation of clozapine in treatment-resistant schizophrenia: A cost-utility analysis. Pharmacoeconomics 2001; 8(4):199-206.

(6) Fink M. Convulsive therapy: A review of the first 55 years. Journal of Affective Disorders 2001; 63(1-3):1-15.

(7) Sterling P. ECT damage is easy to find if you look for it. Nature 2000; 403:242.

(8) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association, 2000.

(9) World Health Organisation. International Classification of Diseases, 10th Revision. Geneva: World Health Organisation, 1992.

(10) Kruger S, Braunig P. Catatonia in affective disorder: new findings and a review of the literature. CNS Spectrums 2000; 5(7):48-53.

(11) Singleton N, Bumpstead R, O'Brien M, Lee A, Meltzer HY. Psychiatric morbidity among adults living in private households, 2000: summary report. 2002. London: Office for National Statistics.
Ref Type: Report

(12) Office for National Statistics. Key Health Statistics from General Practice 1998. 2000. MB6 No.2.
Ref Type: Report

(13) Hale A. ABC of mental health: depression. British Medical Journal 1997; 315:43-46.

(14) Clinical Standards Advisory Group Committee on Schizophrenia. Schizophrenia: Volume 1. 1995. London: HMSO.
Ref Type: Report

(15) Devanand DP, Verma AK, Tirumalasetti F, Sackeim HA. Absence of cognitive impairment after more than 100 lifetime ECT treatments. American Journal of Psychiatry 1991; 148(7):929-932.

(16) Sackeim HA, Devanand DP, Prudic J. Stimulus intensity, seizure threshold, and seizure duration: impact on the efficacy and safety of electroconvulsive therapy. Psychiatric Clinics of North America 1991; 14:803-844.

(17) American Psychiatric Association. The practice of electroconvulsive therapy: Recommendations for treatment, training and priveliging. 2nd ed. Washington DC: American Psychiatric Association, 2001.

(18) Freeman C. The ECT Handbook. The Royal College of Psychiatrists, 1995.

(19) Benbow SM, Tench D, Darvill SP. Electroconvulsive therapy practice in north-west England. PSYCHIATR BULL 1998; 22(4):226-229.

(20) [Anon]. National Audit of Electroconvulsive therapy (ECT) in Scotland: final Report. 1-33. 2002.
Ref Type: Report

(21) Adler DA, Gorelick DA, Rummans TA, Bell C, Greene JA, Shapiro HL et al. Practice guideline for the treatment of patients with major depressive disorder (Revision). AM J PSYCHIATRY 2000; American-Journal-of-Psychiatry. 2000; 157(4 SUPPL.):1-45.

(22) Einarson TR, Arikian S, Casciano J, Doyle JJ. Comparison of Extended-Release Venlafaxine, Selective Serotonin Reuptake Inhibitors, and Tricyclic Antidepressants in the Treatment of Depression: A Meta-Analysis of Randomized Controlled Trials. Clinical Therapeutics 1999; 21(2):296-308.

(23) Fava M, Davidian KG. Definition and epidemiology of treatment resistant depression. Psychiatric Clinics of North America 1996; 19:179-200.

(24) Blashki TG, Mowbry R, Davies B. A controlled trial of amitryptaline in general pracitce. British Medical Journal 1971; 1:133-138.

(25) Nierenberg AA, Amsterdam JD. Treatment resistant depression: Definition and treatment approaches. Journal of Clinical Psychiatry 1990; 51(Suppl 6):39-47.

(26) American Psychiatric Association. Practice guidelines for the treatment of patients with major depressive disorder. American Journal of Psychiatriy 2000; 157(4 Suppl):1-45.

(27) Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY 10(2): 96 104 1990.

(28) Loo C, Mitchell P, Sachdev P MB, Parker G, Gandevia S. A double blind controlled investigation on transcranial megnetic stimulation for the treatment of resistant major depression. American Journal of Psychiatriy 1999; 156:946-948.

(29) Joy C, Adams CE, Laurie SM. Haloperidol vs placebo for schizophrenia. The Cochrane Library (Oxford) ** 2001 issue 2 (13 p) (7 ref 7 bib) (Update Software, online or CD-ROM, updated quarterly). 2001.
Ref Type: Electronic Citation

(30) Thornley B, Adams CE, Awad G. Chlorpromazine versus placebo for schizophrenia. In: The Cochrane Library, Issue 4, 2001 2001.

(31)   Wahlbeck K, Cheine M, Essali MA. Clozapine versus typical neuroleptic medication in schizophrenia. The Cochrane Library, Issue 2, 2002: Oxford: Update Software . 1999.
Ref Type: Electronic Citation

(32)   Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. [Review] [0 refs]. Postgraduate Medicine 2000; Spec No:1-104.

(33)   Ungvari GS, Leung SK, Wai KT, Ng FS. The pharmacological treatment of catatonia: An overview. EUR ARCH PSYCHIATRY CLIN NEUROSCI 2001; European-Archives-of-Psychiatry-and -Clinical-Neuroscience. 2001; 251(Suppl. 1):31-34.

(34)   Weiner R. Treatment optimisation with ECT. Psychopharmacology Bulletin 1994; 30:313-320.

(35)   Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. [see comments]. New England Journal of Medicine 1993; 328(12):839-846.

(36)   Duffett R, Lelliott P. Auditing electroconvulsive therapy: the third cycle. British Journal of Psychiatry 1998; 172:401-405.

(37)   Duffett R, Hill P, Lelliot P. Use of electroconvulsive therapy in young people. The British Journal of Psychiatry 175[9], 228-230. 1999.
Ref Type: Journal (Full)

(38)   Royal College of Psychiatrists. The Royal College of Psychiatrists' memorandum on the use of electroconvulsive therapy. British Journal of Psychiatry 1977; 131:261-272.

(39)   Pippard J, Ellam L. Electroconvulsive therapy in Great Britain: a report to the college. British Journal of Psychiatry 1981; 139(563):568.

(40)   Pippard J. Audit of electroconvulsive treatment in two National Health Service regions. The British Journal of Psychiatry 1992; 160 no p621-637(p621-637):621-637.

(41)   Hillam J, Thompsell A, Tobiansky R. Administration of ECT by trainee psychiatrists. An audit of supervision, adequacy of tuition and attitudes. PSYCHIATR BULL 1997; 21(4):217-220.

(42)   Duffett R, Lelliot P. Junior doctors' training in the theory and the practice of electroconvulsive therapy. Psychiatric Bulletin 1997; 21:563-565.

(43)   Department of health. National Framework fo Mental Health. 1999. Department of Health.
Ref Type: Report

(44)   Oxman AD, Cook DJ, Guyatt GH. User's Guides to the medical literature. IV: How to use an overview. Evidence Based Medicine Working Group. Journal of the American Medical Association 1994; 272(17):1367-1371.

(45)   Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ et al. Assessing the quality of reports of randomised clinical trials: is blinding necessary? Controlled Clinical Trials 1996; 17:1-12.

(46) Clarke M, Oxman AD. Cochrane Collaboartion Handbook. The Cochrane Libary, Issue 3, 2001 . 2002. Oxford: Update Software.
Ref Type: Electronic Citation

(47) Levine M, Walter S, Lee H, Haines T, Holbrook A, Moyer V. User's guides to the medical literature. IV. How to use an article about harm. Evidence-Based Medicine Working Group. Journal of the American Medical Association 1994; 271(20):1615-1619.

(48) Popay J, Rogers A, Williams G. Ratioonal and standards in the systematic review of qualitative literature in health services research. Qualitative Health Research 1998; 8:341-351.

(49) Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMG. The BMJ Economic Evaluation Working Party. British Medical Journal 1996; 313:275-283.

(50) DerSimion R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7:177-188.

(51) Marshall M, Lockwood A, Bradley C, Adams C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. British Journal of Psychiatry 2000; 176:249-252.

(52) Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. 2002.
Ref Type: Report

(53) UK ECT Review Group. Systematic review of the efficacy and safety of electroconvulsive therapy. 2002.
Ref Type: Report

(54) Jagadeesh HN, Gangadhar BN, Janakiramaiah N, Subbakrishna DK, Jain S. Time dependent therapeutic effects of single electroconvulsive therapy (ECT) in endogenous depression. Journal of Affective Disorders 1992; 24(4):291-295.

(55) Service User Research Enterprise and Institute of Psychiatry. Review of consumers perspectives on electro convusive therapy. 2002.
Ref Type: Report

(56) Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. Biological Psychiatry 2000; 47(4):314-324.

(57) Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. Depression & Anxiety 2000; 12(3):118-123.

(58) Mayur PM, Gangadhar BN, Subbakrishna DK, Janakiramaiah N. Discontinuation of antidepressant drugs during electroconvulsive therapy: a controlled study. Journal of Affective Disorders 2000; 58(1):37-41.

