Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies

J Greenhalgh, C Knight, D Hind, C Beverley and S Walters

March 2005
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Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies

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Abstract

Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies

J Greenhalgh,1*† C Knight,2 D Hind,2 C Beverley2 and S Walters2

1 Nuffield Institute for Health, University of Leeds, UK
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* Corresponding author
† Current affiliation: Health Care Practice R&D Unit, University of Salford, UK

Objectives: To establish the clinical effectiveness and cost-effectiveness of electroconvulsive therapy (ECT) for depressive illness, schizophrenia, catatonia and mania.

Data sources: Electronic bibliographic databases. The reference lists of relevant articles and health services research-related resources were consulted via the Internet.

Review methods: Identified studies were examined to ascertain whether they met the inclusion criteria for the review. The study quality of relevant articles was assessed using standard checklists and data were abstracted using standardised forms into a database. Where relevant, results from studies were pooled for meta-analysis. Two economic models were developed primarily based on evidence from the clinical effectiveness analysis and limited quality of life studies.

Results: Two good-quality systematic reviews of randomised evidence of the efficacy and safety of ECT in people with depression, schizophrenia, catatonia and mania were identified. Four systematic reviews on non-randomised evidence were also identified, although 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. The economic modelling results for depression did not demonstrate that any of the scenarios had a clear economic benefit over the others, mainly because of 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. The results of the model for schizophrenia adapted to include ECT suggest that clozapine is a cost-effective treatment compared with ECT. For patients who fail to respond to clozapine, ECT treatment may be preferred to the comparative treatment of haloperidol/chlorpromazine.

Conclusions: Real ECT is probably more effective than sham ECT, but as 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 and limited evidence suggests that ECT is more effective than repetitive transcranial magnetic stimulation. Tricyclic antidepressants (TCAs) may improve the antidepressant effect of ECT during the course of treatment. Continuation pharmacotherapy with TCAs combined with lithium in people who have responded to ECT reduces the rate of relapses. Overall, gains in the efficacy of the intervention depending on the stimulus parameters of ECT are achieved only at the expense of an increased risk of cognitive side-effects. Limited evidence suggests these effects do not last beyond 6 months, but there is no evidence examining the longer term cognitive effects of ECT. There is little evidence of the long-term efficacy of ECT. ECT either combined with antipsychotic medication or as a monotherapy is not more effective than antipsychotic medication in people with schizophrenia. More research is needed to examine the long-term efficacy of ECT and the effectiveness of post-ECT pharmacotherapy, the short-term and longer term cognitive side-effects of ECT, and the impact of ECT 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. More research is also needed on the mechanism of action of ECT. Finally, the quality of reporting of trials in this area would be vastly improved by strict adherence to the Consolidated Standards of Reporting Trials recommendations. Economic analysis may 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 to make the decision on whether ECT is a cost-effective treatment.
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# List of abbreviations

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<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood–brain barrier</td>
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<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
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<tr>
<td>BFCRS</td>
<td>Bush–Francis Catatonia Rating Scale</td>
</tr>
<tr>
<td>BGT</td>
<td>Bender Gestalt Test</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>C.ATP</td>
<td>continuation therapy with antipsychotic drugs</td>
</tr>
<tr>
<td>C.MAOI</td>
<td>continuation therapy with monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>C.placebo</td>
<td>continuation therapy with placebo</td>
</tr>
<tr>
<td>C.SSRI</td>
<td>continuation therapy with selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>C.TCA</td>
<td>continuation therapy with tricyclic antidepressants</td>
</tr>
<tr>
<td>CCTR</td>
<td>Cochrane Controlled Trials Register</td>
</tr>
<tr>
<td>CDSR</td>
<td>Cochrane Database of Systematic Reviews</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical Global Impression</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CODS</td>
<td>Cronholme and Ottoson Depression Scale</td>
</tr>
<tr>
<td>CRD</td>
<td>Centre for Reviews and Dissemination</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DARE</td>
<td>Database of Abstracts of Reviews of Effectiveness</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual</td>
</tr>
<tr>
<td>ECT</td>
<td>electroconvulsive therapy</td>
</tr>
<tr>
<td>F</td>
<td>female</td>
</tr>
<tr>
<td>GAF</td>
<td>Global Assessment of Functioning scale</td>
</tr>
<tr>
<td>GDS</td>
<td>Geriatric Depression Scale</td>
</tr>
<tr>
<td>GRSD</td>
<td>Global Rating Scale for Depression</td>
</tr>
<tr>
<td>HAD</td>
<td>Hospital Anxiety and Depression scale</td>
</tr>
<tr>
<td>HMIC</td>
<td>Health Management Information Consortium</td>
</tr>
<tr>
<td>HRSD</td>
<td>Hamilton Rating Scale for Depression</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases-10</td>
</tr>
<tr>
<td>ITT</td>
<td>intention to treat</td>
</tr>
<tr>
<td>M</td>
<td>male</td>
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<tr>
<td>MADRS</td>
<td>Montgomery and Asberg Depression Rating Scale</td>
</tr>
<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>MDD</td>
<td>major depressive disorder</td>
</tr>
<tr>
<td>MEP</td>
<td>muscular-evoked potential</td>
</tr>
<tr>
<td>MMPI</td>
<td>Minnesota Multiphasic Personality Inventory</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NAA</td>
<td>N-acetylaspartate</td>
</tr>
<tr>
<td>NHB</td>
<td>net health benefit</td>
</tr>
<tr>
<td>NHS EED</td>
<td>NHS Economic Evaluation Database</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
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<tr>
<td>NMB</td>
<td>net monetary benefit</td>
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<tr>
<td>NMS</td>
<td>neuroleptic malignant syndrome</td>
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<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>NNH</td>
<td>number needed to harm</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>NRS</td>
<td>Nurses’ Rating Scale</td>
</tr>
<tr>
<td>NSF</td>
<td>National Service Framework</td>
</tr>
<tr>
<td>OHE HEED</td>
<td>Office of Health Economics Health Economic Evaluations Database</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Symptoms Scale</td>
</tr>
<tr>
<td>PIRS</td>
<td>Psychological Impairments Scale</td>
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<tr>
<td>PSE</td>
<td>Present State Examination</td>
</tr>
<tr>
<td>PSQI</td>
<td>Pittsburg Sleep Quality Index</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
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<tr>
<td>RCP</td>
<td>Royal College of Psychiatrists</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>rTMS</td>
<td>repetitive transcranial magnetic stimulation</td>
</tr>
<tr>
<td>SCI</td>
<td>Science Citation Index</td>
</tr>
<tr>
<td>SMD</td>
<td>standardised mean difference</td>
</tr>
<tr>
<td>SNRI</td>
<td>serotonin and norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>SSCI</td>
<td>Social Sciences Citation Index</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>SURE</td>
<td>Service User Research Enterprise</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
</tr>
<tr>
<td>UKU</td>
<td>Udvalg for Kliniske Undersøgelser</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analogue scale</td>
</tr>
<tr>
<td>VBR</td>
<td>ventricular:brain ratio</td>
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<tr>
<td>WAIS</td>
<td>Weschler Adult Intelligence Scale</td>
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<tr>
<td>WBIS</td>
<td>Weschler–Bellevue Intelligence Scale</td>
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<tr>
<td>WMD</td>
<td>weighted mean difference</td>
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<tr>
<td>WMS</td>
<td>Weschler Memory Scale</td>
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All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.
Objective

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

Background

ECT has been available for use since the 1930s. It involves passing an electric current through a person’s brain after they have been given a general anaesthetic and muscle relaxants, 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.

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 2835 patients, 85% of which were in 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. In England, rates of administration of ECT are highest in the North West and lowest in London.

Methods

Seventeen 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 health technology assessment organisations, guideline-producing bodies, generic research and trials registers, and specialist psychiatric sites. All abstracts were examined to ascertain whether they met the inclusion criteria for the review. The study quality of relevant articles was assessed using standard checklists and data were abstracted by two people using standardised forms in a Microsoft Access database. Where relevant, results from studies were pooled for meta-analysis.

Results and conclusions

Number and quality of studies

Two good-quality systematic reviews of randomised evidence of the efficacy and safety of ECT in people with depression, schizophrenia, catatonia and mania were identified. Four systematic reviews on non-randomised evidence were also identified, although 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 repetitive transcranial magnetic stimulation (rTMS). Limited data suggest that tricyclic antidepressants (TCAs) may improve the antidepressant effect of ECT during the course of ECT, and that continuation pharmacotherapy with TCAs combined with lithium in people who have responded to ECT reduces the rate of relapses. Overall, gains in the efficacy of the intervention depending on the stimulus parameters of ECT are achieved only at the expense of an increased risk of cognitive side-effects. Limited evidence suggests these effects do not last beyond 6 months, but there is no evidence examining the longer term cognitive effects of...
ECT. There is little evidence of the long-term efficacy of ECT. There was much less evidence regarding the efficacy of ECT in schizophrenia and mania, 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 mania or catatonia, older people, younger people and women with psychiatric problems, or the impact of ECT on all-cause mortality. There was limited non-randomised evidence regarding the impact of patient acceptability and choice on the outcomes of ECT, and this produced mixed results.

**Cost-effectiveness**

No previous analysis has been undertaken on the cost-effectiveness of ECT 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 first, second or third line therapy.

Different scenarios that incorporated ECT as a treatment were compared with 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, 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 to 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 guidelines of the American Psychiatric Association and the Royal College of Psychiatrists is patients resistant to pharmacotherapy. Therefore, the economic model constructed for schizophrenia was based on a pharmacological model previously constructed which was the only cost-utility study identified in the treatment of schizophrenia. This model analysed the cost-effectiveness of clozapine compared with 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 with ECT. For patients who fail to respond to clozapine, ECT treatment may be preferred to the comparative treatment of haloperidol/chlorpromazine. However, the clinical evidence underpinning the ECT assumptions in the model is weak and the results should be interpreted with caution.

**Recommendations for further research**

**Clinical effectiveness**

There is a need for further, high-quality randomised controlled trials (RCTs) of the use of ECT in specific subgroups that are most likely to receive this treatment. These include older people with depression, women with postpartum exacerbation 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 resistant to pharmacotherapy in schizophrenia and depression.

There is currently no randomised evidence comparing ECT with, or in addition to newer antipsychotic drugs (e.g. clozapine and risperidone) and antidepressants (e.g. venlafaxine) that are currently used in clinical practice. Further work is needed in these areas. More research is also needed to compare ECT with rTMS, especially in people with schizophrenia. Again, there is a need for further, high-quality RCTs comparing the use of ECT with these treatments.

More research is needed to examine the long-term efficacy of ECT and the effectiveness of post-ECT pharmacotherapy. There is only limited evidence regarding the efficacy of supplementing ECT with
pharmacotherapy in people with depression and the continuation of pharmacotherapy following successful response to ECT to prevent relapses. In most trials, the aftercare 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 patients' perspectives on the impact of ECT into future RCTs. Consideration should be given to the use of both quantitative and qualitative methods. The outcome measures used should reflect both clinical and patient perspectives on the impact of ECT.

There is also little good-quality 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 patients' 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-up within RCTs to explore the impact of ECT 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 into 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 Consolidated Standards of Reporting Trials (CONSORT) recommendations.

Cost-effectiveness
Further economic analysis, such as expected value of perfect information, may 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 to make the decision on whether ECT is a cost-effective treatment.
The aim of this review is to establish the clinical effectiveness and cost-effectiveness of electroconvulsive therapy (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 12 treatments given twice a week. ECT is indicated for severely depressed patients, but 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\(^1\) and those who consider that ECT is probably ineffective and almost certainly causes brain damage.\(^2\)

The specific areas 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 effectiveness 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 and how these may affect outcomes.
Chapter 2
Background

Description of the underlying health problem

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 past 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, blunted emotions and limited speech; and disorganised symptoms include disorganised speech and behaviour and poor attention. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)\(^4\) describes four 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.

Depression

The DSM-IV\(^4\) criteria for a major depressive syndrome are that at least five key symptoms should be present during the same 2-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 guilt 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\(^4\), 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 hallucinations. Moderate depression is defined as symptoms or functional impairment between ‘mild’ and ‘severe’.

Mania

Manic symptoms are considered to be part of bipolar disorder. The DSM-IV\(^4\) minimum criterion for bipolar affective disorder is a single episode of mania or mixed disorder (both episodes of mania and major depression occur). The DSM-IV\(^4\) criteria for mania are:

- distinct period of elation, irritability or mood disturbances lasting for at least 1 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 (e.g. social, at work) or psychomotor agitation
  – discreet 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, 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 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 (four or more affective episodes per year).

**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 of a deficit of movement (catatonic stupor) and excessive movement (catatonic excitement). The International Classification of Diseases (ICD-10) diagnostic criteria for catatonic schizophrenia state that 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 all 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.

**Epidemiology**

In 2000, the prevalence of depressive episode in England, Wales and Scotland was 26 per 1000. 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. 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 five times higher than those for the rest of the population; 10–15% of people with the disorder eventually commit suicide.

**Current service provision**

**Description of intervention**

ECT has been available for use since the 1930s. The practice of ECT has undergone a number of modifications since its introduction, with the use of general anaesthesia and muscle relaxants. The current practice of ECT involves the passage of electricity through a person’s brain while they are under a general anaesthetic and have been given 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 subconvulsive 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. 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 and those who consider that ECT is probably ineffective and almost certainly causes brain damage. 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 at which ECT is administered.

**Patient populations**

**Overall indications for ECT**

Current guidelines from the American Psychiatric
Association (APA)\textsuperscript{13} and the Royal College of Psychiatrists (RCP)\textsuperscript{14} on the patient populations for whom ECT is indicated are summarised below. The APA\textsuperscript{13} 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.\textsuperscript{13} 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\textsuperscript{16} 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 those who received ECT during 1997 to 1998 in Scotland,\textsuperscript{16} 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.

**ECT in depressive illness**

For depressive illness, first line treatment in the acute phase is the use of antidepressant medication.\textsuperscript{17} The APA guidelines indicate that the effectiveness of antidepressant medications is generally comparable,\textsuperscript{17} although a recent meta-analysis\textsuperscript{18} suggests that serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g. venlafaxine) are more effective than selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine) or tricyclic antidepressants (TCAs) (e.g. imipramine). A meta-analysis of 36 open and double-blind trials suggested that 29–46\% of depressed patients failed to respond fully to antidepressant treatment of adequate dose or duration.\textsuperscript{19} The minimum dose of TCAs known to be effective is 100 mg day\textsuperscript{-1}\textsuperscript{20} and treatment resistance has been defined as failure to respond to a trial of more than one antidepressant drug in a dose equivalent to 250–300 mg of imipramine given for a duration of 6–8 weeks each.\textsuperscript{21} The APA\textsuperscript{22} 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 which there is an urgent need for response, such as patients who are suicidal or refusing food. The RCP\textsuperscript{14} suggests 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\%).\textsuperscript{23}

A survey of psychiatrists in the North West of England\textsuperscript{15} found that the most common indication for the use of ECT in depressive illness was in cases of refusal to eat or drink (89\% agreed that it was the treatment of choice), followed by patients who 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.\textsuperscript{24} 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 patient’s 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 session are stimulus parameters that 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.
ECT in schizophrenia

For schizophrenia, first line treatment is with antipsychotic medication. 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, but can produce a range of unwanted side-effects including sedation, dry mouth, tachycardia and extrapyramidal symptoms (medication-induced parkinsonism). Atypical antipsychotics such as clozapine have been shown to be more effective than typical antipsychotics and have fewer extrapyramidal side-effects, but cause potentially fatal agranulocytosis in about 1% of patients. Adequate doses of typical antipsychotic medication are considered to be the equivalent of 300–600 mg of chlorpromazine a day. The APA recommends 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 a recent onset. Similarly, the RCP advises that the practical usefulness of ECT in schizophrenia is limited to acute catatonic states, schizoaffective disorders, acute paranoid syndromes and people with type I schizophrenia who are either intolerant or unresponsive to a dose of a neuroleptic equivalent to 500 mg of chlorpromazine daily.

ECT in mania

In mania, lithium and divalproex are first line treatments. The RCP 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 reserve ECT as a sixth line treatment for euphoric or mixed mania if residual symptoms are still severe following treatment trials with lithium, divalproex and the addition of benzodiazepines, atypical antipsychotics or carbemazepine, as a fifth line treatment for psychotic mania and almost the last resort for rapid cycling mania. Some clinicians believe that ECT needs to be administered more frequently to people with mania to achieve a therapeutic effect (Birkett P, Clinical Lecturer in Psychiatry, University of Sheffield: personal communication, 2002). Although there is no clear agreement on this, the RCP guidelines recommend that this should be considered.

ECT in catatonia

First line treatment of catatonia is usually with benzodiazepines (e.g. Lorazepam) and the APA guidelines recommend that catatonia is an indication for the use of ECT in people with schizophrenia or mania.

ECT in other subgroups

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

Stimulus parameters and administration of ECT

Frequency and schedules

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

Electrode placement

ECT can be administered by placing electrodes on both sides of the head (bilateral placement) or on one side of the head (unilateral), either on the dominant side of the brain or on the non-dominant side. Unilateral ECT was introduced to reduce the cognitive side-effects associated with ECT, but also has a lower antidepressant effect. The RCP recommends 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 that 57% usually used bilateral ECT, 22% used unilateral and 16% used either.

Stimulus

Early ECT machines delivered an alternating sine-wave stimulus at mains frequency and constant voltage. Modern machines 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 use less electrical energy, with the aim of maintaining therapeutic efficacy and reducing cognitive side-effects.
**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. 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 gender, dehydration, low oxygen saturation of the blood, and electrical parameters that raise impedance such as poor contact between electrodes and the scalp. The APA recommends 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.