(59) Shiah IS, Yatham LN, Srisurapanont M, Lam RW, Tam EM, Zis AP. Does the addition of pindolol accelerate the response to electroconvulsive therapy in patients with major

depression? A double-blind, placebo-controlled pilot study. Journal of Clinical Psychopharmacology 2000; 20(3):373-378.

(60)   Arfwidsson L, Arn L, Beskow J, d'Elia G, Laurell B, Ottosson JO et al. Chlorpromazine and the anti-depressive efficacy of electroconvulsive therapy. Acta Psychiatrica Scandinavica 1973; 49(5):580-587.

(61)   Kirkegaard C, Moller SE, Bjorum N. Addition of L-tryptophan to electroconvulsive treatment in endogenous depression. A double-blind study. Acta Psychiatrica Scandinavica 1978; 58(5):457-462.

(62)   d'Elia G, Lehmann J, Raotma H. Evaluation of the combination of tryptophan and ECT in the treatment of depression. I. Clinical analysis. Acta Psychiatrica Scandinavica 1977; 56(4):303-318.

(63)   Seager CP, Bird RL. Imipramine with electrical treatment in depression: a controlled trial. Journal of Mental Science 1962; 108:704-707.

(64)   Imlah NW, Ryan E, Harrington JA. The influence of antidepressant drugs on the response to electroconvulsive therapy and on subsequent relapse rates. Neuropharmacology 1965; 4:438-442.

(65)   Kay DW, Fahy T, Garside RF. A seven-month double-blind trial of amitriptyline and diazepam in ECT-treated depressed patients. British Journal of Psychiatry 1970; 117(541):667-671.

(66)   Lauritzen L, Odgaard K, Clemmesen L, Lunde M, Ohrstrom J, Black C et al. Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. [see comments]. Acta Psychiatrica Scandinavica 1996; 94(4):241-251.

(67)   Coppen A, Abou-Saleh MT, Milln P, Bailey J, Metcalfe M, Burns BH et al. Lithium continuation therapy following electroconvulsive therapy. British Journal of Psychiatry 1981; 139:284-287.

(68)   Grunhaus L, Hirschman S, Dolberg OT, Schreiber S, Dannon PN. Coadministration of melatonin and fluoxetine does not improve the 3-month outcome following ECT. J ECT 2001; Journal-of-ECT. 2001; 17:2-128.

(69)   Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: A randomized controlled trial. J AM MED ASSOC 2001; 285:10-1307.

(70)   Westreich L, Levine S, Ginsburg P, Wilets I. Patient knowledge about electroconvulsive therapy: Effect of an informational video. CONVULSIVE THER 1995; 11(1):32-37.

(71)   Rey JM, Walter G. Half a century of ECT use in young people. [Review] [96 refs]. American Journal of Psychiatry 1997; 154(5):595-602.

(72)   Cohen D, Taieb O, Flament M, Benoit N, Chevret S, Corcos M et al. Absence of cognitive impairment at long-term follow-up in adolescents treated with ECT for severe mood disorder. American Journal of Psychiatry 2000; 157(3):460-462.

(73) Rubin EH, Kinscherf DA, Wehrman SA. Response to Treatment of Depression in the Old and Very Old. Journal of Geriatric Psychiatry & Neurology 1991; 4:65-70.

(74) Rubin EH, Kinscherf DA, Figiel GS, Zorumski CF. The nature and time course of cognitive side effects during electroconvulsive therapy in the elderly. Journal of Geriatric Psychiatry & Neurology 1993; 6(2):78-83.

(75) Manly DT, Oakley SP, Jr., Bloch RM. Electroconvulsive therapy in old-old patients. American Journal of Geriatric Psychiatry 2000; 8(3):232-236.

(76) Kroessler D, Fogel BS. Electroconvulsive therapy for major depression in the old. Am J Geriatric Psych 1993; 1:30-37.

(77) Philibert RA, Richards L, Lynch CF, Winokur G. Effect of ECT on mortality and clinical outcome in geriatric unipolar depression. Journal of Clinical Psychiatry 1995; 56(9):390-394.

(78) Hawkins JM, Archer KJ, Strakowski SM, Keck PE. Somatic treatment of Catatonia. International Journal of Psychiatry in Medicine 1995; 25(4):345-369.

(79) Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia .2. Treatment with lorazepam and electroconvulsive therapy. Acta Psychiatrica Scandinavica 1996; 93(2):137-143.

(80) Malur C, Pasol E, Francis A. ECT for Prolonged Catatonia. Journal of Ect 2001; 17(1):55-59.

(81) Miller LJ. Use of electroconvulsive therapy during pregnancy. H&Cp - Hospital & Community Psychiatry 1994; 45(5):444-450.

(82) Bhatia SC., Baldwin SA., Bhatia SK. Electroconvulsive therapy during the third trimester of pregnancy. Journal of Ect 15(4):270-4, 1999 Dec 1999.

(83) Echevarria Moreno M., Martin Munoz J., Sanchez Valderrabanos J., Vazquez Gutierrez T. Electroconvulsive therapy in the first trimester of pregnancy. [Review] [18 refs]. Journal of Ect 14(4):251-4, 1998 Dec 1998.

(84) Polster DS., Wisner KL. ECT-induced premature labor: a case report. Journal of Clinical Psychiatry 60(1):53-4, 1999 Jan 1999.

(85) Einarson TR, Addis A, Mittmann N, Iskedjian M. Meta-analysis of venlafaxine, SSRIs and TCAs in the treatment of major depressive disorder. Can J Clin Pharmacol 1998; 5(4):205-216.

(86) Battersby M, Ben Tovim D, Eden J. Electroconvulsive therapy: a study of attitudes and attitude change after seeing an educational video. Australian & New Zealand Journal of Psychiatry 1993; 27(4):613-619.

(87) Gregory S, Shawcross CR, Gill D. The Nottingham ECT Study. A double-blind comparison of bilateral, unilateral and simulated ECT in depressive illness. British Journal of Psychiatry 1985; 146:520-524.

(88) McDonald IM, Perkins M, Marjerrison G, Podilsky M. A controlled comparison of amitriptyline and electroconvulsive therapy in the treatment of depression. American Journal of Psychiatry 1966; 122(12):1427-1431.

(89) Brandon S, Cowley P, McDonald C, Neville P, Palmer R, Wellstood-Eason S. Electroconvulsive therapy: results in depressive illness from the Leicestershire trial. British Medical Journal Clinical Research Ed 1984; 288(6410):22-25.

(90) Johnstone EC, Deakin JF, Lawler P, Frith CD, Stevens M, McPherson K et al. The Northwick Park electroconvulsive therapy trial. Lancet 1980; 2(8208-8209):1317-1320.

(91) Lambourn J, Gill D. A controlled comparison of simulated and real ECT. British Journal of Psychiatry 1978; 133:514-519.

(92) Freeman CP, Basson JV, Crighton A. Double-blind controlled trail of electroconvulsive therapy (E.C.T.) and simulated E.C.T. in depressive illness. Lancet 1978; 1(8067):738-740.

(93) Wilson IC, Vernon jt, Guin T. A controlled study of treatments of depression . Journal of Neuropsychiatry 1963; 4:331-337.

(94) West ED. Electric convulsion therapy in depression: a double-blind controlled trial. British Medical Journal Clinical Research Ed 1981; 282(6261):355-357.

(95) Kendrick DC, Parboosingh R, Post F. A synonym learning test for use with elderly psychiatric subjects: a validation study. British Journal of Social & Clinical Psychology 1965; 4:63-71.

(96) Davidson J, McLeod M, Law-Yone B, Linnoila M. A comparison of electroconvulsive therapy and combined phenelzine-amitriptyline in refractory depression. Archives of General Psychiatry 1978; 35(5):639-642.

(97) Janakiramaiah N, Gangadhar BN, Naga Venkatesha Murthy PJ, Harish MG, Subbakrishna DK, Vedamurthachar A. Antidepressant efficacy of Sudarshan Kriya Yoga (SKY) in melancholia: a randomized comparison with electroconvulsive therapy (ECT) and imipramine. Journal of Affective Disorders 2000; 57(1-3):255-259.

(98) Shepherd M. Clinical trail of the treament of depressive illness. BMJ 1965; 1:881-886.

(99) Bruce EM, Crone N, Fitzpatrick G. A comparative trial of ECT and Tofranil. AM J PSYCHIATRY 1960; 117:76.

(100) Bagadia VN, Shah LP, Pradhan PV, Doshi J, Abhyankar RR. Evaluation of cognitive effects of ECT:preliminary observations. Indian Journal of Psychiatry 1981; 23(4):324-329.

(101) Hutchinson j, Smedberg D. Treatment of depression: a comparative study of ECT and six drugs. BR J PSYCHIATRY 1963; 109:536-538.

(102) Steiner M, Radwan M, Elizur A. Failure of L-triiodothyronine(Tsub 3) to potentiate tricyclic antidepressant response. Current Therapeutic Research 1978; 23:655-659.

(103) MacSweeney DA. Letter: Treatment of unipolar depression. Lancet 1975; 2(7933):510-511.

(104) Herrington RN, Bruce A, Johnstone EC. Comparative trial of L-tryptophan and E.C.T. in severe depressive illness. Lancet 1974; 2(7883):731-734.

(105) Gangadhar BN, Kapur RL, Kalyanasundaram S. Comparison of electroconvulsive therapy with imipramine in endogenous depression: a double blind study. British Journal of Psychiatry 1982; 141:367-371.

(106) Dinan TG, Barry S. A comparison of electroconvulsive therapy with a combined lithium and tricyclic combination among depressed tricyclic nonresponders. Acta Psychiatrica Scandinavica 1989; 80(1):97-100.

(107) Folkerts HW, Michael N, Tolle R, Schonauer K, Mucke S, Schulze-Monking H. Electroconvulsive therapy vs. paroxetine in treatment-resistant depression -- a randomized study. Acta Psychiatrica Scandinavica 1997; 96(5):334-342.

(108) Greenblatt M, Grosser G. Differential response of hospitalised depressed patients to somatic therapy. AM J PSYCHIATRY 1964; 120:935-943.

(109) Stanley W, Fleming H. A clinical comparison of phenelzine and electro-convulsive therapy in the treatment of depressive illness. Journal of Mental Science 1962; 108:708-710.

(110) Robin A, Harris JA. A controlled comparison of imipramine and electroplexy. BR J PSYCHIATRY 1962; 108:217-219.

(111) Abraham KR, Kulhara P. The efficacy of electroconvulsive therapy in the treatment of schizophrenia. A comparative study. British Journal of Psychiatry 1987; 151:152-155.

(112) Agarwal AKWGC. TI: Role of ECT phenothiazine combination in schizophrenia. Indian Journal of Psychiatry 1985; 27(3):233-236.

(113) Brandon S, Cowley P, McDonald C, Neville P, Palmer R, Wellstood-Eason S. Leicester ECT trial: results in schizophrenia. British Journal of Psychiatry 1985; 146:177-183.

(114) Eiduson S, Brill NG, Crumpton E. The effect of electroconvulsive therapy on spinal fluid constituents. British Journal of Psychiatry 1958;692-698.

(115) Goswami U. Efficacy of electro convulsive therapy in treatment resistant schizophrenia syndrome:a double blind study. Efficacy of electro convulsive therapy in treatment resistant schizophrenia syndrome:a double blind study. Efficacy of electroconvulsive therapy in treatment resistant schizophrenia syndrome:a double blind study. 53rd Annual Conference of the Indian Psychiatry Society 2001 Jan 9th-11th; Pune 2001; conference proceedings.

(116) Janakiramiah N. Ect-chlorpromazine combination compared with chlorpromazine only in schizophrenia. Indian Journal of Psychiatry 1981; 23:230-233.

(117) Janakiramaiah N, Channabasavann ASM, Narasimha-Murphy N. ECT/chlorpromazine combination versus chloropromazine alone in acutely ill schizophrenia patients. Acta Psychiatrica Scandinavica 1982; 66(464-470).

(118) Miller DH. A comparison between unidirectional current nonconvulsive eletrical stimulation given with reiter's machine, standard alternating current electroshock (cerletti

method), and pentothal in chronic schizophrenia. American Journal of Psychiatry 1953; 109:617-620.

(119)   Sarkar P, Andrade C, Kapur B, Das P, Sivaramakrishna Y, Harihar C et al. An exploratory evaluation of ECT in haloperidol-treated DSM-IIIR schizophreniform disorder. Convulsive Therapy 1994; 10(4):271-278.

(120)   May PR. Treatment of schizophrenia
PG: Science House, 1968
NO: ~. science house 1968; 1968.

(121)   Taylor P, Fleminger JJ. ECT for schizophrenia. Lancet 1980; 1(8183):1380-1382.

(122)   Naidoo D. The effects of reserpine (serpasil) on the chronic disturbed schizophrenic: a comparative study of rauwolfia alkaloids and electroconvulsive therapy. Journal of Nervous and Mental Disease 1956; 123:1-13.

(123)   Small JG. Ect combined with neuroleptics in the treatment of schizophrenia. Psychopharmacology Bulletin 1982; 18:34-35.

(124)   Sarita E, Janakiramaiah N, Gangadhar BN, Subbakrishna DK, Rao K. Efficacy of combined ECT after two weeks of neuroleptics in schizophreina: a double blind controlled study. NIMHANS J 1998;243-251.

(125)   Baker A. Physical treatment for schizophrenia. British Journal of Psychiatry 1958; 1958:860-864.

(126)   Ungvari G, Petho B. High-dose haloperidol therapy:its effectiveness and a comparison with electroconvulsive treatment. Journal of Psychiatric Treatment and Evaluation 1982; 4:279-283.

(127)   Wu D, et a. Using bprs and serial numbers and picture recall to test the effectiveness of ect versus chlorpromazine versus chlorpromazine alone in the treatment of schizophrenia: 40 cases, single blind observations. Chinese Journal of Nervous and Mental Disorders 1989; 15:26-28.

(128)   Doongaji DR, Jeste DV, Saoji NJ, Kane PV, Ravindranath S. Unilateral versus bilateral ECT in schizophrenia. British Journal of Psychiatry 1973; 123(572):73-79.

(129)   Chanpattana W, Chakrabhand ML, Buppanharun W, Sackeim HA. Effects of stimulus intensity on the efficacy of bilateral ECT in schizophrenia: a preliminary study. Biological Psychiatry 2000; 48(3):222-228.

(130)   Abrams R. Daily administration of unilateral ECT. American Journal of Psychiatriy 1967; 124(3):384-386.

(131)   Baker JC. Ect in schizophrenia. Journal of Mental Science 1960; 1960:1506-1511.

(132)   Chanpattana W, Chakrabhand ML, Sackeim HA, Kitaroonchai W, Kongsakon R, Techakasem P et al. Continuation ECT in treatment-resistant schizophrenia: a controlled study. Journal of Ect 1999; 15(3):178-192.

(133) Moore P, Landolt HP, Seifritz E, Clark C, Bhatti T, Kelsoe J et al. Clinical and physiological consequences of rapid tryptophan depletion. [Review] [125 refs]. Neuropsychopharmacology 2000; 23(6):601-622.

(134) Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. [see comments]. Archives of General Psychiatry 2000; 57(5):425-434.

(135) Dardennes RM, Lafuma A, Fagnani F, Pribil C, Bisserbe JC, Berdeaux G. Economic Assessment of a Maintenance Treatment Strategy in Prevention of Recurrent Depressive Disorder. Value in Health 2000; 3:40-47.

(136) Kamlet MS, Paul N, Greenhouse J, Kupfer DJ, Frank E, Wade M. Cost Utility Analysis of Maintenance Treatment for Recurrent Depression. Control Clin Trials 1995; 16:17-40.

(137) Revicki DA, Brown RE, Palmer W, Bakish D, Rosser W, Anton SF et al. Modelling the Cost Effectiveness of Antidepressant Treatment in Primary Care. Pharmacoeconomics 1995; 8(6):524-540.

(138) Janicak PG, Davis JM, Gibbons RD, Ericksen S, Chang S, Gallagher P. Efficacy of ECT: a meta-analysis. American Journal of Psychiatry 1985; 142(3):297-302.

(139) Sackeim HA. Continuation Therapy Following Ect - Directions for Future- Research. Psychopharmacology Bulletin 1994; 30(3):501-521.

(140) Prudic J, Sackeim HA, Devanand DP. Medication resistance and clinical response to electroconvulsive therapy. PSYCHIATRY RESEARCH 31(3): 287 296 1990.

(141) Einarson TR, Arikian S, Sweeney S. A Model to Evaluate the Cost-Effectiveness of Oral Therapies in The Management of Patients with Major Depressive Disorders. Clinical Therapeutics 1995; 17(1):136-153.

(142) Burke WI, Rubin EH, Zorumski CF, Wetzel RD. The safety of ECT in geriatric psychiatry. Journal of Merican Geriatrics Society 1987; 35(6):516-521.

(143) Doyle JJC. A multinational pharmacoeconomic evaluation of acute major depressive disorder (MDD): a comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs. Value in Health 2001; 4(1):16-31.