**Seizure duration**

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

**Equipment and staffing**

Both the RCP and the APA recommend that the 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 two trained nurses, plus four untrained nurses, an anaesthetist, a psychiatrist and an operating department assistant. The machines currently recommended for use by both the APA and the RCP are Mecta SR2 and JR2, Thymatron-DGx and Ectron series 5A Ectonus machines.

**Information and consent**

The RCP guidelines 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 may be 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
- of the likely risks and effects of treatment, including its likely success
- of the alternatives to the treatment
- of 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 advises 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 are strong grounds for the use of ECT the RCP recommends 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 patient’s 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, 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, 12% were treated as an emergency and 59% did not consent to treatment but were treated after a second opinion was gained.

**Current service provision in England and Wales**

A recent survey of ECT use in England reported that between January and March 1999 there were 16,482 administrations of ECT to 2835 patients. Eighty five per cent of all administrations were in 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 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\textsuperscript{34} 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\textsuperscript{35} found that 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 (e.g. 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 imply a causal relationship between variations in the prevalence of a condition and a treatment, they 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 earlier, 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, then drops between 65 and 74, then increases again between 75–84 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 65–74 to comparable levels with people aged 35–44, increases again at 75–84 years and drops at 85-plus years to comparable levels with people aged 35–44 years.

Since 1985, the use of ECT in England has been decreasing.\textsuperscript{8} The estimated 65,930 administrations in 1998/99 compares with 105,466 reported administrations in 1990/91 and 137,940 in 1985.\textsuperscript{8}

\section*{Training and the quality of ECT services}

The RCP first issued guidance on the administration of ECT in 1977.\textsuperscript{36} In 1981, Pippard and Ellam\textsuperscript{37} conducted an audit against those standards and visited about half of the ECT clinics in the UK (180 clinics). 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\textsuperscript{38} conducted a second audit of ECT practice in the UK against the 1989 standards, visiting 35 NHS and five 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 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 disseminated through the publication of a revised edition of the handbook in 1995,\textsuperscript{32} 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\textsuperscript{34} took place between 1995 and 1996. They visited all 33 NHS clinics and five 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 Senior House Officer (SHO) level. Around the same time Hillam and colleagues\textsuperscript{39} 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\textsuperscript{34} found that despite improvements in some aspects of care, only one-third of the clinics rated met the college guidelines. Fifty-nine per cent 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 Lelliot\textsuperscript{34} report that the training of junior doctors was still of a low quality. Only one-third of clinics had clear policies to guide junior doctors to administer ECT effectively. In a survey of junior doctors, Duffett and Lelliot\textsuperscript{40} 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 and colleagues.\textsuperscript{39} Duffett and Lelliot\textsuperscript{40} found that 45\% of respondents lacked knowledge about one or more basic issues relating to the administration of ECT. Hillam and colleagues\textsuperscript{39} 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.

**Current mental health policy in England and Wales**

As a recent survey of ECT use in England\textsuperscript{8} 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\textsuperscript{41} 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\textsuperscript{41} 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.
Chapter 3

Effectiveness

Methods for reviewing effectiveness

Search strategy: clinical effectiveness
The search aimed to identify all references relating to the clinical effectiveness and cost-effectiveness of ECT for depression, schizophrenia, catatonia and mania.

Sources searched
Seventeen 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 health technology assessment 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.

Search terms
A combination of free-text and thesaurus terms was used. ‘Population’ terms (e.g. depression, schizophrenia, catatonia, bipolar disorder, mania, mood disorders, adjustment disorders, psychotic disorders, mental disorders) were combined with ‘intervention’ terms (e.g. electroconvulsive therapy, electro convulsive therapy, electroshock therapy, electro shock therapy). Copies of the search strategies used in the major databases are included in Appendix 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, namely, practice guidelines, systematic reviews and randomised controlled trials (RCTs), 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).

Search strategy: cost-effectiveness
In addition to the searches conducted above, searches were conducted in the NHS Economic Evaluation (NHS EED) and Office of Health Economics Health Economics Evaluations Database (OHE HEED) to identify specifically 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.

Inclusion and exclusion criteria

Populations
Papers were included in the review if they studied the following populations: depressive illness (both unipolar and bipolar), schizophrenia and schizoaffective disorder, catatonia and mania. A further aim was to explore the clinical effectiveness of ECT in particular subgroups including people who are resistant to pharmacotherapy, older people (defined as aged 65 years and over), younger people (defined as aged 18 years or under), and women with disorders associated with pregnancy and the puerperium. Papers were excluded if they included populations with more than one diagnosis (e.g. depression and schizophrenia) and did not stratify randomisation by disease type or report results separately for each diagnosis.

Interventions
Papers were included in the review if they examined the effectiveness or cost-effectiveness of ECT 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. The review 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.

**Comparators**

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

**Outcomes**

Studies were included if they assessed outcomes relating to the efficacy, safety and acceptability of ECT. The primary indicators 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 months or longer. The primary indicators of acceptability were patients’ choice of treatment and their views and experiences of ECT from either questionnaires or interviews.

**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, RCTs or economic evaluations. Where no RCT evidence was available, non-randomised comparator studies (e.g. non-randomised trials, controlled cohort studies and case–control studies) were included in the review. Where no evidence from non-randomised comparator studies was available, non-randomised, non-comparator studies (e.g. case series, case reports, non-controlled cohort studies) were included in the review.

**Language**

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

**Quality assessment and data extraction strategy**

**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 effectiveness and cost-effectiveness 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 users’ guides to evidence-based practice.
- RCTs were assessed with respect to randomisation procedures, blinding, handling of withdrawals and dropouts, guided by Jadad’s scoring system and the Cochrane Collaboration Handbook.
- 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 on the users’ guides to evidence-based medicine.
- Qualitative evidence was assessed using the standards proposed by Popay and colleagues.
- The quality of the economic literature was assessed according to the guidelines for authors and peer reviewers of economic submissions to the British Medical Journal.

**Data extraction and analysis**

Two reviewers (JG and DH) extracted data on clinical effectiveness using three separate, standard abstraction forms for systematic reviews (JG), RCTs (DH and JG) and non-randomised evidence (JG). This procedure was not conducted blind to the authorship of the study.

Where the reviewers 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 dichotomous data the number of responders or relapsers in each treatment arm, as defined by the trialists, was compared. Other binary outcomes were the numbers 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 relapsers used by the trialists was not clear, a clinically meaningful cut-off was decided by an independent clinician 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 [e.g. clinical opinion versus scores on the Hamilton Rating Scale for Depression (HRSD)], this was tested using sensitivity analysis. The data were deemed unusable if the numbers 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. Relative risks and confidence intervals were calculated using the random effects method of DerSimonian and Laird. All analyses were by ITT.

For continuous data group means and standard deviations at baseline, immediately after ECT and at 6 months' follow-up were recorded. The data were 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,
- baseline and follow-up data were based on different samples (e.g. 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. HRSD) the summary statistic used was the weighted mean difference (WMD). Again, a random effects model with the DerSimonian and Laird method was used.

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

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 represented 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.

Results

Quantity of research available

The searches generated 1647 references. Before 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 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 Tharyan and Adams in 2002 on behalf of the Cochrane Schizophrenia Group, 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 before 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 and permission was given to use the report prior to publication in 2003. The majority of the text from this report has been reproduced in this review. The references of the report were checked and one additional study was identified.

This report is largely based on the results of these two reviews and this has been acknowledged 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. The authors were contacted and gave their permission to use the review prior to its publication.

The populations, interventions and outcomes of included studies in these three reviews were compared with the scope of the National Institute for Clinical Excellence (NICE) review to assess the degree of overlap and identify areas not covered (Table 1). There were several gaps in the coverage between the scope of the UK ECT Group and the Cochrane Schizophrenia Group ECT review and the scope of the NICE review. Additional randomised and non-randomised evidence was identified to address these gaps.

For interventions, neither the UK ECT Group review nor the Cochrane Schizophrenia Group ECT review included studies comparing ECT with rTMS, nor did they include studies evaluating the effectiveness of post-ECT drug therapy.

In terms of populations, neither the UK ECT Group review nor the Cochrane Schizophrenia Group ECT review identified any RCTs evaluating the efficacy of ECT specifically in older people, people with catatonia, younger people or children, or 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 were too limited to perform reliable subgroup analyses. The Cochrane Schizophrenia

### Table 1: Overlap between the NICE scope and the six systematic reviews identified

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</tr>
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</tr>
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<td>N</td>
<td>?</td>
<td>Y</td>
<td>N</td>
<td>?</td>
</tr>
<tr>
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<td>Y</td>
<td>?</td>
<td>Y</td>
<td>N</td>
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<td>N</td>
<td>?</td>
<td>Y</td>
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<tr>
<td>Younger people</td>
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<td>N</td>
<td>?</td>
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<tr>
<td>Older people</td>
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<td>?</td>
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<tr>
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<td>?</td>
<td>N</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>Sham vs real</td>
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<td>Y</td>
<td>N</td>
<td>N</td>
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<td>Y</td>
<td>N</td>
<td>N</td>
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</tr>
<tr>
<td>ECT vs psychotherapy</td>
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<td>Y</td>
<td>N</td>
<td>N</td>
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<td>Stimulus parameters</td>
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<tr>
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<td>Y</td>
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</tr>
<tr>
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<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Continuation pharmacotherapy</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
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<tr>
<td>Symptom improvement</td>
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<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Perceived benefit</td>
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<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Cognitive functioning</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>N</td>
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<tr>
<td>Suicide</td>
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<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Brain damage</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Other adverse events</td>
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<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Information and consent</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Y, topic covered by the review; N, topic not covered; ?, insufficient detail to determine whether the topic was covered.
Group ECT review conducted a subgroup analysis for schizophrenia subtype, including one trial that predominantly (although not exclusively) included people with catatonia.

In terms of outcomes, the UK ECT Group review and Cochrane Schizophrenia Group 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, the reviewers identified two RCTs comparing ECT with rTMS and ten RCTs comparing ECT combined with drug treatment versus ECT combined with either placebo or a different drug. In four of these trials, participants continued taking pharmacotherapy following the course of ECT and its impact on relapses was assessed. The search also found three trials that compared different approaches to antidepressant treatment following successful treatment with ECT.

An additional RCT was identified that evaluated the impact of an educational video on patient knowledge about ECT; this was not included in the SURE review.

Owing to the lack of randomised evidence, non-randomised evidence was examined for the efficacy of ECT in older people, younger people, people with catatonia and ECT during or following pregnancy. For children and adolescents, two systematic reviews of case series were identified; the review published in 1999 was an update of a previous review published in 1997 by the same authors. One cohort study published since this review was also identified. For older people, one prospective cohort study comparing older people who had received ECT with those who had not and three retrospective cohort studies were identified. For catatonia one systematic review of case reports and case series of people with catatonia who received ECT, published in 1995, and two prospective case series published since this date were identified. For the use of ECT during pregnancy, one systematic review of case series and case reports published in 1994 and three case reports published since that date were identified.

Table 1 outlines the overlap between the NICE scope and the six systematic reviews identified.

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. Figures of analysis are shown in Appendix 6.

**Quality of studies identified**

**Randomised evidence**

Two systematic reviews including randomised evidence examining the efficacy and safety of ECT were identified. 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.

**UK ECT Group review**

The UK ECT Group review covers the efficacy of ECT in people with depression, schizophrenia and mania. Little information was provided in the review regarding the characteristics of participants in terms of the nature and severity of their condition, medication history and previous use of ECT. Information was provided regarding the inclusion and exclusion criteria of the studies, revealing considerable variation between them.

A wide range of interventions was included in the review comparing the effectiveness of ECT with sham ECT, inpatient care alone and pharmacotherapy. The UK ECT Group review also examined the stimulus parameters of ECT including electrode placement (bilateral versus unilateral, Lancaster versus d’Elia placement, frontotemporal versus temporoparietal), dosage (high versus low), waveform (sine wave versus brief pulse), frequency of ECT administration (twice weekly versus three times weekly), number of ECT treatments (number considered medically sufficient versus medically sufficient and two extra), number of seizures induced per treatment (one versus two) and post-ECT nursing care.

The outcomes considered in the review were improvements in symptoms following a course of ECT and at 6 months’ follow-up, leaving the study early, all-cause and case-specific mortality, cognitive functioning (anterograde, retrograde, orientation, subjective reports and overall functioning) immediately after treatment, at the end of an ECT course and at 6 months’ follow-up, functional impairment and brain damage. The reviewers also included studies examining quality of life, but did not locate any trials using this outcome.
TABLE 2  NICE scope and sources of evidence used

<table>
<thead>
<tr>
<th>NICE scope</th>
<th>Source of evidence</th>
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<tbody>
<tr>
<td>Depression</td>
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<tr>
<td>Real vs sham ECT</td>
<td>UK ECT Group review of randomised evidence and NICE reviewers’ reanalysis of trials identified by UK ECT Group</td>
</tr>
<tr>
<td>ECT vs inpatient care</td>
<td>UK ECT Group review of randomised evidence</td>
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<tr>
<td>ECT vs pharmacotherapy</td>
<td>UK ECT Group review of randomised evidence and NICE reviewers’ reanalysis of trials identified by UK ECT Group</td>
</tr>
<tr>
<td>Unilateral vs bilateral</td>
<td>UK ECT Group review of randomised evidence</td>
</tr>
<tr>
<td>Unilateral: dominant vs non-dominant</td>
<td>UK ECT Group review of randomised evidence</td>
</tr>
<tr>
<td>Bilateral: frontotemporal vs temporoparietal</td>
<td>UK ECT Group review of randomised evidence</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>UK ECT Group review of randomised evidence</td>
</tr>
<tr>
<td>Dosage: high vs low</td>
<td>UK ECT Group review of randomised evidence</td>
</tr>
<tr>
<td>Waveform: sine wave vs brief pulse</td>
<td>UK ECT Group review of randomised evidence</td>
</tr>
<tr>
<td>Ultrabrief vs standard</td>
<td>UK ECT Group review of randomised evidence</td>
</tr>
<tr>
<td>No. of ECT sessions</td>
<td>UK ECT Group review of randomised evidence</td>
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<tr>
<td>Post-ECT nursing care</td>
<td>UK ECT Group review of randomised evidence</td>
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<tr>
<td>ECT vs rTMS</td>
<td>NICE reviewers’ analysis of randomised evidence</td>
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<tr>
<td>ECT + pharmacotherapy vs</td>
<td>NICE reviewers’ analysis of randomised evidence</td>
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<tr>
<td>ECT+ placebo/different pharmacotherapy</td>
<td>NICE reviewers’ analysis of randomised evidence</td>
</tr>
<tr>
<td>Continuation pharmacotherapy</td>
<td>NICE reviewers’ analysis of randomised evidence</td>
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<tr>
<td>Mania</td>
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<tr>
<td>ECT vs pharmacotherapy</td>
<td>UK ECT Group review of randomised evidence</td>
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<td>ECT + pharmacotherapy vs pharmacotherapy alone</td>
<td>UK ECT Group review of randomised evidence</td>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>Real vs sham ECT</td>
<td>UK ECT Group and Cochrane Schizophrenia Group ECT review of randomised evidence</td>
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<tr>
<td>ECT vs pharmacotherapy</td>
<td>UK ECT Group and Cochrane Schizophrenia Group ECT review of randomised evidence</td>
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<tr>
<td>ECT + pharmacotherapy vs pharmacotherapy</td>
<td>UK ECT Group and Cochrane Schizophrenia Group ECT review of randomised evidence</td>
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<tr>
<td>ECT vs psychotherapy</td>
<td>Cochrane Schizophrenia Group ECT review of randomised evidence</td>
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<td>Continuation ECT</td>
<td>UK ECT Group and Cochrane Schizophrenia Group ECT review of randomised evidence</td>
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<tr>
<td>Bilateral vs unilateral</td>
<td>UK ECT Group and Cochrane Schizophrenia Group ECT review of randomised evidence</td>
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<tr>
<td>Unilateral: dominant vs non-dominant</td>
<td>UK ECT Group and Cochrane Schizophrenia Group ECT review of randomised evidence</td>
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<td>Dosage</td>
<td>UK ECT Group and Cochrane Schizophrenia Group ECT review of randomised evidence</td>
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<tr>
<td>Frequency of administration</td>
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<td>No. of treatments</td>
<td>UK ECT Group and Cochrane Schizophrenia Group ECT review of randomised evidence</td>
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<td>Specific outcomes</td>
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<td>Severe adverse events</td>
<td>UK ECT Group review of non-randomised evidence</td>
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<td>Patient acceptability and choice</td>
<td>SURE review of non-randomised evidence</td>
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<td>Patient information</td>
<td>NICE reviewers’ analysis of randomised evidence and SURE review of non-randomised evidence</td>
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<td>Specific subgroups</td>
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<tr>
<td>Catatonia</td>
<td>Cochrane Schizophrenia Group ECT review of randomised evidence, Hawkins’ review of non-randomised evidence and NICE reviewers’ analysis of non-randomised evidence</td>
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<tr>
<td>Children and adolescents</td>
<td>Rey and Walter’s reviews of non-randomised evidence and NICE reviewers’ analysis of non-randomised evidence</td>
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<tr>
<td>Older people</td>
<td>NICE reviewers’ analysis of non-randomised evidence</td>
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<tr>
<td>ECT during pregnancy</td>
<td>Miller’s review of non-randomised evidence and NICE reviewers’ analysis of non-randomised evidence</td>
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</table>
To assess the effectiveness of ECT, the reviewers limited their inclusion criteria to RCTs. To provide further information regarding the safety of ECT, the reviewers included case–control and cohort studies comparing participants who had received ECT with those who had not. The inclusion criteria were applied by two independent reviewers and a list of excluded studies is provided. No information is given regarding reasons for exclusion.

The search strategy used in the review was comprehensive. The reviewers searched a large number of electronic databases supplemented by citation tracking of included articles and key texts and contacting experts in the field and manufacturers of ECT machines to identify unpublished studies. Only published data were included in the review; the reviewers did not contact authors for unpublished data.