(144) Freeman H, Arikian S, Lenox SA. Pharmacoeconomic analysis of antidepressants for major depressive disorder in the United Kingdom. Pharmacoeconomics 2000; PharmacoEconomics. 2000; 18(2):143-148.

(145) Bauer M, Dopfmer S. Lithium Augmentation in Treatment-Resistant Depression: Meta-Analysis of Placebo-Controlled Studies. Journal of Clinical Psychopharmacology 1999; 19(5):427-434.

(146) Clerc GE, Ruimy P, Verdeau-Pailles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. International Clinical Psychopharmacology 1994; 9:139-143.

(147) Byrne SE, Rothschild AJ. Loss of Antidepressant Efficacy During Maintenance Therapy: Possible Mechanisms and Treatments. J CLIN PSYCHIATRY 1998; 59(6):279-288.

(148) Hirschfeld-Robert MA. Clinical importance of long-term antidepressant treatment. British Journal of Psychiatry 2001; 179:s4-s8.

(149) Swoboda E, Conca A, Konig P, Waanders R, Hansen M. Maintenance electroconvulsive therapy in affective and schizoaffective disorder. Neuropsychobiology 2001; 43(1):23-28.

(150) Hirschfeld RM. Efficacy of SSRIs and newer antidepressants in severe depression: comparison with TCAs. [Review] [58 refs]. Journal of Clinical Psychiatry 1999; 60(5):326-335.

(151) Montgomery SA, Brown RE, Clark M. Economic Analysis of Treating Depression with Nefazodone *v*. Imipramine. British Journal of Psychiatry 1996; 168:768-771.

(152) Fraser RM, Glass IB. Unilateral and bilateral ECT in elderly patients. A comparative study. Acta Psychiatrica Scandinavica 1980; 62(1):13-31.

(153) Revicki DA, Wood M. Patient-assigned health state utilities for depression-related outcomes: differences by depression sverity and anti-depressant medications. Journal of Affective Disorders 1998; 48:25-36.

(154) Bennett KJ, Torrance GW, Boyle MH, Guscott R. Cost-Utility Analysis in Depression: The McSad Utility Measure for Depression Health States. PSYCHIATR SERV 2000; 51(9):1171-1176.

(155) Raftery J. NICE: Faster access to modern treatments? Analysis of guidance on health technologies. BMJ 2001; 323:1300-1303.

(156) Royal College of Psychiatrists. The Practical Administration of Electroconvulsive Therapy. London: Gaskell, 1989.

(157) Fink M, Sackeim HA. Convulsive therapy in schizophrenia? Schizophrenia Bulletin 1996; 22:27-39.

(158) McCall WV, Dunn AG, Kellner CH. Recent advances in the science of ECT: Can the findings be generalized? Journal of Ect 2000; 16(4):323-326.

(159) Heikman P, Katila H, Sarna S, Wahlbeck K, Kuoppasalmi K. Differential response to right unilateral ECT in depressed patients: impact of co-morbidity and severity of illness. BMC Psychiatry 2[2]. 2002.
Ref Type: Electronic Citation

(160) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Discorders. third ed. American Psychiatric Association, 1987.

(161) Feighner JP, Robins E, Guze SB, Woofruff R A, Winokur G, Munoz -RA. Diagnostic criteria for use in psychiatric research. Archives of General Psychiatry 1972; 26(1):57-63.

(162) Klein DF. Endomorphic depression. Archives of General Psychiatry 1974; 31:447.

(163) Leonhard K. The Classification of endeogenous psychoses. New York: Irvington, 1979.

(164) Langfeldt G. Diagnosis and prgnosis of schizophrenia. Proceedings of the Royal Society of Medicine 1960; 53:1047-1052.

(165) Chanpattana W. Maintenance ECT in treatment-resistant schizophrenia. Journal of the Medical Association of Thailand 2000; 83(6):657-662.

(166) Kane JM, Honigfeld G, Singer J Meltzer H Clozaril Collaborative study Group. Clozapine for the treatment of treatment resistant schizophrenia: a double blind comparison with chlorpormazine. Archives of General Psychiatry 1988; 45:789-796.

Appendix 6: results of included studies

Comparison: 09 Real ECT vs Sham ECT
Outcome:　01 Bilateral ECT

Study	Favours Real ECT n/N	Favours Sham ECT n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Freeman et al.	16 / 20	20 / 20		37.7	0.80[0.64,1.00]
Jagadeesh et al.	10 / 12	8 / 12		33.0	1.25[0.78,2.01]
Johnstone et al.	20 / 37	9 / 33		29.4	1.98[1.05,3.73]
Total(95%CI)	46 / 69	37 / 65		100.0	1.21[0.61,2.40]

Test for heterogeneity chi-square=15.42 df=2 p=0.0004
Test for overall effect z=0.55 p=0.6

.2　.5　1　2　5
Favours Sham ECT　　Favours Real ECT
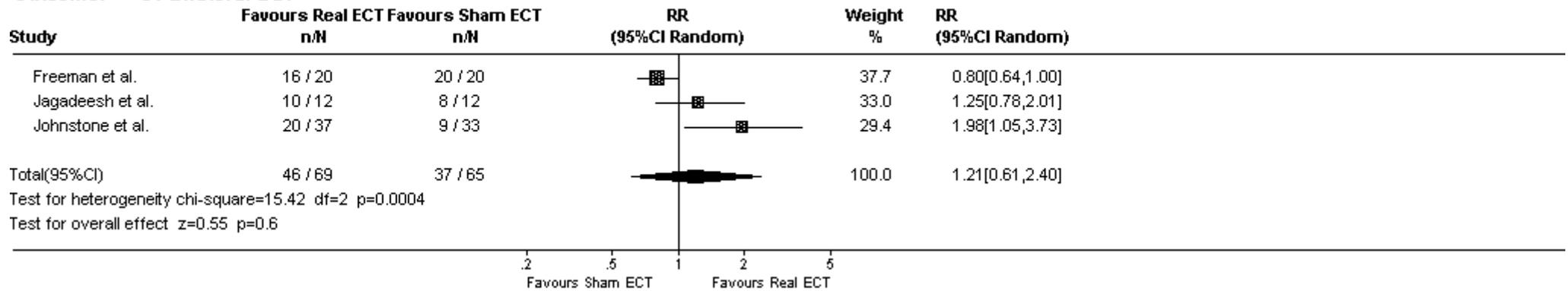
Comparison: 02 Real ECT vs sham ECT
Outcome:　01 Improved

Study	real ECT n/N	sham ECT n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Jagadeesh	10 / 12	8 / 12		58.6	1.25[0.78,2.01]
Johnstone et al	20 / 37	9 / 33		41.4	1.98[1.05,3.73]
Total(95%CI)	30 / 49	17 / 45		100.0	1.51[0.92,2.49]

Test for heterogeneity chi-square=1.64 df=1 p=0.2
Test for overall effect z=1.63 p=0.10

.1　.2　1　5　10
Favours sham ECT　　Favours real ECT
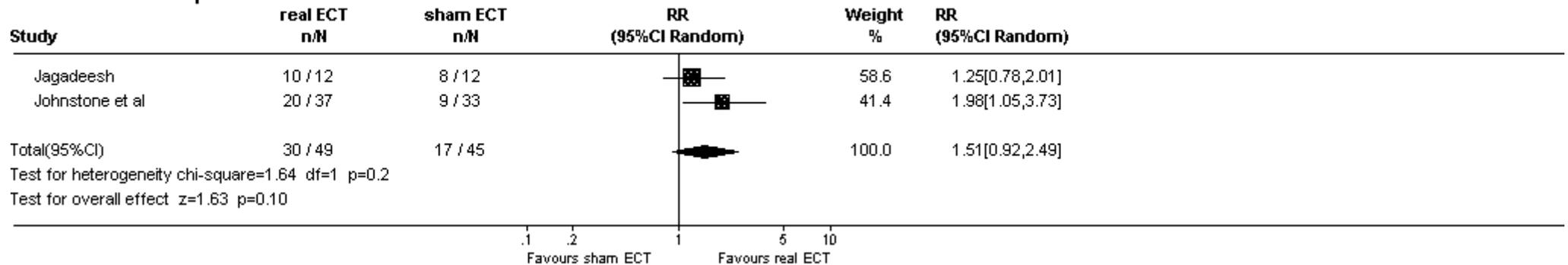
Comparison: 02 Real ECT vs sham ECT
Outcome: 03 Bilateral ECT RR of improvement Johnstone only

Study	real ECT n/N	sham ECT n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Johnstone et al	20 / 37	9 / 33		100.0	1.98[1.05,3.73]
Total(95%CI)	20 / 37	9 / 33		100.0	1.98[1.05,3.73]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=2.12 p=0.03

.1 .2 1 5 10
Favours treatment   Favours control
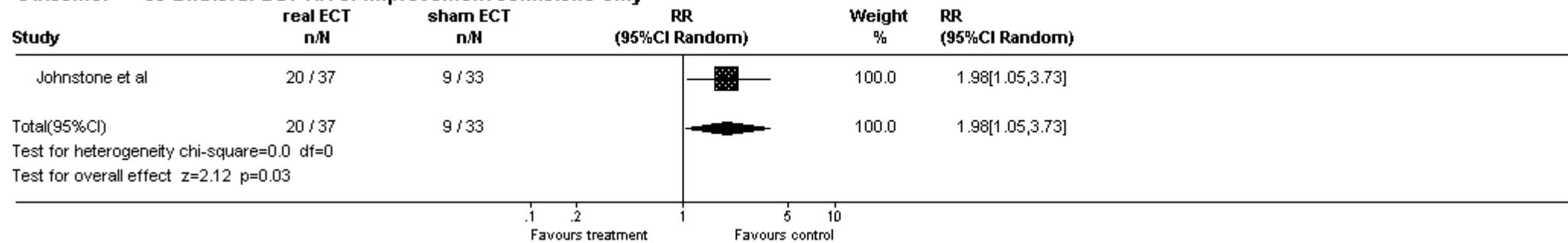
RR of improvement: unilateral

Comparison: 09 Real ECT vs Sham ECT
Outcome: 03 Unilateral ..

Study	Real ECT n/N	Sham ECT n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Lambourn/Gill	9 / 16	9 / 16		100.0	1.00[0.54,1.84]
Total(95%CI)	9 / 16	9 / 16		100.0	1.00[0.54,1.84]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=0.0 p=1

.1 .2 1 5 10
Favours Sham ECT   Favours Real

175

Comparison: 01 ECT vs TCA's

Outcome: 03 Relative risk of achieving moderate or marked improvement (inlcuding trials based on clinical opinion)

Study	ECT n/N	TCA's n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Bruce et al.	21 / 23	16 / 27		21.1	1.54[1.10,2.16]
Greenblatt et al.	48 / 63	36 / 73		27.4	1.54[1.18,2.02]
Janakiramaiah et al.	14 / 15	11 / 15		21.4	1.27[0.91,1.78]
Robin/Harris	12 / 15	3 / 16		3.2	4.27[1.49,12.20]
Shepherd	41 / 74	30 / 65		21.5	1.20[0.86,1.67]
Steiner et al.	3 / 4	3 / 4		5.4	1.00[0.45,2.23]
Total(95%CI)	139 / 194	99 / 200		100.0	1.42[1.17,1.72]

Test for heterogeneity chi-square=7.14 df=5 p=0.21

Test for overall effect z=3.51 p=0.0004

.1 .2   1   5 10

Favours TCA's   Favours ECT

Comparison: 01 ECT vs TCA

Outcome: 01 Not improved

Study	ECT n/N	TCA n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Bruce 1960	2 / 23	11 / 27		8.0	0.21[0.05,0.87]
Greenblatt 1964	6 / 63	19 / 63		21.8	0.32[0.14,0.74]
Janakiramaiah 2000	1 / 15	4 / 15		3.7	0.25[0.03,1.98]
Robin and Harris	2 / 15	7 / 16		8.0	0.30[0.07,1.24]
Shepherd 1965	17 / 74	23 / 65		55.8	0.65[0.38,1.10]
Steiner 1978	1 / 4	1 / 4		2.7	1.00[0.09,11.03]
Total(95%CI)	29 / 194	65 / 190		100.0	0.47[0.31,0.69]

Test for heterogeneity chi-square=4.75 df=5 p=0.45

Test for overall effect z=-3.77 p=0.0002

.1 .2   1   5 10

Favours ECT   Favours TCAs

Comparison: 01 ECT vs TCA
Outcome: 03 Improvement: clinical opinion only

Study	ECT n/N	TCAs n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Bruce 1960	21 / 23	16 / 27		29.0	1.54[1.10,2.16]
Greenblatt 1964	48 / 53	36 / 73		34.9	1.84[1.43,2.35]
Robin and Harris	12 / 15	3 / 16		6.9	4.27[1.49,12.20]
Shepherd 1965	41 / 74	30 / 65		29.3	1.20[0.86,1.67]
Total(95%CI)	122 / 165	85 / 181		100.0	1.63[1.21,2.20]

Test for heterogeneity chi-square=7.44 df=3 p=0.059
Test for overall effect z=3.22 p=0.001

.1   .2   1   5   10
Favours treatment   Favours control
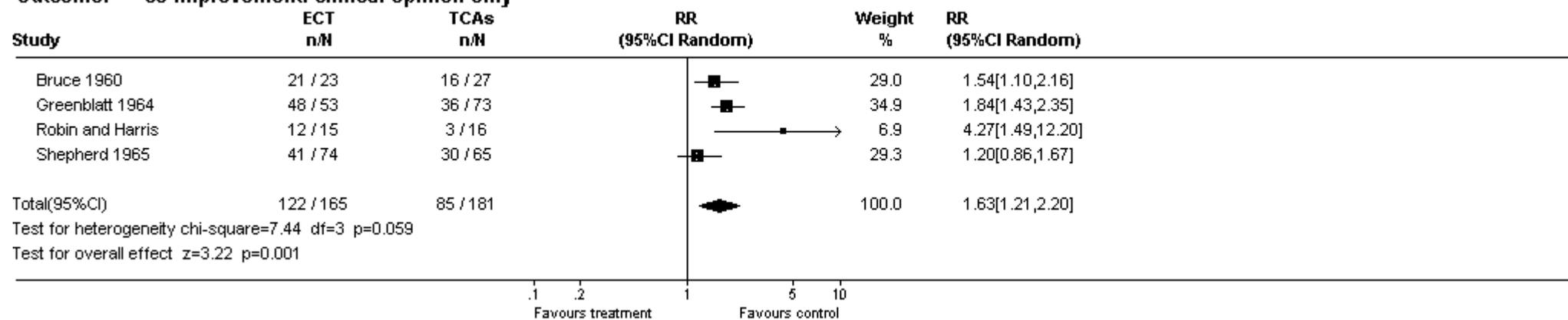
Comparison: 01 ECT vs TCA
Outcome: 02 Improved quantitative defn only

Study	ECT n/N	TCAs n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Janakiramaiah 2000	14 / 15	11 / 15		85.2	1.27[0.91,1.78]
Steiner 1978	3 / 4	3 / 4		14.8	1.00[0.45,2.23]
Total(95%CI)	17 / 19	14 / 19		100.0	1.23[0.90,1.67]

Test for heterogeneity chi-square=0.30 df=1 p=0.58
Test for overall effect z=1.31 p=0.19

.1   .2   1   5   10
Favours treatment   Favours control

177
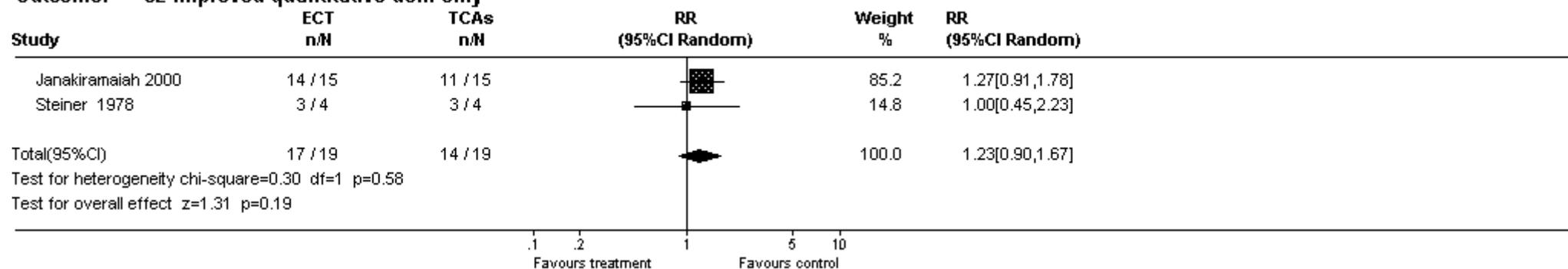
Comparison: 03 ECT vs rTMS
Outcome: 01 ECT vs rTMS