Data quality was not assessed blindly and the reviewers did not quantify study quality with rating scales, as they argued that the validity and reliability of such scales are uncertain. Instead, the study quality of RCTs was assessed according to allocation concealment, blinding, loss to follow-up and length of follow-up; cohort studies were assessed on measurement bias, handling of confounding factors, number of cases and loss to follow-up; case–control studies were assessed on measurement bias, handling of confounding factors and number of cases. The reviewers reported which paired reviewers extracted specific sections of the data and any disagreements were resolved by discussion.

The primary outcome of the review was continuous data from depression rating scales such as the HRSD.87 The reviewers did not consider any dichotomous data of improvement in their analysis, which may mean that important evidence regarding the effectiveness of ECT is lost. It has been acknowledged that health status measures providing continuous data can be difficult to interpret clinically,85 and the clinical significance of ‘X points change’ on the HRSD has yet to be clarified. Guidance on interpreting the HRSD relates to its use as a discriminant instrument used to divide people into groups based on the severity of their depression. For example, McDowell and Newell86 advise that a score of 7 indicates the absence of depression, 7–17 mild depression, 18–24 moderate and 25 or above severe depression. As a measure of change, the HRSD has been criticised for its lack of responsiveness owing to its multidimensional nature.89 Furthermore, many different versions of the HRSD exist and such guidelines do not necessarily translate to other versions of the scale.

It is evident from the table of studies in the UK ECT Group report that not all trials used the HRSD and no discussion was provided of the extent to which unpublished symptom rating scales have been psychometrically validated. They did not examine whether these trials had different results from those that did use validated scales, and do not provide any raw data to give readers sufficient information to decide for themselves. It has been demonstrated that unpublished scales are an important source of bias in systematic reviews in psychiatry; studies using unvalidated scales are more likely to find statistically significant differences between treatments than validated scales.89 Furthermore, with continuous summary measures it is not possible to conduct an ITT analysis, only one based on a completer sample. The reviewers did not discuss how this may have influenced their results.

Where appropriate, data from individual trials were summarised by meta-analysis using a random effects model. The reviewers calculated standardised WMDs, which were summarised to produce a standardised effect size according to the method of Hedges and Olkin.90 The standardised effect size is the difference in means divided by the pooled study standard deviation. The pooled study standard deviation is based on a weighted mean of the intervention and control group variances. The reviewers used this method to allow information from different instruments measuring the same construct (i.e. severity of symptoms) to be summarised, and to take into account the number of trial participants from each trial when other usable data were not available. Dichotomous and categorical data were combined to produce estimates of odds ratios and absolute risk differences. All estimates had confidence intervals.

The reviewers investigated heterogeneity between studies, but did not describe how this was done. Sensitivity analyses were conducted excluding studies of inferior quality. Subgroup analyses were identified a priori and included psychotic depression, retarded depression, the effect of age, treatment resistance, gender and severity at entry to trial. However, no subgroup analyses were conducted owing to limited information on these subgroups. Publication bias was assessed using funnel plots.

There were two important areas in the review in which data may have been pooled inappropriately.
In the comparison of ECT and pharmacotherapy for depression, the reviewers pooled data from trials comparing ECT with different classes of antidepressants including TCAs, MAOIs and SSRIs. Some trials also used l-tryptophan, which in current clinical practice is not used as a first line treatment and is used only rarely in combination with other antidepressants. In the comparison of real versus sham ECT for depression, the reviewers pooled trials that used bilateral and unilateral ECT. In a later section of the report the reviewers provided evidence that bilateral ECT is more effective than unilateral ECT. No reference to this finding was made and no justification for pooling the trials using different electrode placements was given. The reviewers did not provide any raw data to allow the reader to investigate these issues.

To assess whether the conclusions drawn by the UK ECT Group would be affected by different methods of data analysis, further analysis of the trials was undertaken in the following ways.

- Trials comparing sham ECT with real ECT and ECT versus pharmacotherapy were reabstracted using dichotomous data.
- Trials comparing real ECT with sham ECT were reanalysed, with separate analyses for bilateral ECT, unilateral ECT and trials that used both methods.
- Trials comparing ECT with pharmacotherapy were reanalysed, with separate analyses by drug class (e.g. SSRIs and TCAs).

Cochrane Schizophrenia Group ECT review
The Cochrane Schizophrenia Group ECT review conducted by Tharyan and Adams included people with schizophrenia, schizoaffective 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 provided 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 described 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 (e.g. psychotherapy). They also assessed the effectiveness of continuation ECT compared with continuation pharmacotherapy. The review also examined ECT stimulus parameters including electrode placement (bilateral versus unilateral), dose (threshold versus suprathreshold), frequency of ECT administration (three times weekly versus five days a week) and the number of ECT treatments (long courses versus 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 by the decision of either 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 was 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. The manufacturers of ECT machines were also contacted for additional studies.

The reviewers limited their review to RCTs 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. 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 used dichotomous data of global improvement as defined by the trialists as their primary outcome measure of efficacy. They argued 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 ITT 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 was provided regarding how ‘no improvement’ was defined within the various trials. Trials\textsuperscript{91} of pharmacotherapy for depression often use the criterion of a 50\% reduction in HRSD to define responders. Fink\textsuperscript{1} points out that trials of ECT often use a different criterion to distinguish responders from non-responders. There are two important disadvantages to using dichotomous data. First, it is difficult to know what degree of improvement was made in those people who did improve. Second, it is not known whether the non-responders did not change or got worse. These changes are not taken into account when dichotomous data are 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 a priori criteria for parametric data.

Data were combined using both fixed and random effects models. Heterogeneity was investigated with the Mantel–Haenszel $\chi^2$ 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 were combined using a random effects model, the data were not pooled and results are reported and discussed separately.

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 undertaken to detect any differences in outcomes between (1) people with operationally defined schizophrenia as opposed to those diagnosed by clinical consensus, (2) people with varying degrees of treatment resistance and those whose illness was not designated as such, (3) people having predominantly positive or negative symptoms of schizophrenia and those without this designation, and (4) people ill for less than 2 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 this issue to be explored in more detail if necessary.

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

The two reviews both explored the effectiveness of ECT in people with schizophrenia. Although there was a good degree of overlap between the two reviews in the trials included, there were important differences. These differences arose for several reasons: (1) in a minority of cases, some trials were included in one review and excluded in another; (2) the trials were grouped differently for analysis, particularly with respect to comparisons with ECT and antipsychotic drugs; (3) the different methods of analyses between the reviews resulted in different trials providing usable data for analysis; and (4) some trials were identified by one review but missed by the other. The Cochrane Schizophrenia Group provides reasons why each study was excluded, whereas the UK ECT Group does not, so it was not always possible to identify why one study was included in one review but not the other. Despite using different primary methods to analyse the outcome data, the two reviews drew similar conclusions regarding the effectiveness of ECT in people with schizophrenia.

Although a large number of trials explored the effectiveness of ECT in people with schizophrenia and depression, both reviews reported that the overall quality of trials is generally low. The method of allocation was rarely described and blinding was also inadequately explained. Often, continuous data were only presented in graphical form or only presented for the completer samples and dropouts 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 postpartum depression. There was little randomised evidence of the effectiveness of ECT in people with mania and catatonia. There was 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 were no trials exploring the impact of ECT on quality of life. This had important implications for the cost-effectiveness modelling within the NICE review.

**Quality of RCTs identified by the NICE reviewers**

The quality of the RCTs identified was also generally low. Of the trials comparing ECT with rTMS, one used concealed randomisation\(^55\) and both were single blind.\(^54,55\) None of 13 trials examining the efficacy of adjunctive or continuation pharmacotherapy adequately described the method of randomisation. Seven of these trials were double blind,\(^56-61,63,66-68\) four were single blind,\(^57,58,62,64\) and in two it was not clear whether the clinician or the patient was blind to treatment allocation.\(^56,65\) One RCT examining the impact of the educational video on patient knowledge\(^69\) 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.\(^59\)

**Non-randomised evidence**

Owing to the gaps in the randomised evidence, the non-randomised evidence was explored. Four systematic reviews of non-randomised evidence were identified that covered different aspects of the NICE scope.

**SURE review**

The review conducted by SURE at the Institute of Psychiatry\(^53\) aimed to summarise systematically patients’ perspectives of ECT and to understand the sources and nature of controversy about ECT between some user and professional groups.

The review included all patients who had received ECT, although little information was provided regarding the types of participants included in the studies and their conditions. Information was provided on certain studies regarding the gender and age of participants and the percentage of the study sample who were sectioned and the percentage who were legally compelled to have ECT. No information was provided regarding the stimulus parameters of ECT received by participants included in the review, or whether such information was reported in the original studies. The review was more concerned with the methods through which patients’ views were elicited and the influence that this had on the accuracy of such views.

Six main outcomes were considered in the review: long-term memory loss, information and consent, objective knowledge, felt compulsion, perceived benefit of ECT and emotional reactions to ECT. Long-term memory loss was defined as subjective amnesia or gaps in memory still present at least 6 months after the course of treatment. Information and consent was defined as the extent to which patients felt that they had adequate or sufficient information about ECT or were told about the risks of ECT. Objective knowledge of ECT was defined as how far people knew that ECT involved the use of anaesthetic, an electric current and a convulsion. Felt compulsion was defined as the extent to which voluntary patients felt that they had no choice but to have ECT. Perceived benefit was defined as either the degree to which consumers felt that ECT had helped them or whether the user would agree to have ECT again. Emotional responses were not defined in absolute terms and included any comments indicating the emotional tone of participants’ responses.

The review included both research studies and testimonies. Testimonies were defined as an individual speaking or writing directly about their own experience of ECT. Reviewers did not restrict inclusion of research studies by study type. The studies included in the review used a wide range of study designs and methods. They included quasi-experimental studies, surveys and case reports, and cross-sectional, retrospective and prospective longitudinal study designs. The studies used both quantitative and qualitative methods.

The search strategy was described in detail and combined searches of electronic databases for research studies reporting patients’ views and searches of a variety of other sources for testimonies. The electronic sources searched included PsycINFO, MEDLINE, Web of Science and the King’s Fund database 1975–2001, Proquest newspaper database, Mental Health Media Testimony archive, searches of the Internet, e-mail forums and chat rooms. Patient groups were also contacted to identify unpublished patient-led studies, local patient group newsletters, patient-authored chapters and collections of accounts of ECT. Thirty-five research studies and an unquantified volume of testimonies were identified.

No attempt was made by the reviewers to rank the studies according to a hierarchy of evidence. Instead, the reviewers describe a number of key methodological issues that they identified as having an influence on the ability of the studies to
reflect patients’ views of ECT adequately and accurately. These included the setting in which attitudes to ECT were elicited, who conducted the interview, the sample included in the study (whether from clinical research studies or patient-led surveys), the interval since ECT, the depth and complexity of the questions asked, the degree to which the questions are value laden and the different methods (e.g. dichotomous, Likert scales or in-depth interviews) used to quantify patients’ views.

A template was developed to analyse the research studies and testimonies. When research studies using a range of methodologies produced the same results, findings were presented in terms of ‘at least X% of patients experience Y’. The degree of variation in these percentages across the different methodological factors discussed above was explored to identify whether it was possible to provide an overall percentage across the studies and to explore the source of any variations.

The testimonies were analysed using a mixture of content and discourse analysis. A grid was developed with the review theme on the horizontal axis and the testimony on the vertical axis to illustrate the extent to which each testimony contained each theme. Illustrative quotations of each theme were used to allow the reader to interpret the interpretative strength of each theme. The inter-rater reliability of allocating testimonies to categories in a subset of 25 testimonies was 83%.

This review did not conform to the traditional methods of a systematic review because of important differences in the focus and nature of the review question. The review was conducted rigorously, although the methods used to demonstrate this rigour have not been used previously or empirically tested. The reviewers’ conclusions follow from the results.

Reviews on younger people and children by Rey and Walter
Two systematic reviews examining the evidence of the efficacy of ECT in younger people and children were identified. The reviews were by the same authors and one review was an update on a previous review.

The review included all studies examining the effectiveness of ECT in younger people, defined as people aged 18 years 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 out of 396 (39%) of cases in 1997. The present authors’ searches did not identify any studies published before 1999 that were not included in the review.

No information was provided regarding how data were abstracted. Two independent reviewers rated the quality of the studies and only included those that provided sufficient information on 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 were 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 was not clear whether this was undertaken on an ITT 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 and those published after DSM-III in 1980. 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 ($t = 3.06, df = 58, p = 0.003$).

It was difficult to ascertain whether this review may have missed important studies owing to the lack of information on search strategies. The reviewers rated 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 is likely that these reviews are currently the most comprehensive available.

**Hawkins and colleagues’ review of ECT in catatonia**

One systematic review examining non-randomised evidence of the effectiveness of somatic treatments for people with catatonia was identified. 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 of catatonia, although this was not defined a priori but appeared to be governed by the content of the studies identified. The treatments considered included benzodiazepines, antipsychotics, ECT, amobarbital, benztpine, amantadine, duntrolene, 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 three-point scale of none, partial or complete. None was defined as no improvement or worsening requiring a change in treatment, partial as some improvement but incomplete requiring a switch in treatment, and complete 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 was 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. The present authors' 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 and NMS suspected. In total, 270 treatment episodes in 178 patients were included.

No information was provided regarding how the data were 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 no, 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 was 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.

**Miller’s review of ECT in pregnancy**

One systematic review of the use of ECT in pregnancy was identified. 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. The present authors’ 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 were extracted and no attempt was made to rate study quality. As such, the results of the review may be biased owing to the 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 used by this review, the lack of information about how data were extracted and the relatively poor quality of the available evidence, the results of this review should be interpreted with caution.

Supplementary non-randomised evidence identified by NICE reviewers

The authors 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, two prospective case series were identified. Both used a validated instrument to measure outcomes and ECT was used in participants who had failed to respond to lorazepam.

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

In adolescents an additional cohort study was identified. There was a large loss to follow-up in the ECT group, with only ten out of 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, a further three case studies of the use of ECT in pregnancy were identified. In all four 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 evaluated the quality of the studies included and only one provided sufficient detail of the search strategies used. In three of the reviews 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 the present authors is poor. Most studies were subject to confounding by baseline differences between groups who received ECT and those that did not, or lacked any control group at all.

Results of clinical effectiveness

Depression

One systematic review evaluating the efficacy of ECT in people with depression was identified. The results of this review and the present authors’ additional analyses are presented here.

ECT versus sham ECT

The UK ECT Group identified six trials including a total of 256 patients that compared real with sham ECT. In four trials the position of the electrodes was reported: two used unilateral placement, one bilateral and one both. In four trials participants received
ECT twice weekly and in the remaining two\textsuperscript{95,97} it was administered three times weekly. Two trials reported the waveform of ECT: one used sine wave\textsuperscript{96} and the other brief pulse.\textsuperscript{97}

Nine trials comparing real ECT with sham ECT\textsuperscript{52,65,93–99} were identified. In four trials the position of electrodes was reported: two used unilateral placement,\textsuperscript{95,97} one bilateral\textsuperscript{96} and one both.\textsuperscript{93} In four trials,\textsuperscript{65,93,94,96} participants received ECT twice weekly and in the remaining two,\textsuperscript{95,97} it was administered three times weekly.

Five trials specified the machine used to deliver ECT: two used Duopulse Mk IV machines,\textsuperscript{93,97} two used Ectron Mk IV machines\textsuperscript{95,96} and one used a Transycon machine.\textsuperscript{94} Of the seven trials that specified the dosage and waveform of ECT, none used stimulus dosing but gave a fixed dose. Two used sine wave at 150 V,\textsuperscript{52,97} one used sine wave but did not specify the dosage,\textsuperscript{96} one used chopped sine wave (dosage not specified),\textsuperscript{98} one used 60\% sine wave at 400 V,\textsuperscript{96} one used a double-sided unrectified wave at 40 J\textsuperscript{94} and only one used brief pulse at 10 J.\textsuperscript{95}

In two trials\textsuperscript{52,96} the control arm also received at least one real ECT. In Jagadeesh,\textsuperscript{95} participants in the control arm received one real and five sham ECT administrations. In Freeman,\textsuperscript{96} participants in the control arm received two initial sham ECT administrations and the remaining ones were real.

Efficacy at end of course The UK ECT Group\textsuperscript{51} found six trials that provided usable data on depressive symptoms. The standardised difference between real and simulated ECT was –0.91 [95\% confidence interval (CI) –1.27 to –0.54], indicating a significant effect of real ECT. This result translates to a mean difference in the HRSD score of 9.67 (95\% CI 5.72 to 13.53) in favour of real ECT. Eighty-two per cent of patients receiving ECT would be less depressed than the average patient treated with sham ECT.

Four trials provided dichotomous data for analysis of improvement at the end of an ECT course.\textsuperscript{52,95–97} One trial used unilateral ECT\textsuperscript{95} and the other three used bilateral ECT\textsuperscript{52,96,97} and were analysed separately. The relative risk (RR) of a reduction of at least a 50\% in HRSD score 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 the Freeman study,\textsuperscript{96} resulted in a homogeneous 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 two sham ECTs; the rest were real ECTs. A further remaining trial\textsuperscript{52} also included one real ECT treatment in the control arm along with five sham ECT treatments. Removal of this trial,\textsuperscript{52} 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 Discontinuations occurred in both groups and three trials provided usable data.\textsuperscript{93,94,97} The odds ratio for the comparison was 0.80 (95\% CI 0.30 to 2.40), which indicates no difference between treatment groups. The risk difference was –0.003 (95\% CI –0.06 to 0.06).

Efficacy at 6-month follow-up Only one study\textsuperscript{97} reported depression rating scores at 6 months following the end of ECT. This study reports a two-point difference in final HRSD score in favour of the sham group.

Adverse events: mortality No deaths occurred in these trials.