Study	ECT n	mean(sd)	rTMS n	mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Grunhaus et al.	20	17.20(9.72)	20	10.40(7.54)		100.0	6.80[1.41,12.19]
Total(95%CI)	20		20			100.0	6.80[1.41,12.19]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=2.47 p=0.01

```
        -10    -5     0     5    10
      Favours rTMS        Favours ECT
```
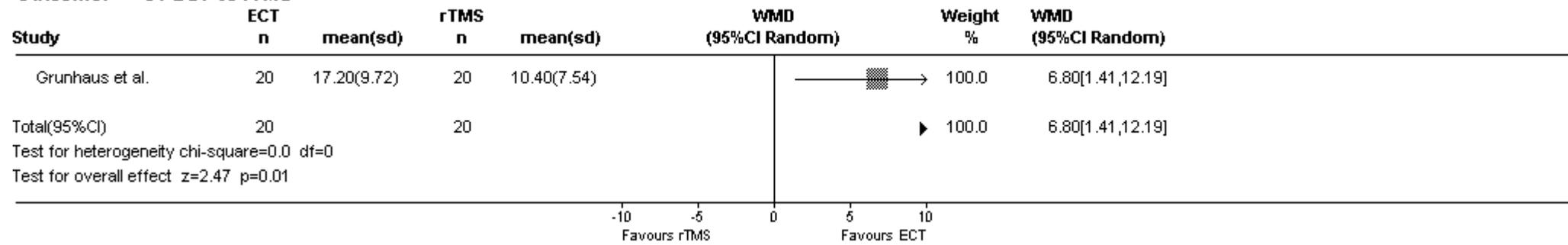
Comparison: 04 Cont. Pharma vs Cont. Placebo
Outcome: 01 Continuation Pharmacotherapy vs Continuation Placebo dichotomous

Study	Cont. Pharma n/N	Cont. Placebo n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Arfwidsson et al.	24 / 28	22 / 29		100.0	1.13[0.88,1.46]
Total(95%CI)	24 / 28	22 / 29		100.0	1.13[0.88,1.46]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=0.94 p=0.3

.5 .7 1 1.5 2
Favours Cont Placebo Favours Cont. Pharma

Comparison: 04 ECT+ antidepressants vs ECT alone
Outcome: 01 HRSD scores at 6 weeks follow up

Study	ECT+ antidepressants n	mean(sd)	ECT alone n	mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Mayur	12	7.70(9.80)	10	6.00(7.50)		100.0	1.70[-5.54,8.94]
Total(95%CI)	12		10			100.0	1.70[-5.54,8.94]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=0.46 p=0.6

-10 -5 0 5 10
Favours control Favours treatment
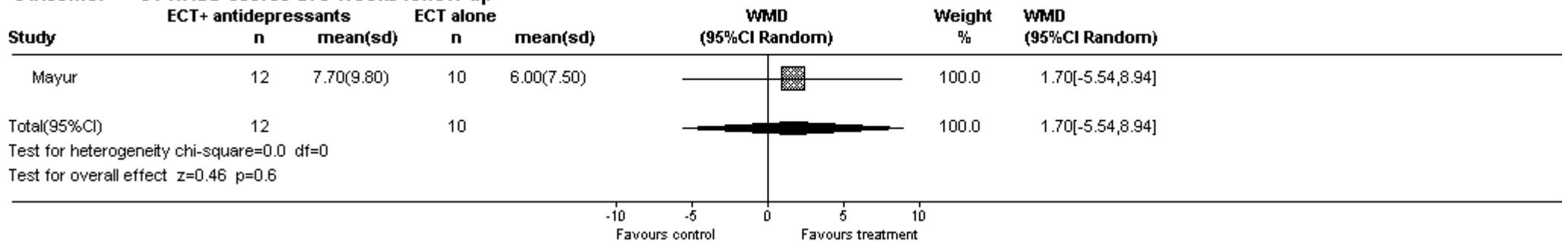
Comparison: 07 ECT+L-Tryptophan vs ECT+placebo
Outcome: 01 RR of recovery or much improved 4 days after end of ECT course

Study	ECT+L-Tryptophan n/N	ECT+placebo n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
D'Elia	27 / 30	29 / 31		100.0	0.96[0.83,1.12]
Total(95%CI)	27 / 30	29 / 31		100.0	0.96[0.83,1.12]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=-0.50 p=0.6

.1 .2 1 5 10
Favours treatment Favours control
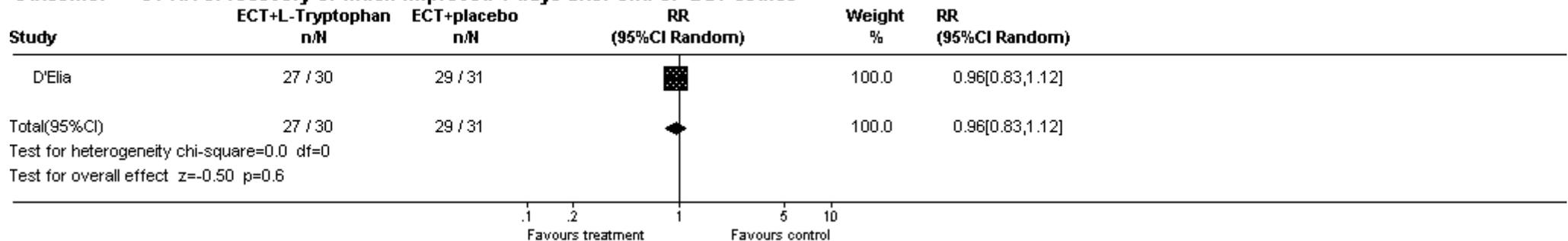
Comparison: 04 Cont. Pharma vs Cont. Placebo

Outcome: 02 Continuation Pharmacotherapy vs Continuation Placebo continuous

Study	Paroxetine n	mean(sd)	Placebo n	mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Lauritzen et al. (a)	18	22.00(4.80)	17	21.20(25.53)		100.0	0.80[-11.54,13.14]
Total(95%CI)	18		17			100.0	0.80[-11.54,13.14]

Test for heterogeneity chi-square=0.00 df=0 p=1

Test for overall effect z=0.13 p=0.9

```
         -10    -5     0     5    10
              Favours Placebo    Favours Cont. Pharmo
```
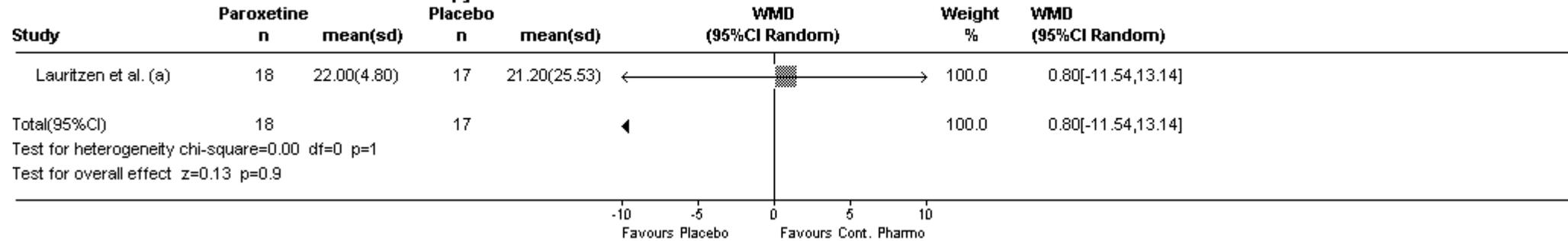
Comparison: 05 CP1 vs CP2

Outcome: 01 Continuation Paroxetine (CP1) vs Continuation Imipramine (CP2)

Study	CP1 n	mean(sd)	CP2 n	mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Lauritzen et al. (b)	27	22.20(5.36)	25	25.00(5.04)		100.0	-2.80[-5.63,0.03]
Total(95%CI)	27		25			100.0	-2.80[-5.63,0.03]

Test for heterogeneity chi-square=0.0 df=0

Test for overall effect z=1.94 p=0.05

```
         -10    -5     0     5    10
              Favours CP2       Favours CP1
```
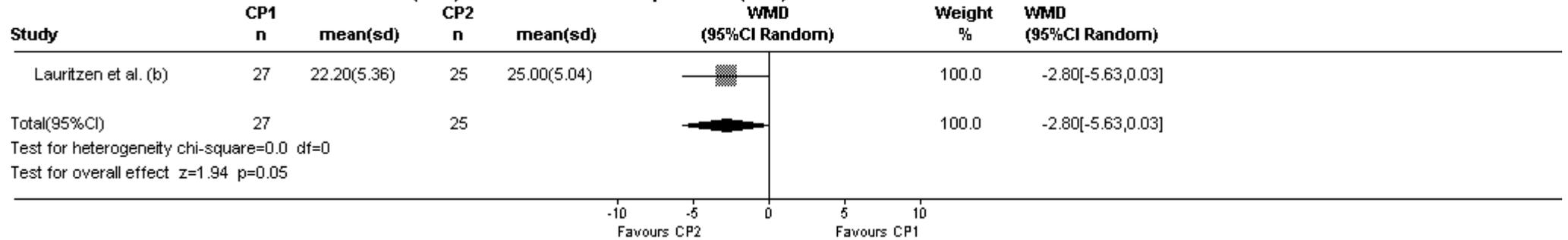
Comparison: 03 ECT+pindol vs ECT+placebo
Outcome: 02 HRSD scores

Study	ECT+pindol n	mean(sd)	ECT+placebo n	mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Shiah	8	11.80(8.40)	7	20.90(5.20)		100.0	-9.10[-16.08,-2.12]
Total(95%CI)	8		7			100.0	-9.10[-16.08,-2.12]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=2.56 p=0.01

```
      -10    -5     0     5     10
      Favours treatment    Favours control
```
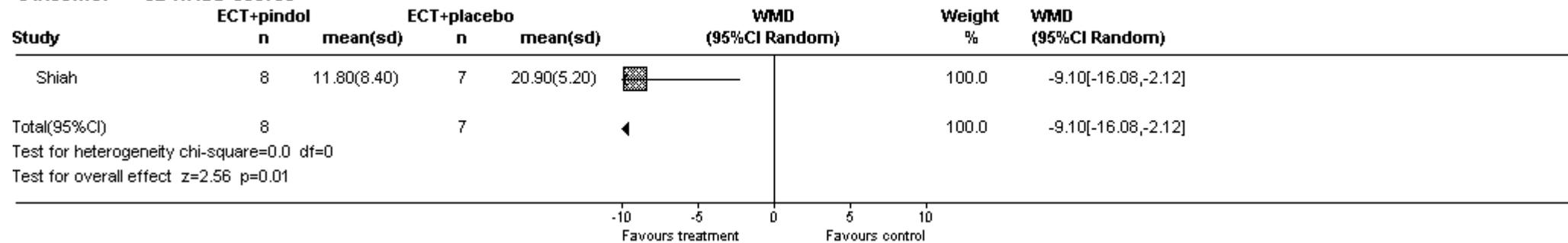
Comparison: 03 ECT+pindol vs ECT+placebo
Outcome: 01 Reponder (less than 12 on 29 item HRS

Study	ECT+pindol n/N	ECT+placebo n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Shiah	4 / 9	0 / 11		100.0	10.80[0.66,177.37]
Total(95%CI)	4 / 9	0 / 11		100.0	10.80[0.66,177.37]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=1.67 p=0.10

```
      .1    .2          1          5    10
      Favours control       Favours treatment
```
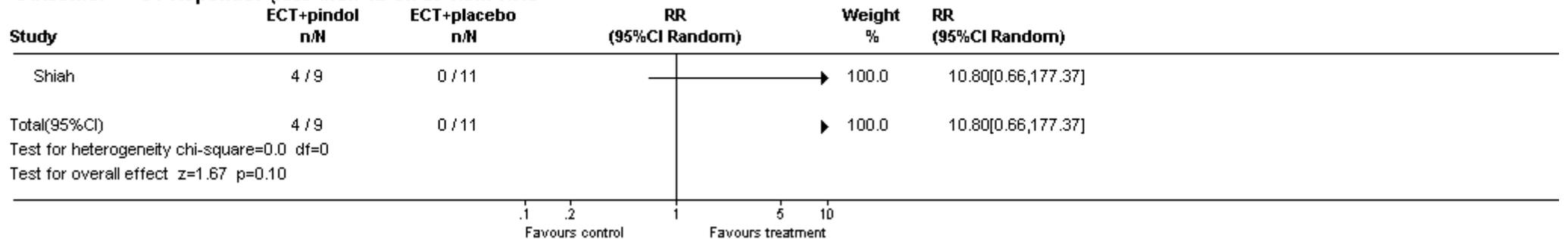
Comparison: 06 Relapse 01
Outcome: 02 Number of weeks in first six months of follow-up spent with a depressive episode

Study	Placebo n	mean(sd)	Lithium n	mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Coppen et al.	20	2.40(1.10)	18	1.50(0.80)		100.0	0.90[0.29,1.51]
Total(95%CI)	20		18			100.0	0.90[0.29,1.51]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=2.90 p=0.004

```
        -4      -2       0       2       4
        Favours Placebo      Favours Lithium
```
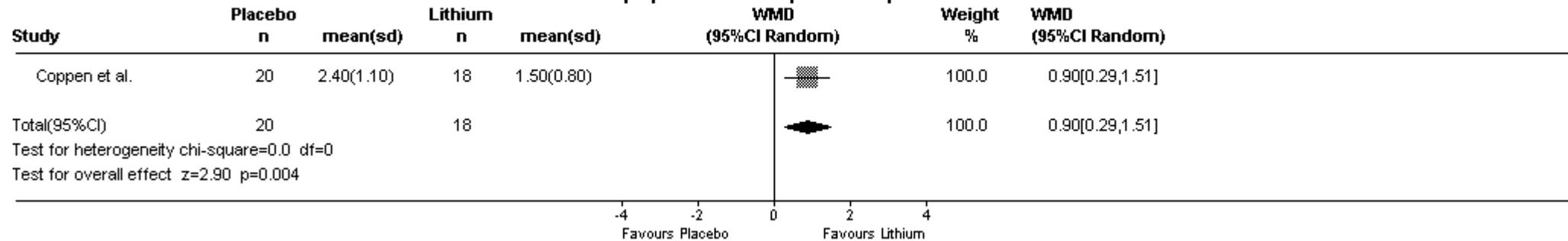
Comparison: 06 Relapse 01
Outcome: 04 Relative risk of a relapse in the first six months

Study	Cont. Pharma 1 n/N	Cont. Pharma 2 n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
01 Completers only					
Grunhaus completers	5 / 20	5 / 20		37.2	1.00[0.34,2.93]
Subtotal(95%CI)	5 / 20	5 / 20		37.2	1.00[0.34,2.93]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=0.0 p=1

02 Completers and withdrawals					
Grunhaus all	6 / 20	9 / 20		62.8	0.67[0.29,1.52]
Subtotal(95%CI)	6 / 20	9 / 20		62.8	0.67[0.29,1.52]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=-0.96 p=0.3

Total(95%CI)	11 / 40	14 / 40		100.0	0.78[0.40,1.49]

Test for heterogeneity chi-square=0.35 df=1 p=0.56
Test for overall effect z=-0.76 p=0.4

```
        .1      .2              1       5      10
        Favours CP1           Favours CP2
```

Comparison: 05 Continuation TCA vs Continuation placebo
Outcome: 01 Relapse in first 6 months: completers and withdrawals

Study	TCA n/N	placebo n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Imlah	25 / 50	30 / 50		45.0	0.83[0.58,1.19]
Sackeim	17 / 27	25 / 29		55.0	0.73[0.53,1.01]
Total(95%CI)	42 / 77	55 / 79		100.0	0.78[0.61,0.99]

Test for heterogeneity chi-square=0.30 df=1 p=0.58
Test for overall effect z=-2.08 p=0.04

.1 .2   1   5 10
Favours TCAs   Favours placebo
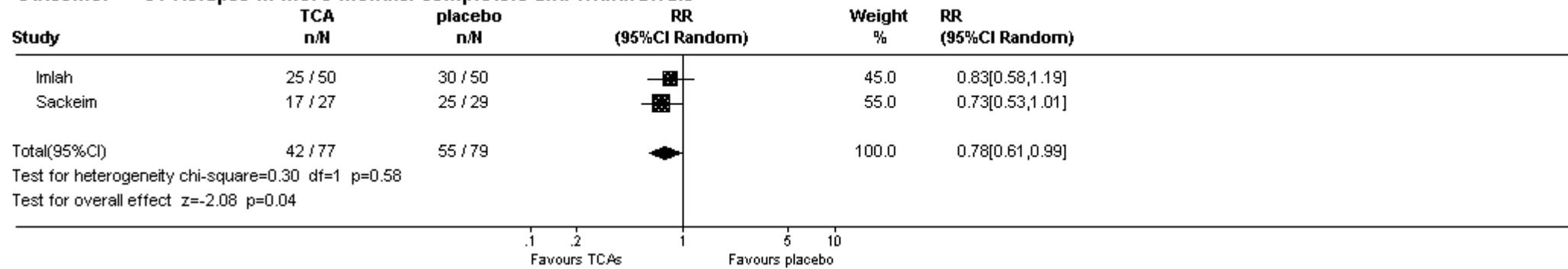
Comparison: 05 Continuation TCA vs Continuation placebo
Outcome: 02 Relapse in first 6 months: completers only

Study	TCAs n/N	placebo n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Imlah	7 / 50	21 / 50		53.9	0.33[0.16,0.71]
Sackeim	5 / 27	21 / 29		46.1	0.26[0.11,0.58]
Total(95%CI)	12 / 77	42 / 79		100.0	0.30[0.17,0.52]