Adverse events: cognitive functioning One trial\textsuperscript{97} provided data on cognitive functioning as an immediate consequence of ECT, at the end of a course of treatment and at 6 months’ follow-up. A meta-analysis was not conducted because of limited data and the UK ECT Group reviewers describe the results as reported by the trial author with a warning of the risk of bias due to selective reporting.

Immediately after ECT, patients treated with real ECT were more able to retrieve remote memories than those treated with real ECT (retrograde memory), but also had more word recognition errors than those treated with sham ECT (anterograde memory). The differential in anterograde memory deficits between the two groups was still present at the end of the course of ECT and those treated with real ECT reported more subjective memory complaints. At 6 months’ follow-up the authors reported no statistically significant differences between those treated with real or with sham ECT on measures of subjective
memory complaints, new learning and remote memories.

ECT versus inpatient care alone
The UK ECT Group identified one trial that compared ECT with inpatient care alone\(^{100}\) and included 139 patients. The mean decrease in depression scores was 3.6 points greater on the HRSD Scale in the ECT group. There was one suicide in the ECT group and one death due to other causes in the control arm.

ECT versus pharmacotherapy
Although these trials provide an estimation of the relative efficacy of ECT compared with drug therapy, most trials did not include sham ECT in the control arm. As such, any difference may not be due to the electrical stimulus and induction of a seizure alone, but could be due to other components of the ECT procedure, including anaesthesia and nursing care.

Eighteen trials containing 1144 patients that were included in the analysis\(^{65,99–115}\) were identified. Bilateral ECT was used in five trials\(^{102,103,107,110,111}\) and unilateral in two\(^ {108,112}\). ECT was administered twice a week in four studies\(^ {65,107–109}\) and three times a week in five studies\(^ {99,102,103,112,113}\). In five trials\(^ {65,103,107,110}\) participants were treated with TCAs at doses between 75 and 150 mg of imipramine or 150 mg of amitriptyline\(^ {99}\). L-Tryptophan was used in two trials at doses of 3 g\(^ {108}\) and 6–8 g\(^ {109}\). The remaining trials used paroxetine 40–50 mg\(^ {112}\), lithium 800 g\(^ {111}\), phenelzine 15–45 mg, either imipramine 50 g or phenelzine 15 mg\(^ {100}\) or a TCA or an MAOI.\(^ {113}\) Only four studies\(^ {102,107,111,112}\) required participants to have failed to respond to at least one trial of antidepressant drugs for inclusion in the study. Treatment was continued for a range of durations. Three studies\(^ {65,111,113}\) reported the end of treatment at 3 weeks, one at 3–5 weeks\(^ {102}\), four trials reported 4 weeks\(^ {99,108,109,112}\) one at 5 weeks\(^ {107}\), one at 12 weeks\(^ {110}\) and one at approximately 2–4 weeks.\(^ {100}\) Only three of the 18 trials identified used sham ECT in the pharmacotherapy arm.\(^ {65,105,115}\)

The UK ECT Group identified 18 trials containing 1144 patients that were included in the analysis.\(^ {65,99–115}\) Only published data are reported by the reviewers. Not all studies provided usable data.

Efficacy at the end of treatment The UK ECT Group\(^ {21}\) found 13 trials that contributed sufficient data to be included in the pooled analysis.

Treatment with ECT led to a significantly greater decrease in depressive symptoms than drug treatment (standardised effective size –0.80, 95% CI –1.29 to –0.29). This translates to a mean difference of 5.2 (95% CI 1.37 to 8.87) in the HRSD in favour of ECT.

Our own analysis compared ECT to each drug class separately. One trial compared right unilateral ECT with an SSRI (paroxetine 40–50 mg) 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 relative risk 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; in one trial the TCA was combined with an MAOI\(^ {102}\) and in another it was combined with lithium\(^ {111}\) in people with treatment-resistant depression. Six trials including 394 participants provided dichotomous data for analysis.\(^ {104,107,113,115}\) The criteria used to define responders varied between trials. Two trials\(^ {107}\) defined responders using different criteria specified a priori based on scores from quantitative outcome measures, while the remaining four\(^ {100,104,113,115}\) 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 six 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\(^ {103,107}\) based on a quantitative assessment of improvement separately resulted 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\(^ {100,104,113,115}\) based on clinical opinion gave a relative risk 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 The UK ECT Group\(^ {21}\) found that discontinuations commonly occurred in both groups. The odds ratio for the
different types of treatment was 0.34 (95 CI 0.06 to 0.90), indicating a significant difference between treatment groups. The risk difference was 0.03 (95% CI –0.09 to 0.03) in favour of ECT.

**Depression at 6-month follow-up** The UK ECT Group found a single study that reported depression rating at 6 months' follow-up. The results showed a lower score in the ECT group of five points on the HRSD.

**Adverse events: mortality** The UK ECT Group found one trial that reported a death in each arm of the trial.

**Adverse events: cognitive functioning** The UK ECT Group reported that the data on cognitive functioning were heterogeneous owing to the different tests of cognitive functioning used. The reviewers reported the data on cognitive functioning as reported by the authors of the trials, with the warning of a risk of bias due to selective reporting.

The UK ECT Group reported that no trials were identified that provided data on orientation, new learning or subjective distress as an immediate consequence of ECT treatment. Three randomised trials measured cognitive functioning at the end of a course of ECT, comparing patients treated with drugs with those treated with ECT. One assessed retrograde memory, but only reported within-group results of tests, which are difficult to interpret. With regard to anterograde memory, McDonald and colleagues reported no statistically significant difference between patients treated with ECT and those treated with drug therapy on the Weschler–Bellevue Intelligence Scale (WBIS). Bagadia and colleagues only reported within-group results of tests, which are difficult to interpret. Finally, Gangadhar reported that more patients treated with ECT complained of loss of memory than those treated with drug therapy. No trials reported on cognitive function at longer than 6 months.

**Unilateral versus bilateral ECT**

The UK ECT Group identified 28 trials using 1408 patients; in 21 of these, data were available to calculate effect size.

Various electrode placements were used for both unilateral and bilateral ECT. Two studies reported bitemporal placement, two used bifrontal and one reported bifrontotemporal. In three trials either dominant or non-dominant unilateral placements were reported and the remaining studies where placement was described used non-dominant or right unilateral placement. Three types of unilateral placement were used: d’Elia and Lancaster, and in one trial Raotma placement.

The trials rarely defined the course, duration and frequency of treatment and those that did demonstrated a significant degree of heterogeneity in the methods used.

**Efficacy at end of course** The UK ECT Group reports that the standardised effect size between the two types of electrode placement was –0.32 (95% CI 0.46 to –0.20), which is a significant result in favour of bilateral ECT. This translates to a 3.58 (95% CI 2.24 to 5.15) change in depression score in favour of bilateral ECT. A test of heterogeneity produced no effects of publication year on this outcome. Removal of trials by Sackeim that may have included different populations from the rest of the studies shifted the point estimate of effect size, but it remained statistically significantly in favour of bilateral ECT.

**Discontinuations** The UK ECT Group found two trials that reported events for this outcome, so it was not possible to summarise results. Numbers were similar for each group.

**Adverse events: cognitive functioning** The UK ECT Group reported that the data on cognitive functioning were heterogeneous owing to the different tests of cognitive functioning used. The reviewers reported the data on cognitive functioning as reported by the authors of the trials, with the warning of a risk of bias owing to selective reporting. Their findings are as follows.

(a) As an immediate consequence of ECT

- **Orientation**

  Six studies found that the time to recovery of orientation was longer for patients treated with bilateral ECT than for those treated with unilateral ECT. Similarly, Fleminger and colleagues found greater impairment of orientation among those treated with bilateral compared with either non-dominant or dominant unilateral ECT when assessed at 10 minutes post-treatment.

- **Retrograde memory**

  Two studies assessed retrograde memory postictally and both found greater
impairment in people treated with bilateral ECT. Sackeim and colleagues found no difference in retrograde memory between those treated with bilateral ECT and high-dose unilateral ECT. Levy reported data during the course of ECT with results given after the sixth session of ECT. No difference was found on tests of recent personal events between groups, although there was a significant deterioration in memory for general events among patients treated with bilateral ECT compared with non-dominant unilateral ECT.

- Anterograde memory
  One study reported repeated testing of new learning and episodic memory during the course of ECT and found that bilateral ECT resulted in greater impairment of new learning at 36 hours post-ECT than unilateral ECT.

The Weschler Memory Scale (WMS) was used in six studies to compare pre-ECT memory functioning with functioning at a point during the course of ECT. Overall, these studies show that where there are differences in cognitive functioning, people treated with bilateral ECT fared worse than those treated with unilateral ECT. People who received high-dose or dominant unilateral ECT also reported greater memory impairment than those receiving low-dose or non-dominant unilateral ECT.

- Subjective distress
  One study reported on subjective complaints of memory impairment during the course of ECT. In this study, patients receiving bilateral ECT reported both greater post-treatment confusion and memory problems than the group receiving non-dominant unilateral ECT. Complaints of cognitive side-effects were essentially non-existent among patients treated with non-dominant unilateral ECT.

(b) At the end of a course of ECT

- Retrograde memory
  Four studies reported results from testing of retrograde memory within a week of end of a course of ECT. All these studies reported greater impairment among patients treated with bilateral ECT.

- Anterograde memory
  Seven studies reported results from tests assessing anterograde memory within 7 days of the end of the randomised phase of treatment. Five studies found that where differences did occur, those receiving bilateral ECT fared worse than those receiving unilateral ECT. Two studies showed no differences in new learning tasks between bilateral and non-dominant unilateral ECT, while one study found that those treated with bilateral ECT performed better than those treated with dominant unilateral ECT.

Three studies described cognitive testing subsequent to testing at the end of the course of treatment: Bidder and colleagues at 10 days, Letemendia and colleagues and Halliday and colleagues at 3 months. In addition, Fraser and Glass reported results at 3 weeks. Bidder and colleagues and Fraser and Glass found no statistically significant differences between bilateral and unilateral ECT. At 3 months following treatment, Halliday and colleagues reported that patients who had been treated with non-dominant unilateral ECT performed better on digit span and delayed non-verbal learning compared with those treated with bilateral ECT, with no difference between dominant unilateral and bilateral ECT. Letemendia and colleagues found no difference between non-dominant unilateral and bitemporal ECT on four tests of verbal and non-verbal functioning when patients were tested 3 months post-ECT.

- Overall cognitive functioning
  Three studies reported results from overall cognitive testing in the week following the end of the randomised phase of treatment. These studies showed that where differences did occur, people who received bilateral ECT showed greater cognitive impairment than those receiving unilateral ECT. Two studies reported results at later stages: Sackeim and colleagues at 2 months and Heise at 3 months. They showed no statistically significant differences between bilateral and unilateral ECT.

- Subjective reports
  Two studies described subjective report of cognitive functioning at the end of the course of ECT. Horne and colleagues found that patients treated with bilateral ECT described more subjective impairment of memory than those treated with non-dominant unilateral ECT, including a subjectively greater impairment of recall of the events surrounding their admission. Weiner and colleagues however, reported no statistically significant
difference in global self-rating of memory function 2–3 days post-ECT.

(c) Long-term (>6 months)
Two studies\textsuperscript{120,140} reported long-term data. Weiner and colleagues\textsuperscript{120} found no between-group difference in anterograde memory function at 6 months, with scores returning to at least pretreatment levels. Long-term personal memory was more impaired in the bilateral than in the non-dominant unilateral ECT group, although there were no differences in recall of famous events or faces. At 1 year following treatment, Bidder and colleagues\textsuperscript{140} found no difference between bilateral and unilateral ECT-treated patients on assessment of verbal memory and both groups had improved since they were tested at 10 days post-treatment.

Unilateral electrode placement
The UK ECT Group\textsuperscript{51} found five trials\textsuperscript{125,138,139,147,148} that provided data on 174 patients. The trials provided limited descriptive information concerning the parameters of ECT administration. Their analyses of these trials are detailed below.

**Efficacy: end of course and 6 months** The standardised effect size between the two types of electrode placement was 0.387 (95% CI –0.09 to 0.87), which does not represent a significant effect. The result translates to a 3.87-point (95% CI –0.90 to 8.70) non-significant change on the HRSD in favour of unilateral dominant rather than non-dominant electrode placement. No studies reported depression ratings at 6 months.

There were no discontinuations or deaths reported in these trials.

**Adverse events: cognitive functioning**
(a) As an immediate consequence of ECT
Three randomised trials\textsuperscript{138,139,148} measured cognitive functioning immediately after ECT. It was not possible to perform a meta-analysis because of the interstudy variations in the measures used.

- Orientation
  Two studies assessed recovery following ECT\textsuperscript{138,139} and both reported that patients treated with unilateral ECT to the non-dominant hemisphere recovered orientation more quickly than those treated with unilateral ECT to the dominant hemisphere.

- Anterograde memory,\textsuperscript{148} but the reviewers found the results difficult to interpret.

(b) At the end of a course of ECT
Four randomised trials\textsuperscript{125,138,139,147} measured cognitive functioning at the end of a course of ECT, comparing ECT applied to the dominant hemisphere with ECT applied to the non-dominant hemisphere, but in one the results were difficult to interpret.\textsuperscript{147} The remaining three all showed that people treated with unilateral ECT to the dominant hemisphere did worse than those treated with unilateral ECT to the non-dominant hemisphere on tests of new learning (anterograde memory).\textsuperscript{125,138,139} The trials did not assess retrograde memory or subjective distress and none of the trials assessed cognitive functioning at 6 months.

Bilateral electrode placement
The UK ECT Group\textsuperscript{51} found two trials\textsuperscript{128,149} that compared frontotemporal and temporoparietal bilateral electrode placement and included results for 100 patients. Participants received brief-pulse ECT three times a week in both trials. In one trial\textsuperscript{128} the dose was given at seizure threshold and in the other\textsuperscript{149} it was given at 1.5 times this value. In the latter trial patients were treated until remission or up to a maximum of 12 weeks. The UK ECT Group’s\textsuperscript{51} analyses of these trials are described below.

**Efficacy at end of course** The pooled standardised effects analysis showed no difference between the two forms of bilateral placement, with a result of –0.01 (95% CI –0.75 to 0.74). This translates to a mean change in HRSD score of 0.05 (95% CI –4.34 to 4.28).

**Depression rating at 6-month follow-up** One study\textsuperscript{128} reported follow-up data for efficacy scores. The final scores of the two groups had a difference of two points in favour of temporoparietal positioning.

**Adverse events: mortality** No deaths occurred in either of the trials.

**Adverse events: cognitive functioning**
(a) As an immediate consequence of ECT
No trials were identified describing results for orientation, cognitive change or subjective distress.

(b) At the end of a course of ECT
Two randomised trials\textsuperscript{128,149} measured cognitive functioning at the end of a course of ECT. It was
not possible to perform a meta-analysis because of the interstudy variations in the measures used. Bailine and colleagues\textsuperscript{149} reported that patients treated with bitemporal ECT had lower Mini Mental State Examination (MMSE) scores after treatment than patients treated with bifrontal ECT. Letemendia and colleagues\textsuperscript{128} reported that there were no statistically significant differences on several cognitive measures between patients treated with bitemporal ECT at 7 days or 3 months after treatment.

No trials were identified that provided data on cognitive function at 6 months or more post-ECT.

**Frequency of ECT**

The UK ECT Group\textsuperscript{51} identified six trials containing results for 210 patients.\textsuperscript{150-155} Two trials\textsuperscript{153,155} compared once-weekly with three times-weekly ECT, while the remaining four\textsuperscript{150-152,154} compared twice-weekly and three times-weekly administrations. Their analyses are set out below.

**Efficacy at end of course**

The reviewers analysed the four trials comparing ECT twice weekly versus three times weekly separately and together with the two that reported once versus three times weekly. The standardised effect size was –0.30 (95\% CI –0.76 to 0.20) for twice versus three times weekly and 0.83 (95\% CI –0.39 to 1.89) for once versus three times weekly. When all the results were combined there was no significant difference between the two regimens, with a mean change in depression score of 0.40 (95\% CI –5.26 to 6.30) in favour of more frequent ECT administration.

**Discontinuation**

Two trials\textsuperscript{151,154} reported discontinuations and they were equivalent for both groups.

**Depression rating at 6-month follow-up**

No data were available.

**Adverse events: mortality**

One trial\textsuperscript{150} reported a death due to suicide. No analysis was possible based on the limited data.

**Adverse events: cognitive functioning**

(a) As an immediate consequence of ECT

One randomised trial\textsuperscript{151} measured cognitive functioning immediately after ECT. Lerer and colleagues\textsuperscript{151} reported no difference in time to reorientation in patients treated three times weekly compared with those treated twice weekly. No trials provided data on retrograde memory, anterograde memory or subjective distress.

(b) At the end of a course of ECT

Four randomised trials\textsuperscript{131,152,154,155} measured cognitive functioning at the end of a course of ECT. The reviewers were not able to conduct a meta-analysis because of variations between studies in the measures used.

- **Retrograde memory**

  Two studies\textsuperscript{151,152} reported that patients treated with ECT three times weekly did worse than those treated twice weekly on tests of personal memory. No statistically significant differences were apparent 1 month after the course of treatment.

- **Anterograde memory**

  Kellner and colleagues\textsuperscript{155} reported no statistically significant difference in WMS scores between patients treated with ECT once weekly and those treated three times weekly. Lerer and colleagues\textsuperscript{151} reported a poorer performance on anterograde and retrograde immediate and delayed facial recognition and digits backwards in patients treated three times weekly compared with those treated twice weekly. No statistically significant differences were apparent 1 month after the course of treatment.

- **Overall cognitive functioning**

  Kellner and colleagues\textsuperscript{155} reported no statistically significant difference in MMSE scores between patients treated with ECT once weekly and those treated three times weekly. Lerer and colleagues\textsuperscript{151} reported a greater deterioration in overall function in patients treated three times weekly than in those treated twice weekly. No statistically significant differences were apparent 1 month after the course of treatment. Vieweg and Shawcross\textsuperscript{154} reported no statistically significant differences in MMSE scores between patients treated three times weekly and those treated twice weekly.

No trials reported data on subjective distress or any aspect of cognitive functioning at 6 months.

**Dose of electrical stimulus**

The UK ECT Group\textsuperscript{51} identified seven trials containing results for 342 patients.\textsuperscript{31,135,153,156-159} The actual doses used in the trials varied and the reviewers classed the dose as ‘higher’ and ‘lower’ for the purposes of analysis. In the McCall trial,\textsuperscript{158} lower dose was defined as 2.5 times the convulsive threshold and higher dose was 408 mC for 2 seconds, Janakiramaiah and colleagues\textsuperscript{153} used threshold for lower dose and 240 mC for higher dose, Sackeim and colleagues\textsuperscript{135} used either 50\% or
150% above threshold as lower dose and 500% above threshold as higher dose, McCall and colleagues\textsuperscript{157} had lower dose as 2.5 times the convulsive threshold compared with a higher dose of 403 mC for 2 seconds, and Warren and Tissera\textsuperscript{159} used 7–10 J for lower and 40–555 J for higher dose. The UK ECT Group\textsuperscript{51} analyses are detailed below.

**Efficacy** Six trials provided usable data for analysis.\textsuperscript{31,135,153,157–159} The results indicated a standardised treatment effect of 0.73 (95% CI 0.41 to 1.08) or mean change in HRSD score of 5.24 (95% CI 2.94 to 7.75) in favour of the higher dose group. No trials provided information on depression ratings at 6 months.

**Discontinuations** One trial\textsuperscript{157} reported events for discontinuations, with similar numbers in each arm, so analysis was not possible.

**Adverse events: mortality** No deaths were reported in these trials.

**Adverse events: cognitive functioning**

(a) As an immediate consequence of ECT

- **Orientation**
  Three trials found that people treated with high-dose unilateral ECT took longer to recover than those treated with low-dose unilateral ECT.\textsuperscript{31,135,158}

- **Anterograde memory**
  Sackeim\textsuperscript{135} reported that patients treated with high-dose unilateral ECT had worse scores on some measures of new learning than patients treated with low- or moderate-dose unilateral ECT.

  No trials provided data on retrograde memory or subjective distress.

(b) At the end of a course of ECT

Five randomised trials measured cognitive functioning at the end of a course of ECT.\textsuperscript{31,135,157–159} The reviewers did not conduct a meta-analysis because of the interstudy variations in the measures used.

- **Retrograde memory**
  None of the studies found any differences between people treated with high-dose or low-dose energy pulses on tests of personal, autobiographical, subjective or overall memory.\textsuperscript{31,135,157–159}

- **Anterograde memory**
  Two studies found no differences between people treated with high-dose or low-dose energy pulses on tests of new learning.\textsuperscript{158,159}

Two studies found worse scores on tests of new learning in those treated with high-dose pulse compared with low or moderate doses.\textsuperscript{31,135}

- **Overall cognitive functioning**
  Sackeim and colleagues\textsuperscript{31} reported no statistically significant differences between high- and low-dose bilateral and unilateral ECT on total MMSE score. McCall and colleagues\textsuperscript{158} reported that patients treated with fixed high-dose unilateral ECT performed worse on the MMSE than patients treated with titrated, moderate-dose unilateral ECT.

**Stimulus waveform**

The UK ECT Group\textsuperscript{51} found eight trials containing results for 296 patients.\textsuperscript{120,126,129,131,139–162} Five trials provided data for a meta-analysis which compared brief-pulse and sine-wave ECT for electrical stimulation.\textsuperscript{129,131,159,160,162} The UK ECT Group’s\textsuperscript{51} analyses of these trials are described below.

**Efficacy at end of course: depression rating**

The standardised effect size was 0.62 (95% CI –0.31 to 1.54) in favour of sine wave. This translates to a mean change in HRSD score of 4.21 (95% CI –2.08 to 10.5). The trials did not provide any data on depression ratings at 6 months or discontinuations.

**Adverse events: mortality** No deaths occurred in the trials.

**Adverse events: cognitive functioning**

(a) As an immediate consequence of ECT

Two trials measured cognitive functioning immediately after ECT, comparing sinusoidal with brief pulse.\textsuperscript{126,129}

- **Orientation**
  Valentine and colleagues\textsuperscript{129} reported that patients receiving brief-pulse ECT began breathing, recovered consciousness and became orientated more quickly than patients receiving sinusoidal ECT.

- **Retrograde memory**
  Daniel and Crovitz\textsuperscript{126} reported no statistically significant difference between brief-pulse and sine-wave ECT on several measures of perceptual learning and autobiographical memory. Valentine and colleagues\textsuperscript{129} reported that patients receiving brief-pulse ECT had
better recall of word associations learned shortly before the treatments than did patients receiving sinusoidal ECT. No trials were identified that reported data for anterograde memory or subjective distress as an immediate consequence of ECT.

(b) At the end of a course of ECT
Two randomised trials\textsuperscript{120,159} measured cognitive functioning at the end of a course of ECT, comparing sinusoidal with brief-pulse ECT. The reviewers did not conduct a meta-analysis because of the interstudy variations in the measures used. The results are described as reported by the authors, with the consequent risk of bias due to selective reporting.

- Retrograde memory
  Warren and Tissera\textsuperscript{159} reported no statistically significant difference between pulse (high and low energy) and sine-wave ECT on logical memories, verbal recognition, facial recognition or a measure of remote memories. Weiner and colleagues\textsuperscript{120} reported no statistically significant difference in overall self-rating memory (which seemed to improve in all groups) between patients treated with pulse and sine-wave ECT, but found that patients treated with sine-wave ECT received more electrical energy and performed worse on measures of retrograde memory.

- Anterograde memory
  Warren and Tissera\textsuperscript{159} reported no statistically significant difference between pulse (high and low energy) and sine-wave ECT on digit span. Weiner and colleagues\textsuperscript{120} reported that patients treated with sine-wave ECT performed worse on measures of anterograde memory, including verbal paired associations, paragraph recall, facial recognition and complex figure reproduction.

- Overall cognitive functioning
  Weiner and colleagues\textsuperscript{120} reported no statistically significant difference on a neuropsychological test battery between patients treated with pulse and sine-wave ECT.

No data were available on subjective distress at the end of a course of ECT.

(c) At 6 months
Weiner and colleagues\textsuperscript{120} reported no statistically significant difference at 6 months post-treatment in overall self-rating memory between patients treated with pulse and sine-wave ECT.

Ultrabrief ECT versus standard ECT
The UK ECT Group\textsuperscript{51} found one study\textsuperscript{163} that considered the use of ultrabrief stimulus for ECT administration. The study contained 72 patients but did not report efficacy scores. On cognitive testing, 1 week after last treatment, all patients showed improvement on tests of immediate reproduction and delayed reproduction, with no significant difference between the groups. There was no significant difference between the two groups on tests of subjective memory change or overall on tests of forgetting. No discontinuations or mortality were reported.

Number of ECT sessions
The UK ECT Group\textsuperscript{51} identified a single trial\textsuperscript{164} that considered this comparison. Twenty-six patients were recruited and available for assessment; no depression rating scores were given but none of the patients discontinued treatment or died. No usable data on cognitive functioning were reported.

Number of seizures per treatment session
The UK ECT Group\textsuperscript{51} found a single study\textsuperscript{162} that compared the induction of one seizure per treatment session with the induction of two seizures per treatment session. The study contained data on 29 patients with no deaths or discontinuations. The change in HADS score was greater in the multiple monitored ECT group by 4.1 points. Charts recorded significantly greater post-treatment confusion among patients treated with multiple monitored ECT. No other tests of cognitive functioning were performed.

Extra sessions of ECT
The UK ECT Group\textsuperscript{51} identified one trial\textsuperscript{166} that considered the effect of performing two additional ECT sessions above what they classified as medically sufficient. Seventy-five patients were recruited; four patients in the sufficient group and five in the extra group refused ECT at some point. No usable efficacy data or cognitive data were reported and no deaths occurred.

Post-ECT nursing care
The UK ECT Group\textsuperscript{51} found one study\textsuperscript{167} that compared usual nursing care post-ECT with a procedure in which patients were taken to a small, dimly lit room for 2–4 hours, where ambient noise was minimised but nurses monitored patients as usual (rest). The trial recruited 19 patients, none of whom discontinued treatment or died. No measure of efficacy of the techniques was made. They found that there were statistically significantly fewer subjective memory complaints.
in the rest group then in the ward group. There were no other significant differences on cognitive testing.

**ECT versus rTMS**

Two RCTs were identified that evaluated the efficacy of rTMS with ECT in people with depression, including 63 participants. One trial compared ECT alone with rTMS, while the other compared ECT with ECT plus rTMS. One trial specifically included people with medication-resistant depression. Both trials used unilateral ECT placement and only one described the frequency of administration, which was three times per week. The rTMS methods differed between the two studies. In Pridmore, a Magtism Super Rapid Stimulator was used, with a Magstim 70-mm double coil, at an intensity of 100%, a frequency of 20 Hz and a train length of 2 seconds. The number of trains was 30, with an intertrain interval of 20 seconds. In Grunhaus, the motor threshold was determined daily by electromyography and stimulus intensity was the lowest machine power output that would provide five of ten stimulations with a muscular-evoked potential (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 provided usable data on 40 participants for analysis. The efficacy of the treatment was measured using continuous data from the HRSD. The WMD between ECT and rTMS was 6.8 (95% CI 1.41 to 12.19, 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 than or equal to 60 on the Global Assessment of Functioning (GAF) scale and had decreased by at least 50% on the HRSD from baseline, but the data were 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 and colleagues (ECT versus rTMS) found that five patients in the rTMS group complained of mild headache, which responded to analgesics. In one patient and only during one of the treatment sessions an MEP discharge was noted 20 ms after each magnetic pulse.

Pridmore (ECT versus ECT + rTMS) used a six-item subjective side-effects questionnaire derived from a report on the side-effects of ECT. Over the 2-week study period the ECT-only stream scored 56 positive responses on the side-effects questionnaire, while the ECT plus 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’; these 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.

**ECT plus pharmacotherapy versus ECT plus placebo/different pharmacotherapy**

The present review identified 11 trials that compared ECT combined with pharmacotherapy versus ECT combined with either placebo or a different type of pharmacotherapy. Two trials compared unilateral ECT combined with l-tryptophan versus unilateral ECT and placebo. Three trials compared ECT combined with imipramine versus ECT combined with placebo. In one study the dosage of imipramine ranged from 25 to 50 mg, in another the dosage was 25 mg three times daily and in the third it ranged from 150 to 220 mg. Imlah and colleagues also had an arm in the trial where ECT was combined with phenelzine (15 mg three times daily). None of the trials reported any details of electrode placement. Lauritzen and colleagues had two arms in the trial that were separately randomised to receive either bilateral then unilateral ECT combined with paroxetine (30 mg) or placebo (Group A), or bilateral then unilateral ECT combined with paroxetine (30 mg) or imipramine (150 mg). Kay and colleagues compared ECT combined with either amitriptyline (50–150 mg) or diazepam (4–12 mg). Mayur and colleagues compared unilateral ECT combined with continuation of the antidepressants (either TCAs or SSRIs, dose or type not defined) that participants were taking on entry to the trial versus ECT alone. Arfwidsson and colleagues compared bilateral ECT combined with chlorpromazine (30–150 mg) versus bilateral ECT combined with placebo. Shiah and colleagues compared either unilateral or bilateral ECT combined with pindolol (7.5 mg) with ECT and placebo. Coppen and colleagues compared...
compared ECT and lithium (plasma levels between 0.8 and 1.2 mmol l⁻¹) continuation therapy with ECT and placebo. In five trials, the length of ECT treatment was determined by a clinical decision on response to ECT, while Shah and colleagues fixed the number of treatments at six in each arm. In the remaining four trials, the length of ECT treatment was unclear. In five of the trials, participants continued to take the pharmacotherapy they had been randomised to after ECT treatment and were followed up at 3 months, 6 months, or 1 year 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, but were analysed separately owing to the different types of drugs in the comparison. Shah and colleagues defined responders as those scoring less than 12 on the 29-item version of the HRSD, whereas Arfwidsson and colleagues and d’Elia and colleagues defined improvement according to clinical opinion. One trial provided dichotomous data on relapses at end of ECT course based on clinical opinion.

In the Arfwidsson 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). Shah and colleagues also found a non-significant trend for people treated with pindolol to have responded after six ECTs compared with 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 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). Kay and colleagues found that those treated with ECT plus diazepam were more likely to have relapsed at the end of ECT course than those treated with ECT plus amitriptyline (RR = 0.55, 95% CI 0.33 to 0.90, p = 0.02, n = 132).

Three trials provided continuous data on completer samples for analysis and all used the HRSD; Mayur and Lauritzen used the 17-item version and Shah and colleagues used the 29-item version. All trials were analysed separately owing to the different drugs involved in the comparisons.

Lauritzen and colleagues found no statistically significant differences in scores on the HRSD between those treated with ECT plus paroxetine and those treated with ECT plus placebo at the end of the course of ECT. The WMD was –0.50 (95% CI –0.301 to 2.4, n = 35, p = 0.83) in favour of paroxetine. The WMD between paroxetine plus ECT and imipramine plus ECT was –3.00 (95% CI –5.65 to 0.33, n = 52), which is a statistically significant difference at the 0.05 level in favour of imipramine.

Mayur and colleagues 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 = 0.6, n = 22).

Shiah and colleagues found statistically significantly lower scores in participants treated with ECT plus pindolol compared with participants treated with ECT plus placebo after six ECTs (WMD = –9.10, 95% CI –16.08 to –2.12, p = 0.01, n = 15).

**Efficacy: prevention of relapses** Only one trial provided usable data for analysis regarding the efficacy of continuing to take pharmacotherapy following the course of ECT in preventing relapses. There was a statistically non-significant trend for those treated with imipramine to have a reduced risk of experiencing a relapse (RR = 0.83, 95% CI 0.58 to 1.19, p = 0.32, n = 100). However, if those who withdrew from the trial or were lost to follow-up were not allocated the worst outcomes and removed from the nominator in the analysis then those who continued to take imipramine were statistically significantly less likely to experience a relapse at 6 months (RR = 0.33, 95% CI 0.16 to 0.71, p = 0.005). There were no statistically significant differences in the likelihood of relapsing between those treated with TCA and MAOIs (RR = 0.80, 95% CI 0.52 to 1.24, p = 0.3, n = 100).

Coppen and colleagues compared the mean number of weeks spent depressed during the following 6 months. They 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 WMD was 0.90 (95% CI 0.29 to 1.51, p = 0.004).

In the study by Arfwidsson and colleagues, chlorpromazine was discontinued at the end of the ECT course and patients were followed up at 3 months. They found that those who received chlorpromazine in addition to ECT were not
Effectiveness

statistically significantly less likely to experience a relapse at this time compared with those who received ECT plus diazepam (RR = 1.17, 95% CI 0.76 to 1.79, \(p = 0.48, n = 57\)).

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

Mayur and colleagues found no significant differences between groups in the mean number of side-effects at the 2- or the 4-week stage of the acute phase as measured by the Columbia checklist. The antidepressant group had significantly higher mean ratings on the anticholinergic subscale of UKU. There were no significant differences in any other UKU subscale. No patient had significant arrhythmias. There were no intolerable anticholinergic side-effects among patients with tricyclic drugs and ECT warranting discontinuation of the drug during the ECT course.

**Continuation pharmacotherapy** The present group identified a further two double-blind trials 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 and colleagues defined responders as those with an HRSD (17-item version) score of less than or equal to 10 that was maintained for a week. Sackeim and colleagues defined responders as those who had a decrease of at least 60% on the HRSD (17-item version) from baseline.

Sackeim and colleagues compared continuation with nortriptyline (25 mg) alone versus nortriptyline plus lithium (300 mg) versus placebo. Grunhaus and colleagues compared fluoxetine (20 mg day\(^{-1}\) combined with melatonin (5 mg) with fluoxetine (20 mg) and placebo. Sackeim used either bilateral or unilateral ECT and Grunhaus used unilateral ECT that was switched to bilateral if a response was not achieved within six treatments. In the Sackeim trial, ECT was administered three times weekly for a duration determined on clinical grounds. In both the Grunhaus and Sackeim trials, seizure threshold was determined either using the method of limits or by empirical titration; the stimulus was delivered at 2.5 times threshold in Grunhaus and at 1.5 times threshold in Sackeim.

**Efficacy: relapses** Two trials provided usable data for analysis on relapses within 6 months. All trials were analysed separately owing to the different classes of drugs compared. Withdrawals were assigned to the worst outcome (relapse).

The results of the Sackeim trial showed that there was a non-statistically significant trend for those treated with nortriptyline to have a reduced risk of relapse compared with those treated with placebo (RR = 0.73, 95% CI 0.53 to 1.01, \(p = 0.06, n = 56\)). Those treated with nortriptyline plus lithium had a statistically significant reduced risk of relapse at 6 months compared with those treated with placebo (RR = 0.58, 95% CI 0.39 to 0.86, \(p = 0.007, n = 57\)). However, the absolute rate of relapses across the sample was still high, with 61% of the 73 participants followed up relapsing.

In the Grunhaus 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, \(p = 0.3, n = 40\)).

**Adverse events** Grunhaus and colleagues found no significant differences between the fluoxetine–melatonin and fluoxetine–placebo group in cognitive functioning measured by the MMSE or sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI). Sackeim and colleagues found no statistically significant differences in the mean number of clinically significant side-effects per patient between the three treatment groups (\(F = 0.13, p = 0.88\)).

**Mania** The UK ECT Group found very little randomised evidence regarding the effectiveness of ECT in people with mania.