Test for heterogeneity chi-square=0.22 df=1 p=0.64
Test for overall effect z=-4.29 p=0.00002

.1 .2   1   5 10
Favours treatment   Favours control

183
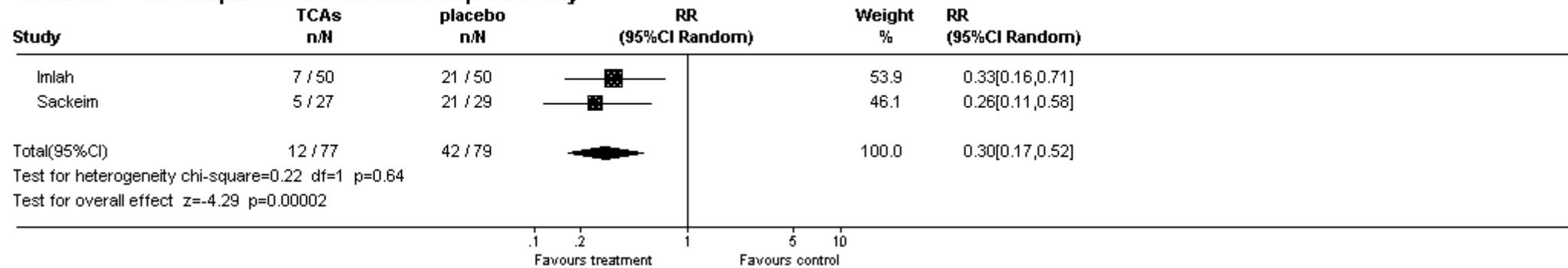
Comparison: 06 Continuation TCA vs contiuation MAOI
Outcome: 01 Relative risk of relapse in first 6 months

Study	MAOI n/N	TCA n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Imlah	20 / 50	25 / 50		100.0	0.80[0.52,1.24]
Total(95%CI)	20 / 50	25 / 50		100.0	0.80[0.52,1.24]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=-1.00 p=0.3

.1   .2   1   5   10
Favours MAOI   Favours TCAs
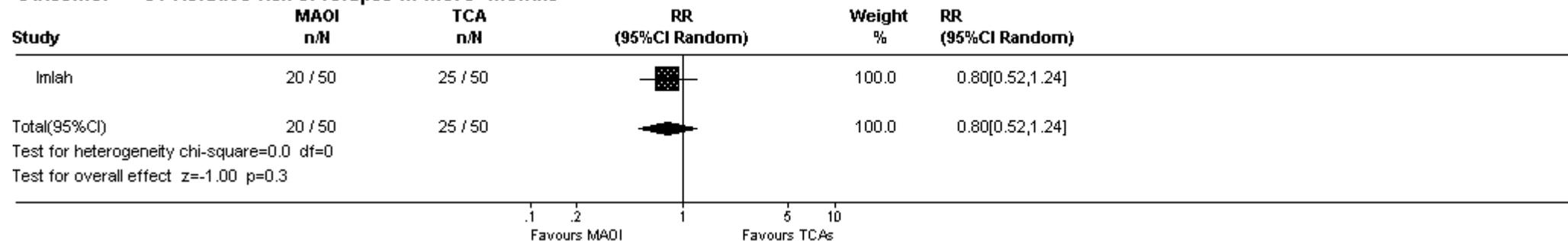
above: completers and withdrawals (imlah)

Comparison: 08 Relative risk of a relapse in the first six months
Outcome: 02 TCA's vs TCA + Li

Study	TCA's n/N	TCA + Li n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
01 completers only					
Sackeim completers	15 / 27	9 / 28		37.5	1.73[0.92,3.26]
Subtotal(95%CI)	15 / 27	9 / 28		37.5	1.73[0.92,3.26]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=1.69 p=0.09

Study	TCA's n/N	TCA + Li n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
02 completers and withdrawals					
Sackeim all	17 / 27	13 / 28		62.5	1.36[0.83,2.22]
Subtotal(95%CI)	17 / 27	13 / 28		62.5	1.36[0.83,2.22]

Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=1.21 p=0.2

Study	TCA's n/N	TCA + Li n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Total(95%CI)	32 / 54	22 / 56		100.0	1.49[1.01,2.19]

Test for heterogeneity chi-square=0.36 df=1 p=0.55
Test for overall effect z=1.99 p=0.05

.1   .2   1   5   10
Favours TCA   Favours TCA + Li

184

Comparison: 08 Information video+written consent vs written consent alone
Outcome: 03 Pooled knowledge scores

Study	Treatment n	mean(sd)	Control n	mean(sd)	SMD (95%CI Random)	Weight %	SMD (95%CI Random)
Battersby	11	6.00(1.41)	7	6.81(0.87)		41.0	-0.62[-1.60,0.35]
Westreich et al	35	12.63(2.98)	34	11.35(3.39)		59.0	0.40[-0.08,0.87]
Total(95%CI)	46		41			100.0	-0.02[-1.01,0.96]

Test for heterogeneity chi-square=3.40 df=1 p=0.065
Test for overall effect z=0.04 p=1

-10 -5 0 5 10
Favours treatment   Favours control
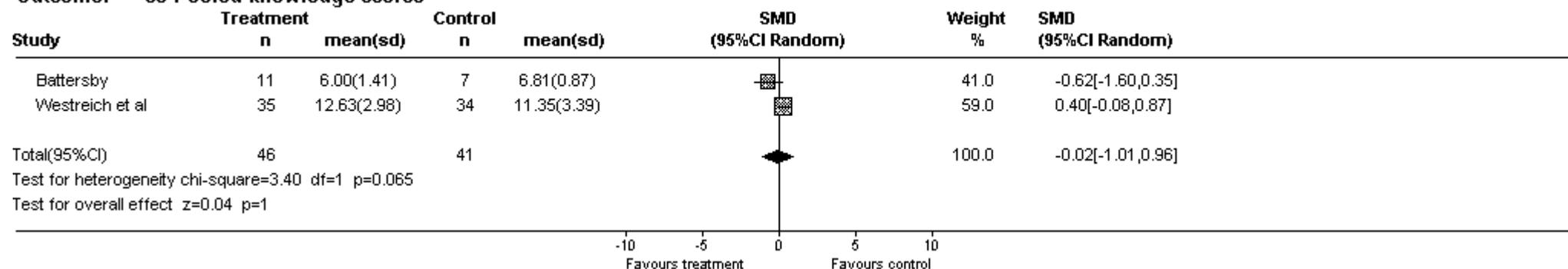
Comparison: 08 Information video+written consent vs written consent alone
Outcome: 02 Mean knowledge score

Study	video n	mean(sd)	No video n	mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Battersby	35	12.63(2.98)	34	11.35(3.39)		100.0	1.28[-0.23,2.79]
Total(95%CI)	35		34			100.0	1.28[-0.23,2.79]

Test for heterogeneity chi-square=0.00 df=0 p=1
Test for overall effect z=1.66 p=0.10

-10 -5 0 5 10
Favours treatment   Favours control
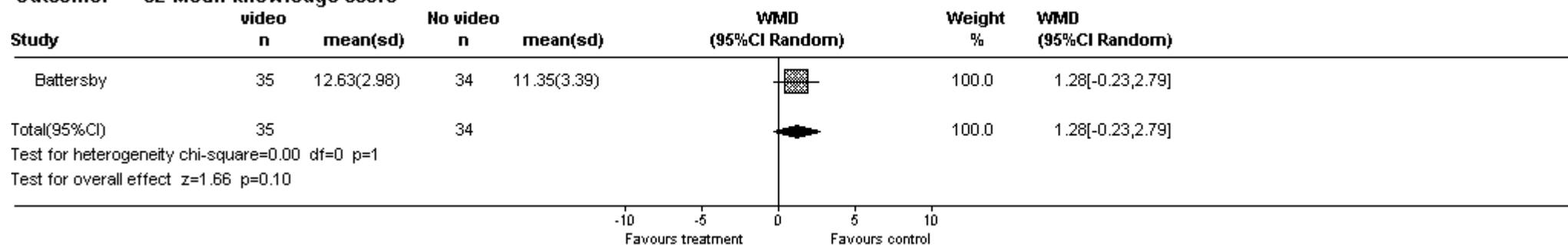
Comparison: 08 Information video+written consent vs written consent alone
Outcome: 01 Mean no of question correct post consent

Study	Video+written consen n	mean(sd)	Written consent n	mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Westreich et al	11	6.00(1.41)	7	6.81(0.87)		100.0	-0.81[-1.86,0.24]
Total(95%CI)	11		7			100.0	-0.81[-1.86,0.24]

Test for heterogeneity chi-square=0.00 df=0 p=1
Test for overall effect z=1.51 p=0.13

-10 -5 0 5 10
Favours treatment   Favours control

185