**ECT versus pharmacotherapy** The UK ECT Group found one trial that compared these treatment regimens. Forty-four patients were initially recruited and 34 completed the investigation, the remainder being lost to follow-up. No efficacy scores were available. No final cognitive testing results were reported.
ECT plus pharmacotherapy versus pharmacotherapy alone
The UK ECT Group\textsuperscript{51} found one trial\textsuperscript{169} that included 30 patients who completed the trial and had results for the mania rating scale. The decrease in these scores was greater in the combined therapy group by a factor of two. No cognitive testing was reported.

Schizophrenia
Two systematic reviews evaluated the effectiveness of ECT in schizophrenia.\textsuperscript{50,51} The results are reproduced here.

Real versus sham ECT
Efficacy immediately after a course of ECT
The UK ECT Group\textsuperscript{51} included six trials containing 140 patients that compared sham ECT with real ECT.\textsuperscript{170-174} All participants had been diagnosed as having schizophrenia, apart from one small trial\textsuperscript{174} where the duration of symptoms was less than 2 months and was characterised as schizophreniform. Two small trials\textsuperscript{171,175} predominantly included people with catatonia, but the UK ECT Group\textsuperscript{51} reports that they were too small to conduct reliable subgroup analyses.

The primary outcome measure used by the UK ECT Group\textsuperscript{51} was continuous data on change in symptoms from baseline to post-ECT treatment. Four of these trials\textsuperscript{170,172-174} provided usable continuous data for analysis. They found significant heterogeneity within the trials and two trials were not included in the analysis. The standardised effect size of real compared with sham ECT was –0.22 (95\% CI –1.7 to 1.27) in favour of real ECT. The result is not statistically significant and represents a mean change in the Brief Psychiatric Rating Scale (BPRS) score of 0.10 (95\% CI 0.56 to 0.75) in favour of real ECT.

The UK ECT Group also identified two trials\textsuperscript{176,177} that compared ECT with placebo, or inpatient care alone. A meta-analysis could not be conducted since one trial did not report efficacy ratings. In the other trial, the ECT group had a 3.5-point advantage on the Menninger Health–Sickness Scale at the end of treatment.

The Cochrane Schizophrenia Group ECT review\textsuperscript{50} reported one trial\textsuperscript{174} that showed that the benefit of ECT on global improvement in the short to medium term was equivocal (RR = 0.71, 95\% CI 0.3 to 1.8, n = 30).

Other outcomes
The Cochrane Schizophrenia Group ECT review\textsuperscript{50} 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 are summarised below.

Relapses and discharge from hospital
The Cochrane Schizophrenia Group ECT review\textsuperscript{50} found that results from two trials\textsuperscript{170,178} suggested that ECT resulted in fewer relapses in the short term than sham ECT (RR\textsubscript{fixed} = 0.26, 95\% CI 0.03 to 2.2, n = 47) and a greater likelihood of being discharged from hospital (RR\textsubscript{fixed} = 0.59, 95\% CI 0.34 to 1.01, n = 98),\textsuperscript{170} although the data on which these outcomes are based are 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 6-month and 2-year follow-up.
period, although the trend favoured ECT. Again, however, the data on which these results are based were sparse.

Leaving the study early The UK ECT Group\textsuperscript{51} included one trial\textsuperscript{170} that reported discontinuations and these were similar in each group. The Cochrane Schizophrenia Group ECT review\textsuperscript{50} found homogeneous data from the 14 trials comparing ECT with sham ECT which did not suggest that people treated with ECT dropped out of treatment earlier than those treated with sham ECT (RR fixed = 0.71, 95% CI 0.33 to 1.52, n = 495).

Efficacy at 6 months The UK ECT Group\textsuperscript{51} identified two trials\textsuperscript{170,174} that reported efficacy scores at 6 months post-treatment, but these did not provide sufficient data for analysis. One trial\textsuperscript{170} indicated a 5-point greater efficacy score in the ECT group than in the sham group, but the other\textsuperscript{174} showed a 1.5 greater improvement in the sham group over time. The Cochrane Schizophrenia Group ECT review\textsuperscript{50} reported that no data were available for the effects of ECT versus sham ECT in the medium to long term.

Adverse events: cognitive functioning The UK ECT Group\textsuperscript{51} did not find any data in the included trials on cognitive functioning. The Cochrane Schizophrenia Group ECT review\textsuperscript{50} found very limited data from one trial\textsuperscript{184} on cognitive functioning. This indicated that visual memory declined after ECT compared with sham ECT (one RCT, WMD = –14.0, 95% CI –23 to –5, n = 24); the results of verbal memory tests were equivocal.

Adverse effects: mortality There were no deaths in the trials included by the UK ECT Group.\textsuperscript{51} The Cochrane Schizophrenia Group ECT review\textsuperscript{50} identified one trial\textsuperscript{176} that reported on mortality over a 3-year follow-up. No deaths were discovered (n = 98).

ECT versus antipsychotic drugs The UK ECT Group\textsuperscript{51} separated the analysis into trials comparing ECT combined with pharmacotherapy versus pharmacotherapy and trials comparing ECT alone with pharmacotherapy. The Cochrane Schizophrenia Group ECT review\textsuperscript{50} included at least one trial in their analysis of ECT versus pharmacotherapy\textsuperscript{183} that had been classed by the UK ECT Group as a combination of ECT and antipsychotics versus ECT. It appears that the Cochrane Schizophrenia Group ECT review\textsuperscript{50} analysed all trials that compared ECT with antipsychotics together and completed a separate subanalysis of ECT in combination with antipsychotic drugs. For this analysis they included five\textsuperscript{175,174,178,182,184} of the eight trials that contributed data on clinical global improvement in the comparison of ECT and sham/placebo ECT plus antipsychotics against sham ECT plus antipsychotics. The UK ECT Group\textsuperscript{51} included three of these trials\textsuperscript{174,186,187} in their analysis of ECT alone versus pharmacotherapy. Only one\textsuperscript{173} of these trials had been included in the ECT versus sham ECT analysis in the UK ECT Group review.\textsuperscript{51}

ECT alone versus pharmacotherapy The UK ECT Group\textsuperscript{51} included four trials\textsuperscript{171,176,186,187} containing 163 patients. One trial\textsuperscript{187} used sham ECT and drug placebos to blind study participants to treatment allocation. Treatment lasted for between 3 weeks\textsuperscript{171} and 1 year.\textsuperscript{176} Two trials\textsuperscript{176,187} provided sufficient data for analysis. The standardised effect size of 0.26 shows a non-significant difference between the two treatment groups (95% CI –0.92 to 1.42). This translates as a mean change in efficacy score of 1.8 (95% CI –6.35 to 9.84) in favour of pharmacotherapy.

ECT in combination with antipsychotics versus pharmacotherapy, plus or minus sham ECT/placebo The UK ECT Group\textsuperscript{51} identified three trials containing 147 patients.\textsuperscript{171,185,188} One trial\textsuperscript{182} included participants as young as 13 years, but results are not reported separately for this subgroup. Comparable doses of neuroleptic medication were administered in both arms of these studies, except for the Ungvari trial\textsuperscript{185} where the pharmacotherapy group received a higher dose of haloperidol than the ECT group. There was a positive trend associated with treatment with ECT and pharmacotherapy compared with ECT alone. The standardised effect size is 0.43 (95% CI –0.62 to 1.48) and the mean change in efficacy score 2.04 (95% CI –2.92 to 6.96) in favour of combined therapy.

The Cochrane Schizophrenia Group ECT review\textsuperscript{50} included eight trials\textsuperscript{105,176,177,183,185,186,188,189} that compared ECT directly with antipsychotic drugs. They report that four of these\textsuperscript{105,186,188,189} used chlorpromazine as the comparator drug, Small\textsuperscript{183} compared ECT with thiothixine, May\textsuperscript{176} with trifluoperazine and Naidoo\textsuperscript{177} used reserpine, a drug that pre-dated chlorpromazine. Ungvari and Petho\textsuperscript{185} compared ECT plus low-dose haloperidol with very high-dose haloperidol, while
Janakiramiah compared ECT in two groups of people treated with low- and high-dose chlorpromazine with two other groups given the two strengths of the drug without ECT.

The Cochrane Schizophrenia Group ECT review reported 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 and Fleminger and Brandon and colleagues 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 reported that when ECT is directly compared with antipsychotic drug treatment, the pooled dichotomous results strongly favour the medication group (three RCTs, RRfixed = 2.18, 95% CI 1.3 to 3.6, n = 175). Homogeneous data also favoured antipsychotic drugs over ECT with regard to numbers discharged after treatment (two RCTs, RRfixed = 1.98, 95% CI 0.97 to 4, n = 135). The Cochrane Schizophrenia Group ECT review identified very limited data indicating that people treated with ECT are less likely to relapse than those treated with antipsychotics (one RCT, RRfixed = 0.33, 95% CI 0.1 to 0.9, n = 32). Continuous measures of global improvement from one trial favoured ECT in the short term, although 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 analysed five of the eight trials that contributed data on clinical global improvement in the comparison of ECT and sham placebo 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 (RRrandom = 0.74, 95% CI 0.4 to 1.3, n = 165).

**Efficacy at 6 months** The UK ECT Group found no usable data relating to the efficacy of ECT compared with antipsychotics at 6 months’ follow-up. The Cochrane Schizophrenia Group ECT review found only one study reporting on the long-term outcome of ECT compared with antipsychotic, and the results were equivocal.

**Discontinuations/leaving the study early** The UK ECT Group did not find any usable data relating to discontinuations in studies comparing combined ECT and pharmacotherapy with ECT alone. No discontinuations occurred in studies comparing ECT alone with pharmacotherapy. The Cochrane Schizophrenia Group ECT review found no differences in numbers leaving the study early in the trials that compared ECT to treatment with antipsychotics (seven RCTs, RRfixed = 0.99, 95% CI 0.8 to 1.3, n = 419). They report that similar numbers remained in the trial by May 5 years after treatment with ECT or antipsychotics, although by this time 73% of the people in both arms had been lost to follow-up.

**Adverse effects: mortality** The UK ECT Group found no deaths reported in any of the trials comparing ECT with pharmacotherapy, either alone or in combination with antipsychotic drugs. The Cochrane Schizophrenia Group ECT review found that one patient who had not received ECT died within the 3-year follow-up by May (one RCT, RR = 0.63, 95% CI 0.03 to 15, n = 149).

**Adverse effects: cognitive functioning** The UK ECT Group identified one randomised trial that compared cognitive functioning of patients who had received ECT with those who had received chlorpromazine at the end of a course of ECT. Only data on retrograde memory were identified and the trial reported no difference on several measures of retrograde memory between patients treated with ECT and those treated with chlorpromazine.

**ECT versus psychotherapy** The Cochrane Schizophrenia Group ECT review reported limited data from one study comparing ECT alone with individual psychoanalytic psychotherapy alone, showing a consistent, although non-significant, trend favouring ECT (both short term and 2 years later) on several outcomes. When antipsychotics were added to psychoanalytic psychotherapy, however, a significant advantage of the drug group over ECT was seen in the short term (WMD = –5.0, 95% CI –0.54 to –9.46, n = 90), with a continuing trend 2 years later.

**Unilateral versus bilateral ECT** The UK ECT Group included two trials containing 147 patients. Adolescents were included in one trial and unmodified ECT was used in the other. Neuroleptic medication was not coadministered in either of these studies. The Cochrane Schizophrenia Group ECT review identified an additional trial that involved trial arms that compared unilateral with bilateral ECT.
for people who had also been given concurrent haloperidol.

**Efficacy**  The UK ECT Group\(^5\) found that the standardised effect size between the two electrode placements was 0.03 (95% CI –0.91 to 1.03), with a mean change in efficacy score of 0.32 (95% CI –10.56 to 11.99), indicating no difference between the two electrode placements. The Cochrane Schizophrenia Group ECT review\(^5\) found neither unilateral nor bilateral ECT to be superior in terms of global improvement (two RCTs,\(^184,191\) RR = 0.79, not improved at end of course of ECT, 95% CI 0.5 to 1.4, \(n = 78\)). They report that none of the three trials reported long-term efficacy data.

**Discontinuations/leaving the study early**  None of the three studies reported data on discontinuations.

**Adverse events: mortality**  No deaths were reported in the trials.

**Adverse events: cognitive functioning**  The UK ECT Group\(^5\) reports that one randomised trial\(^192\) measured cognitive functioning at the end of a course of ECT, comparing patients treated with unilateral ECT with those treated with bilateral ECT. The trial reported no difference on learning tasks between patients treated with unilateral ECT and those treated with bilateral ECT. Four patients treated with bilateral ECT complained of subjective forgetfulness compared with one of those treated with unilateral ECT.

**Unilateral placement**  The Cochrane Schizophrenia Group ECT review\(^5\) identified one trial\(^191\) that compared the effect of dominant and non-dominant electrode placements on schizophrenic patients. BPRS scores were available for pretreatment 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.

**Dose of ECT**  Both reviews\(^5,5\) identified one trial\(^195\) 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 the threshold (4T). End-point average scores for global impression (GAF), mental state (BPRS) and cognitive function (MMSE) were not extractable.

**Efficacy**  The Cochrane Schizophrenia Group ECT review\(^5\) 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, 95% CI 2.4 to 10). Similarly, those given 4T required fewer treatments than those treated at threshold doses (WMD = 9.4, 95% 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, 95% 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, 95% CI 2.1 to 16.8).

**Leaving the study early**  The Cochrane Schizophrenia Group ECT review\(^5\) reported that only five out of 67 people left this study before completion, with no clear trend favouring any one group.

**Adverse events: cognitive functioning**  The UK ECT Group\(^5\) reported that there were no significant differences between the groups on scores on the MMSE at the end of a course of ECT.

**Frequency of administration**  Both reviews\(^5,5\) identified only one study\(^194\) comparing unilateral ECT given three versus five times a week, which included only ten participants. This trial had usable data for cognitive functioning only. Average end-point scores on the MMSE indicated no significant advantage for the less frequent treatments, and no one developed clinical evidence of cognitive impairment.

**Number of ECT treatments**  The Cochrane Schizophrenia Group ECT review\(^5\) reported limited data from one trial\(^195\) that showed a significant advantage for 20 treatments over 12 treatments in numbers globally improved at the end of the ECT course (RR\(_{\text{fixed}}\) = 2.53, 95% CI 1.1 to 5.7, \(n = 43\)). No one was taking concurrent antipsychotics. This trial was excluded by the UK ECT Group.\(^5\)

**Continuation ECT**  Both reviews\(^5,5\) identified one trial\(^196\) 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\textsuperscript{50} reported that when continuation ECT was compared with antipsychotics at the end of the 6-month trial, results for overall functioning as measured on the GAF scale were equivocal (one RCT, WMD = –1.24, 95% CI –6.4 to 3.9, \(n = 30\)). However, when continuation ECT was added to antipsychotic drugs, the combination was clearly superior to the use of antipsychotics alone (WMD = 19.1, 95% CI 9.7 to 28.5, \(n = 30\)). Similarly, at 6 months, continuation ECT was no better than treatment with antipsychotic drugs in reducing BPRS scores, although the combination of continuation ECT and antipsychotics was superior to continuation ECT alone (WMD = 18.6, 95% CI 8.6 to 27.6, \(n = 30\)) or antipsychotics alone (WMD = –19.8, 95% CI –10.3 to 29.2, \(n = 30\)).

Relapses  The Cochrane Schizophrenia Group ECT review\textsuperscript{50} reported that equal numbers (14 and 15) of people on continuation ECT alone or antipsychotics alone relapsed over the 6-month trial period. The addition of continuation ECT to antipsychotic drugs, however, was clearly beneficial in reducing relapses compared with antipsychotics alone or continuation ECT alone (RR\text{fixed} = 0.43, 95% CI 0.23 to 0.81, \(n = 30\), NNT = 2, 95% CI 1.5 to 2.5).

Leaving the study early  The Cochrane Schizophrenia Group ECT review\textsuperscript{50} reported that few people (six out of 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\textsuperscript{50} reported that no significant differences were seen in cognitive impairment scores between those treated for 6 months with continuation ECT or antipsychotics. Continuation ECT added to antipsychotics resulted in non-significant trends favouring antipsychotic drugs used alone and the combination versus continuation ECT used alone.

Specific outcomes not covered by the randomised evidence  The randomised evidence reviewed by the UK ECT Group,\textsuperscript{51} the Cochrane Schizophrenia Group ECT review\textsuperscript{50} 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) consumers’ views and experiences of ECT and whether these experiences influenced the outcomes of ECT. Therefore, sources that reviewed the non-randomised evidence for these outcomes were identified.

Severe adverse events  The UK ECT Group\textsuperscript{51} included cohort studies and case–control studies that compared people with depression, schizophrenia and mania who had received ECT at some point during their care with those who had not. The reviewers examined evidence on five key outcomes: all-cause mortality, suicide, cerebral haemorrhage, functional impairment and structural brain damage. Their findings are set out below.

The search strategy used by the UK ECT Group\textsuperscript{51} to locate non-randomised studies could not be comprehensive before 1966 owing to limitations in time and resources. For earlier studies, they used the review of ECT and mortality (particularly suicide risk) by Prudic and Sackeim.\textsuperscript{197} These early studies provided the main evidence that ECT reduces mortality. Prudic and Sackeim described six studies comparing the suicide rates in the pre-ECT and ECT eras. The results were variable, with four studies reporting some evidence of reduced suicide and mortality rates following the introduction of ECT. They also identified six studies comparing suicide rates in the era before the introduction of psychotropic drugs (ECT alone) with those after the introduction of drugs. Four of these studies claimed that the rate increased following the introduction of drugs. As identified by Prudic and Sackeim,\textsuperscript{197} all these historical comparison studies are methodologically unreliable because of the lack of control for other confounders between the cohorts. Their results are reproduced below.

All-cause mortality  The UK ECT Group\textsuperscript{51} reports that all the studies described in the review of severe adverse events suffer from the major methodological shortcoming of patient selection. For example, ECT may not have been used for medically ill patients, which may explain any observed lower mortality. Conversely, patients selected for ECT may have been very severely ill or suicidal, or both, and therefore any failure to find a difference may be because ECT has reduced suicide in a high-risk group.

Five non-randomised cohort studies compared mortality rates in patients contemporaneously treated with ECT with those not treated with ECT.
Babigian and Guttmacher\textsuperscript{198} compared mortality rates in depressed patients receiving treatment with ECT during their first hospitalisation with patients who did not receive ECT. All-cause mortality at up to the 20-year follow-up was significantly lower in the ECT-treated group; this difference remained following age standardisation.

Avery and Winokur\textsuperscript{199} reported a 3-year follow-up of 519 consecutively admitted patients with depression. In the ECT-treated group, the mortality rates were 0.7\% at 1 year and 2.2\% at 3 years. In the groups with adequate treatment with antidepressant drugs, the corresponding figures were 1.4\% and 2.8\%. In patients who were treated with neither drugs nor ECT, the mortality rates were 10\% and 11.4\%.

Tsaung and colleagues\textsuperscript{200} followed up 74 (out of 85 consecutive admissions) patients with a diagnosis of schizoaffective disorder. Seventeen (34\%) of the patients treated with ECT were deceased at follow-up compared with two (8\%) of the patients who did not receive ECT.

Black and colleagues\textsuperscript{201} reported a follow-up of 1076 patients with primary affective disorders, carefully controlling for medical co-morbidity and length of follow-up, and attempting to control for other important confounders. They found no differences in total mortality between patients treated with ECT, antidepressants or no adequate treatment, but the numbers were very small and the study had very limited power to detect a moderate, but important effect.

The UK ECT group\textsuperscript{51} found two case–control studies\textsuperscript{202,203} comparing the rates of use of ECT in patients who committed suicide with control patients who did not commit suicide.

Sharma\textsuperscript{202} compared the use of ECT in 45 inpatients who committed suicide with a matched group of inpatients who did not commit suicide. Eight patients in the ECT group killed themselves compared with four in the control group.

Brådvik and Berglund\textsuperscript{203} compared the last treatment received by 89 patients with severe depression admitted to Lund Hospital in Sweden between 1956 and 1969 who committed suicide by 1984 with a matched control group who did not commit suicide. There was no difference in the rates of ECT between the two groups.

No studies were identified that examined cerebral haemorrhage or functional impairment.

**Brain scanning and ECT**

**Computerised tomography** Nasrallah and colleagues\textsuperscript{204} measured ventricular:brain ratios (VBRs) with X-ray computed tomography (CT) for young patients with mania compared with age-matched controls. A high VBR reflects loss of brain mass. Patients had a higher VBR than controls and the effect was not associated with a history of exposure to ECT.

Kolbeinsson and colleagues\textsuperscript{205} compared VBR and cortical atrophy (another measure that reflects loss of brain mass) measured with X-ray CT for age-matched unipolar and bipolar patients with or without a history of exposure to ECT. Both patient groups showed increased VBR and cortical atrophy compared with controls, with a trend
towards a larger effect in the ECT group. However, there was no confirmatory correlation between lifetime ECT exposure and VBR. Instead, the measures were strongly correlated with age within all groups. This is a common finding in groups with an average age over 40 years.

Calloway and colleagues,206 in a technically similar X-ray CT study, compared much older patients with and without previous ECT using judgements or regional atrophy. They also found more evidence of atrophy in the ECT group, specifically in the frontal areas, but again there was no correlation with the total number of ECT treatments.

Magnetic resonance imaging Magnetic resonance imaging (MRI) is a more sensitive neuroimaging technique than CT. Hickie and colleagues207 investigated a cohort of elderly patients. They measured the extent of a pathology not specific for depression but associated with it: the density of subcortical hyperintensities. They showed a strong association between age and the severity of these lesions in white matter, but no association with previous ECT emerged as being significant from their analysis.

Experimental investigation of acute effects of ECT on brain images Several studies used within-subject measures before and after ECT. Mander and colleagues208 measured the T1 relaxation time in patients receiving ECT with MRI. The T1 reflects tissue fluidity or the extent to which the protons in water are free to distribute in a magnetic field. It was anticipated that it might measure changes relevant to the permeability of the blood–brain barrier (BBB). Patients were studied before and at varying times after ECT. There was a small global increase in T1 with a peak at around 6 hours, after which measures returned to normal. Controls receiving anaesthesia for other reasons showed falls rather than increases in T1. The results were interpreted in relation to other work suggesting that transient reductions in the BBB are probably secondary to the increased systemic blood pressure observed during seizures.

Ende and colleagues209 studied patients during ECT and measured N-acetylaspartate (NAA) in the hippocampus. Brain injury would predict reduced NAA levels and evidence of effects on episodic memory would localise the most likely target as the hippocampus. This investigation therefore tested a specific hypothesis about the integrity of cellular elements in this key structure. No change was observed in NAA during ECT, although the sensitivity of the method was confirmed by the detection of an unexplained rise in choline-containing compounds.

**Patient acceptability and choice**

The reviewers 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.

The results of this review are summarised below.

**Persistent memory loss**

Twenty studies made reference to long-term memory loss in the abstract, but six did not report memory loss at 6 months and seven did not provide raw numbers of the percentage or number of people experiencing the side-effect. Only seven papers210–216 provided usable information on long-term memory loss.

There was no difference in the rates of people reporting persistent memory loss at 6 months between clinical studies and those carried out in collaboration with patients. As a lower limit, at least 28.1% of patients experience persistent memory loss as a result of ECT. It is difficult to differentiate memory loss caused by ECT, memory loss due to depression and the maintenance of depression as a result of memory loss.

The testimonies revealed that the types of memory loss that are important to people who receive ECT, such as autobiographical memories, are not those captured in neuropsychological tests used in RCTs. The reviewers suggested that this may explain the different conclusions between patient reports, where memory loss is a key issue, and RCTs, where only a significant minority of people are reported as having persistent memory loss. The testimonies also revealed complex and important emotional reactions to memory loss following ECT.

**Information and consent**

Sixteen papers included information on information or consent, but only 12211,213,215,216–224 provided usable data and only one study asked whether people had been told about the risks of ECT. Four studies219,220,225,226 included information on objective knowledge of ECT.

There were no important differences between clinical studies and those carried out in collaboration with patients in the rates of people reporting that they had received adequate information before receiving ECT. At least 50% of users felt that they had been given inadequate
information before receiving ECT. Between 7 and 16% were judged to have full knowledge that ECT involved an anaesthetic, the passing of an electric current and the induction of a convulsion. The testimonies revealed that side-effects such as memory loss were the main area where patients felt that they had not received sufficient information.

**Felt compulsion**

Seven studies asked about felt compulsion. There were no important differences between clinical studies and those carried out in collaboration with patients in the rates of people reporting that they had felt they had no choice but to have ECT. Between one-quarter and one-third of people who sign a consent form for ECT do so under pressure or in the belief that they cannot refuse.

**Perceived benefit**

Sixteen research studies asked about the perceived benefit of ECT. These included two main types of questions: perceived helpfulness and whether the user would agree to ECT again.

Fewer respondents from patient-led surveys reported feeling that ECT had helped or that they would have it again compared with the respondents in clinically-led research.

Methodological variables such as the interval since ECT, the setting in which the views were elicited, and the number and complexity of questions used to measure perceived benefit had all important influences on perceived benefit of ECT within both clinical and patient-led surveys. The reviewers concluded that studies that interview patients immediately after ECT are more likely to overestimate the degree of perceived benefit of ECT, especially if the interview is conducted within a hospital setting by a clinician using brief interviews.

The review also explored the relationship between legal compulsion to have ECT and satisfaction with ECT. One clinical study reported no difference in satisfaction between patients who were legally compelled to have ECT and those who consented. However, this study was based on a small sample of people whose legal status with respect to ECT was very different from the national average. Patient-led studies included more representative samples of patients who were legally compelled to have ECT. One of these studies reported a negative association between legal compulsion and satisfaction, and the other did not state whether there was an association between legal compulsion and satisfaction. None of the studies analysed the relationship between legal compulsion and the perceived benefit of ECT.

The testimonies revealed that the perceived benefit of ECT from the patient’s perspective was much more complex and divergent from clinical conceptualisations of benefit that underlie the construction of symptom scales used in RCTs. Many of the issues raised by patients, such as lying about the success of treatment in order to avoid further ECT and wishing to take legal action against clinicians, are not addressed in clinical research. Patients’ views were heterogeneous, with some reporting that it was a life-saving treatment and others feeling violated and not helped by the treatment. Furthermore, patients made trade-offs between the side-effects and benefits of ECT, and for some, the way in which ECT was given was a more important issue than whether or not the treatment had helped. Thus, the review concluded that there is no single, unidimensional patient voice regarding the perceived benefit of ECT, but those opposed to ECT cannot be seen as a small vocal minority.

**Interventions to improve patient knowledge about ECT**

In addition, two RCTs that assessed the impact of a video on knowledge about ECT were identified in the present review. One of these trials was included in the SURE review. A pooled analysis of knowledge scores in the two trials revealed significant statistical heterogeneity and the results are therefore reported separately.

In the trial by Westreich and colleagues, participants were psychiatric inpatients who had received 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). Postconsent knowledge was assessed using an instrument with no assessment of its psychometric properties. There was no statistically significant difference between the two groups in the mean number of items answered correctly (WMD = -0.81, 95% CI -1.86 to 0.24, p = 0.13, n = 18).

In the trial by Battersby and colleagues, 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 watch the video \((n = 40)\). 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 \((WMD = 1.28, 95\% \text{ CI} -2.3 \text{ to } 2.79, p = 0.1, n = 69)\).

**Efficacy of ECT in specific subgroups**

The UK ECT Group\(^{51}\) reported that data were too limited to undertake reliable subgroup analyses. The Cochrane Schizophrenia Group ECT review\(^{50}\) reports the following subgroup analyses in their review of ECT in schizophrenia.

**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 \((RR_{random} = 0.72, 95\% \text{ CI} 0.4 \text{ to } 1.3, n = 165)\). A significant advantage for ECT for this outcome was more evident when the three trials that did not use operational definitions of schizophrenia\(^{176,177,179}\) were analysed separately \((RR_{fixed} = 0.74, 95\% \text{ CI} 0.6 \text{ to } 0.98, n = 205)\). 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.

**Duration of illness**

The Cochrane Schizophrenia Group ECT review\(^{50}\) acknowledges that the power of the review to detect a differential response to ECT for those with a short duration of illness \((<2 \text{ years})\) as opposed to those with chronic schizophrenia was very limited. Six trials restricted inclusion to participants with durations of illness less than 2 years.\(^{170,172,174,181,191,194}\) Two of these\(^{170,172}\) 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 and colleagues\(^{174}\) were acutely ill, with onset of symptoms less than 2 months before the start of treatment. This trial found that 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 and co-authors\(^{179}\) and Miller\(^{175}\) 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 and colleagues\(^{193,196}\) included participants who had been ill for 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.

**Catatonia**

The Cochrane Schizophrenia Group ECT review\(^{50}\) found that ECT did not have significant beneficial effects in people with chronic catatonic schizophrenia, who comprised the participants in the trial by Miller\(^{175}\) although this finding could equally be attributed to chronicity rather than the subtype of schizophrenia. However, they found that ECT did result in significant clinical improvement by the end of the course for those people diagnosed as having paranoid schizophrenia in the study by Taylor and Fleminger\(^{173}\) \((RR_{fixed} = 0.74, 95\% \text{ CI} 0.6 \text{ to } 0.91, n = 20)\). 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\(^{170,173,176,178,189,193,196}\) reported a beneficial effect on positive symptoms. These trials included participants with varying durations of illness. The trial by Chanpattana and colleagues\(^{196}\) on people with treatment-resistant schizophrenia provided data on symptom clusters on BPRS, in those responding to ECT before randomisation to continuation treatments. These data indicate significant reductions in positive and negative symptoms, as well as depressive and aggressive symptoms.

The present analysis also identified one review\(^{78}\) of 270 treatment episodes in 178 cases treated for catatonia. Of these cases, 55 episodes involved the use of ECT and five 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 out of 104 \((70\%)\) episodes involving treatment with benzodiazepines \((70\%)\) had a complete resolution,
57 out of 72 (79%) treatment episodes demonstrated a complete resolution in response to lorazepam and three out of 40 (7.5%) had a complete response to antipsychotics.

Since publication of this review in 1995, two prospective case series studies have reported on eight 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, while the other used bilateral ECT. Both studies used the Bush–Francis Catatonia Rating Scale (BFCRS) to evaluate outcomes. In Bush, four out of five cases offered ECT showed a remission of symptoms, while in Malur two out of three cases showed a full remission of symptoms. No data on adverse effects were recorded.

### Children and adolescents
The authors identified two systematic reviews of non-randomised evidence and one case–control study 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 = 55), manic depression (n = 28), schizophrenia (n = 41), schizoaffective disorder (n = 6), catatonia (n = 29), neuroleptic malignant syndrome (n = 4) and other disorders (n = 29).

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

### Effectiveness

#### TABLE 3 Summary of efficacy of ECT in children and adolescents

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Responders immediately post-ECT</th>
<th>Responders 6 months post-ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>N</td>
</tr>
<tr>
<td>Depression total</td>
<td>58</td>
<td>87</td>
</tr>
<tr>
<td>Major depression</td>
<td>33</td>
<td>52</td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Manic episode</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>54</td>
<td>70</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>17</td>
<td>41</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Catatonia</td>
<td>21</td>
<td>29</td>
</tr>
</tbody>
</table>

Information on electrode placement in the systematic review was provided for 61 patients: 23 (38%) had unilateral ECT, 29 (48%) had bilateral ECT and nine (15%) had both. Information on the number of ECTs administered was available for 95 patients and the mean was 9.6 with a range of 1–23. Thirty-eight patients had received electroencephalographic 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 (Table 3), although no information is given regarding whether this analysis is on an ITT basis. It is therefore difficult to draw reliable conclusions from the review, although the results suggest that ECT is more effective in adolescents with depression, mania and catatonia than in schizophrenia.

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

#### Adverse events: mortality
The 1997 review by Rey and Walter 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 study had committed suicide since receiving ECT.

#### Adverse events: post-ECT seizures
The review reported post-ECT seizures in 15 cases.
Adverse effects: cognitive functioning
The review 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 1940s and 1950s, when the techniques used to administer ECT are not generalisable to current practice and results were not reported systematically. Cohen and colleagues found no significant differences on the MMSE, the WMS and the California Verbal Learning Test at a mean 5.2 years’ follow-up.

Adverse effects: subjective side-effects
The review found that, overall, the most common complaint was headaches, reported in 16 out of 396 cases. Subjective memory loss was described by nine patients, 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 seven out of nine (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%), hypomanic symptoms (2%), subjective memory loss (2%) and vomiting (1%). Cohen and colleagues found that six patients who received ECT reported having subjective memory impairment.

Older people
There was no randomised evidence of the efficacy of ECT in people older than 65 years. In searching for non-randomised evidence the reviewers limited the inclusion criteria to studies whose populations were all aged 65 or over. One prospective and three retrospective case-control studies were identified 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 with pharmacotherapy. Rubin and colleagues conducted an analysis of covariance using 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 covariates, and found that the presence or absence of ECT had a statistically significant effect on GDS scores ($F = 3.56$, df 6,65, $p = 0.004$, $r^2 = 0.25$) and that the other covariates, with the exception of baseline GDS scores, did not. A similar result was obtained for the BDI scores at discharge. Admission 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 out of 46 patients (75%) treated with ECT showed major improvement over baseline level as rated by a physician compared with 23 out of 55 (42%) who did not receive ECT.

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

Manly and colleagues also compared physician-rated outcome, although it is not clear when this outcome was measured. In the ECT group, 30 out of 39 (77%) had a good outcome compared with 13 out of 39 (33%) in the pharmacotherapy group ($p = 0.001$). In the ECT group, nine out of 39 (23%) had a moderate outcome compared with 22 out of 39 (56%) in the pharmacotherapy group ($p = 0.003$). None of the ECT group had a poor outcome, while four out of 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 provided data on relapses and rehospitalisation. At follow-up, 29 out of 37 (78%) in the ECT group had a recurrence, compared with eight out of 28 (29%) in the non-ECT group, and 17 out of 37 (40%) in the ECT group were rehospitalised, compared with four out of 28
(14%) in the non-ECT group. Following treatment, 19 out of 37 (51%) in the ECT group were in a
nursing home compared with 13 out of 28 (46%)
in the non-ECT group. The statistical significance
of these differences was not reported.

**Adverse effects: mortality and survival**

Two studies,76,77 provided data on mortality and
survival and reported conflicting results. Kroessler
and Fogel76 followed up 65 participants for 3
years, of whom 37 had received ECT. They found
that 27 out of 37 (73%) in the ECT group were alive at 1 year, compared with 27 out of 28 (96%)
in the non-ECT group, and eight out of 37 (22%)
in the ECT group were alive at the end-point of
the study, compared with 17 out of 28 (61%) for
the non-ECT group. In terms of mortality, ten out
of 37 (27%) in the ECT group were dead at 1 year
compared with one out of 28 (4%) in the non-ECT
group. At 3 years' follow-up, 18 out of 37 (49%)
in the ECT group were dead at 3 years, compared
with nine out of 27 (33%) in the non-ECT group.
The statistical significance of these differences was
not reported. In contrast, Philibert and
colleagues77 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 out of 84 (53%) in
the non-ECT group and 68 out of 108 (63%) in
the ECT group alive at follow-up (p < 0.05).

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

**Adverse effects: other**

Two studies74,75 reported data on a range of
adverse effects following ECT. Manly and
colleagues75 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 cardiovascular
disease (CVD), confusion/neurological symptoms,
gastrointestinal, pulmonary and metabolic
complications, and falls. The pharmacotherapy
group experienced statistically significantly more
CVD (p = 0.013) and gastrointestinal
complications (p = 0.027), but there were no other
differences between the two groups.

Rubin and colleagues74 reported MMSE scores at
admission and discharge for groups who did or
did not receive ECT, but results were not on an
ITT basis. The results indicate similar scores
between the two groups.

**The use of ECT in pregnancy**

The authors identified one review81 of case reports
and case series on the use of ECT during
pregnancy and three further studies82–84 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
review81 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 use of ECT began in the second trimester and
in 31 (10.3%) in the third. In the remaining 219
(73%) of cases, the timing of ECT with respect to
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 one to 35. In 89 cases (30%)
there was some follow-up of offspring after birth,
with the length of follow-up ranging from 2 months
to 19 years.

**Efficacy**

The review81 provides no information on the
efficacy of ECT during pregnancy. In the three out
of four of the cases82,83 reported subsequently,
improvement in symptoms as judged by clinical
opinion was observed, which was still evident at
1-year follow-up. All of the women 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 review81 provides details of the prevalence of
complications when ECT was used during
pregnancy. Complications were noted in 28 cases
(9.3%) and these are summarised below.

**Foetal cardiac arrhythmia** Five cases reported
transient self-limiting disturbances in foetal
cardiac rhythm including irregular foetal heart
rate postictally (three cases), foetal bradycardia
during the tonic phase (one case) or postictally,
and reduced variability of foetal heart rate (one
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 four cases the source of bleeding was not identified. No adverse effects on the babies were reported in any of these cases. In the subsequent studies, one case of vaginal bleeding was reported, which led 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, in one case uterine contractions were reported following the second, third and sixth ECT treatments. Contractions following the second and sixth treatments were self-limiting, whereas those following the third treatment 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 after women had ECT were reported. In subsequent reports, premature labour was reported in a further two cases. In one case, premature labour occurred 6 days post-ECT, which subsided following hydration and ritodrine hydrochloride tocolytic therapy. In the other case, premature labour occurred immediately after the 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.

**Still birth and neonatal death** Three cases of stillbirth or neonatal death were reported.

**Respiratory distress** One case of the baby having difficulty breathing at birth was reported.

**Teratogenicity** Five cases of 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.

**Conclusions and discussion**

The conclusions and a discussion of the effectiveness review are considered in Chapter 7.
Chapter 4

Economic analysis

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 owing to the lack of published data on these specific depression subgroups. An attempt to estimate the cost per quality-adjusted life-year (QALY) has been made using published data on health state utilities.

Search strategy

Searches were undertaken to identify any economic studies relating to ECT, as reported in Chapter 3. No papers were identified in the economics search. The economics 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 were identified.

Overview of economic literature review and economic evidence

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

Economic modelling of ECT for depressive illness, schizophrenia, catatonia and mania

Modelling depressive illness

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 with another. However, to the authors’ knowledge no one has attempted to evaluate the cost-effectiveness of ECT.

ECT and antidepressant therapy are the primary treatments available to patients suffering from depressive illness. For mild to moderate depression drug therapy is usually the first line of treatment in 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 being resistant to drug therapy or those who have previously been treated successfully with ECT. However, some people support the view that ECT could be seen as a first line treatment for severe depression.

Methodology

As the literature search produced no economic analysis on ECT within depression, a mathematical model was constructed using data from the clinical effectiveness 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 in the model. As ECT is primarily provided on an inpatient basis for severely depressed patients the analysis concentrated on comparing inpatient ECT 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 that the patient receives. The model attempts to evaluate the cost-effectiveness of ECT 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 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, is no longer severely depressed and is receiving maintenance/continuation therapy; is 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 should be undertaken as a final option when all else has failed or should be provided higher up the treatment hierarchy, the model has been constructed to allow the evaluation of cost-effectiveness of ECT provided as a first, second or third line (defined as treatment-resistant) treatment.

ECT can be provided using either bilateral or unilateral placement of electrodes on the head. Bilateral ECT is generally more efficacious, but also results in more side-effects. A randomised trial by Sackeim and colleagues 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 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. The main comparative treatments to ECT analysed here are the three main classes of antidepressants used in the UK: TCAs, SSRIs and 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 to prevent relapse. Following successful ECT, maintenance ECT 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.

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 or 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 owing to an adverse event or 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, patients may be given continuation therapy to help to prevent relapse.

Parameter values used in the model are based on data from the clinical effectiveness element of the review for ECT for depressive illness, schizophrenia, catatonia and mania, together with literature searches on the 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 HRSD or other depression scoring system as used in other economic evaluations in depression.

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 or on combining drug therapies. The model makes no assumptions about previous depressive episodes and previous treatment received.
FIGURE 1 Structure of the decision model
**Assumptions and probabilities**

**Efficacy**

A meta-analysis of ECT efficacy undertaken by Janicak and colleagues\(^{237}\) in 1985\(^{237}\) showed that ECT was approximately 20% more effective than TCAs in the treatment of depressed patients. Although the analysis looked at studies from the 1960s, no comparative study has ever found a medication regimen to be more effective than ECT in the treatment of major depression.\(^{238}\) An RCT by Prudic and colleagues in 1990\(^{239}\) compared ECT in patients who were defined as treatment resistant and those that were not. They found that the success rate (>60% reduction in HRSD score) was 86.2% and 50% for non-treatment-resistant and treatment-resistant patients, respectively. An RCT by Folkerts and colleagues in 1997\(^{112}\) comparing ECT with an SSRI in treatment-resistant depression (defined as failing at least two previous antidepressant trials) showed that 71% of patients fulfilled the response criteria of a 50% decrease in the HRSD score compared with 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 responders 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 and colleagues\(^{240}\) found that the average successful treatment rate for TCA treatment was 58.2%. Applying a relative risk 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 and colleagues\(^{239}\) found for ECT.

The model default assumption for clinical success for the treatment of major depressed patients undertaking ECT was taken from the Prudic study, with first and second line therapy for ECT having an 86.2% success rate and the third line therapy having a 50% success rate.

The failure to complete treatment rates for ECT, derived from Burke and colleagues,\(^{241}\) 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% CI and the mean has been calculated as the midpoint.

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,\(^{242}\) Freeman and colleagues\(^{243}\) and Einarson and colleagues\(^{240}\) which, in turn, were all based on a meta-analysis of randomised trials comparing TCAs, SSRIs and SNRIs undertaken by Einarson and colleagues.\(^{18}\) It has been assumed that each treatment’s failure to complete treatment rate is independent of the line of therapy. The efficacy rates for the pharmacological treatments are from trials undertaken in an inpatient setting on patients who had an HRSD score of at least 15 or a Montgomery and Asberg Depression Rating Scale (MADRS) score of at least 18. The measure of success is the percentage of patients who achieved a 50% reduction in their score. The failure to complete treatment rates are a combination of lack of efficacy and patients experiencing adverse events. For patients who are deemed treatment resistant, lithium augmentation is seen as an effective pharmacological intervention. A meta-analysis by Bauer and Dompfer\(^{244}\) 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 were used as the successful treatment rates for the third line pharmacological therapy. The failure to complete treatment rates for this third line therapy are assumed to be the same as those for an 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 back-up. For a given population of depressed patients there would be a proportion who would respond well to treatment irrespective of whether that treatment was an SSRI or a TCA.

Consider the following simplified example in which it is assumed that there are 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 who 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 of whether it is given as a first or second line therapy, then with a population of 1000 people, 800 (80%) will be successfully treated after both treatments have been given \( (1000 \times 0.6) + (1000 - 1000 \times 0.6) \times 0.5 \).

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 and B. The area where the circles overlap represents the proportion of patients who would have responded to treatment A and also responded to treatment B. The area outside the circles represents the proportion of patients who would not respond to either treatment A or treatment B.

If it is assumed that the success rate for a second line treatment is the same as for a first line treatment then in the example shown in Figure 2 \( X \) must equal 30% to give the overall success rate of both treatments as 80%. However, if the proportion of patients who would respond to both treatment A and treatment 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 second line treatment B is half that if it were given as a first line treatment in this example.

Therefore, the assumption in the model that treatments given as a second line therapy have the same success rate as if they were given as a first line therapy has implications on the assumed proportion of patients who would have responded to either treatment.

Patients requiring third line therapies are deemed “treatment resistant” and thus lithium augmentation has been assumed as the preferred third line pharmacological therapy.

Table 4 summarises the model’s default values for clinical success for each treatment when used as a first, second or third line therapy, together with each treatment’s dropout rates. Table 5 summarises the model default values for failure to complete treatment rates.

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.

### Duration of treatment

Folkerts and colleagues\(^{12}\) found that ECT is considered to be quicker than pharmacological interventions in achieving a positive treatment response. Pharmacological treatments are usually continued for 6 weeks before the full effectiveness is achieved.\(^{24,5}\) Therefore, the model defaults for

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical success</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>TCA</td>
<td>58.2</td>
<td>43.0 to 73.5</td>
</tr>
<tr>
<td></td>
<td>SSRI</td>
<td>58.6</td>
<td>48.2 to 69.0</td>
</tr>
<tr>
<td></td>
<td>SNRI</td>
<td>62.3</td>
<td>49.7 to 74.9</td>
</tr>
<tr>
<td></td>
<td>ECT</td>
<td>82.6</td>
<td>52.1 to 98.8</td>
</tr>
<tr>
<td>Second line</td>
<td>TCA</td>
<td>58.2</td>
<td>43.0 to 73.5</td>
</tr>
<tr>
<td></td>
<td>SSRI</td>
<td>58.6</td>
<td>48.2 to 69.0</td>
</tr>
<tr>
<td></td>
<td>SNRI</td>
<td>62.3</td>
<td>49.7 to 74.9</td>
</tr>
<tr>
<td></td>
<td>ECT</td>
<td>82.6</td>
<td>52.1 to 98.8</td>
</tr>
<tr>
<td>Third line</td>
<td>Lithium augmentation</td>
<td>27.0</td>
<td>9.8 to 44.2</td>
</tr>
<tr>
<td></td>
<td>ECT</td>
<td>50.0</td>
<td>30.0 to 70.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>29.9</td>
<td>22.7 to 37.1</td>
</tr>
<tr>
<td>SSRI</td>
<td>25.8</td>
<td>20.3 to 31.3</td>
</tr>
<tr>
<td>SNRI</td>
<td>20.7</td>
<td>15.3 to 26.1</td>
</tr>
<tr>
<td>Lithium augmentation</td>
<td>25.8</td>
<td>20.3 to 31.3</td>
</tr>
<tr>
<td>ECT</td>
<td>26.5</td>
<td>18.0 to 35.0</td>
</tr>
</tbody>
</table>
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, dropouts averaging 1 week of treatment.

**Continuation/maintenance therapy**

As relapse rates following successful treatment in major depression are high, up to 80% within a year, the common practice is to provide maintenance or continuation therapy to help to prevent relapse. A study by Hirschfeld 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. An RCT by Sackeim and colleagues showed that a combination of lithium and a TCA had the greatest effect in reducing the number of relapses following successful ECT in medication-resistant patients.

Continuation/maintenance ECT has been shown to be an effective treatment in preventing relapse in patients successfully treated with ECT. Swoboda and colleagues found that, for patients with affective and schizoaffective disorders following successful ECT, 33% of patients who received continuation/maintenance ECT relapsed (defined as being readmitted to hospital), while 67% patients who had not received continuation/maintenance 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 is as effective for depressive patients as for patients with affective and schizoaffective disorders.

The Kaplan–Meier survival curves in these studies were 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.

**Caveat**

The survival rates from Sackeim and colleagues were to 24 weeks only. In the model the survival times were extended to 48 weeks. This assumption may not be valid. However, most relapses occur in the first 10 weeks of treatment.

**Costs and treatment dosage**

The cost for each pharmacological therapy was taken from the British National Formulary, 42nd edition, September 2001 (BNF42). The doses of SSRIs and TCAs were taken from Hirschfeld’s study of clinical trials of SSRIs and TCAs conducted on severely depressed patients receiving inpatient treatment. The dosage for venlafaxine (SNRI) was taken from Einarson and colleagues’ pharmacoeconomic analysis of venlafaxine.

The number of ECT treatments was based on the UK practice of two treatments per week and with average treatment duration of 4 weeks; an average of eight ECT treatments is given per therapy. The cost of ECT was taken from Montgomery and colleagues’ study, which had a 1994 cost of £2055 for six sessions. The estimated cost for ECT was increased from 1994 to 2001 values using the Hospital and Community Health Services inflation index from the Unit costs of health and social care. A pharmacoeconomic model by Hatziandreu 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 blood, thyroid and liver tests, and visits to the GP, psychiatrist and psychiatric nurse. This resource pattern was adopted for the maintenance resource use for this model, with the costs increased to 2001 values.

Tables 7 and 8 summarise the default dosage and cost estimates for each acute treatment and maintenance therapy.
The 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 £993253 per week for an average of 8 weeks. This cost averages out at £6951 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 attend 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 estimates made by the authors. The model uses them as a cost offset in that the cost of treating patients in trying to prevent them reaching state 3 is offset by the cost savings of not having to treat them in state 3. The higher the costs of treating patients in states 3 and 4 the higher the potential savings will be.

**Quality of life utility estimates**

In order to estimate QALYs, information is needed on the utility values that can be assigned to different health states. Utility values are defined on a 0–1 scale, where 1 represents perfect health while 0 represents death. The sources for this information were primarily two independent studies in which utility values for severe depression, moderate depression, mild depression and depression in remission were estimated. Other studies have derived utility values for depressed patients receiving different pharmacological treatments and their estimates were also included in the modelling exercise where appropriate.

The utility values from the study by Bennett and colleagues were elicited using the McSad health states classification system. Values were obtained from 105 patients who had experienced at least one episode of major, unipolar depression in the previous 2 years, but who were currently in remission. The health state descriptions referred to untreated depression. The mean utility values for each health state are shown in Table 9.

### TABLE 7 Cost of acute treatment for major depression

<table>
<thead>
<tr>
<th>Acute therapy</th>
<th>Drug</th>
<th>Dosage</th>
<th>Unit cost</th>
<th>Hospital costs per day</th>
<th>Cost per week a</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>Clomipramine (non-proprietary)</td>
<td>150 mg day⁻¹</td>
<td>£0.26</td>
<td>£171</td>
<td>£1198.82</td>
</tr>
<tr>
<td>SSRI</td>
<td>Paroxetine (Seroxat®)</td>
<td>30 mg day⁻¹</td>
<td>£1.04</td>
<td>£171</td>
<td>£1204.27</td>
</tr>
<tr>
<td>SNRI</td>
<td>Venlafaxine (Effexor®)</td>
<td>300 mg day⁻¹</td>
<td>£2.86</td>
<td>£171</td>
<td>£1216.99</td>
</tr>
<tr>
<td>ECT</td>
<td></td>
<td>Two sessions per week</td>
<td>£2475 per six treatments</td>
<td>£171</td>
<td>£2022.00</td>
</tr>
<tr>
<td>Lithium augmentation</td>
<td>Lithium + SSRI</td>
<td>800 mg Lithium + 30 mg paroxetine</td>
<td>£1.12</td>
<td>£171</td>
<td>£1204.84</td>
</tr>
</tbody>
</table>

a 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 two treatments per week (£825).

### TABLE 8 Cost of continuation/maintenance therapy for major depression

<table>
<thead>
<tr>
<th>Acute therapy</th>
<th>Drug</th>
<th>Dosage</th>
<th>Unit cost</th>
<th>Hospital costs per year b</th>
<th>Cost per week a</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>Nortriptyline</td>
<td>50 mg day⁻¹</td>
<td>£0.46</td>
<td>£260</td>
<td>£5.24</td>
</tr>
<tr>
<td>SSRI</td>
<td>Nefazodone (Dutonin®)</td>
<td>412 mg per day</td>
<td>£0.62</td>
<td>£260</td>
<td>£9.33</td>
</tr>
<tr>
<td>Lithium + TCA</td>
<td>Lithium + nortriptyline</td>
<td>600 mg lithium + 50 mg TCA day⁻¹</td>
<td>£0.54</td>
<td>£260</td>
<td>£8.78</td>
</tr>
<tr>
<td>ECT</td>
<td>Average two per month</td>
<td>£2475 per six treatments</td>
<td>Included</td>
<td></td>
<td>£190.4</td>
</tr>
</tbody>
</table>

a Based on tests and visits to the GP, psychiatrist and psychiatric nurse as stated in Hatziandreu. b Based on 24 treatments per year divided by 52 weeks.
The utility values from the Revicki and Wood study\textsuperscript{255} were elicited through the administration of standard gamble questions to 70 patients with major depressive disorder or dysthymia. Unlike the Bennett study\textsuperscript{256}, 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 shown in \textit{Table 10}.

The utility values from the Revicki study\textsuperscript{255} have very large standard deviations. This reduces the confidence that there is any significant difference both between the treatments within each level of severity of depression and between the different severity levels. With this in mind, it was decided to use the Bennett\textsuperscript{256} utility values as the model defaults. Results using the Revicki study\textsuperscript{255} utility values in the model are presented in the sensitivity analysis, later in this chapter.

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

The default model parameter values for QALY utility estimates were taken from Bennett and colleagues\textsuperscript{256}, and translate to the health states within the model. They are shown in \textit{Table 11}.

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 in the QALY assumptions is analysed in the sensitivity analysis section.

\textbf{Caveat}

QALY utilities appear low for severely depressed patients, but reflect what a debilitating illness depression can be. The assignment of QALYs to states 3 and 4 is not based on any research, but is the authors' decision.
Suicide risks

Evidence from the review of clinical effectiveness tends to support the view that there is no significant difference in suicide rate between patients treated with ECT and those treated with pharmacological treatment. A suicide rate of 0.85% per depressive episode is widely quoted and has been used in other economic evaluations. The assumption used in the model is that the longer the patient remains a non-responder the greater the chance of their committing suicide. Once the patient has failed the third 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 was 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.

Summary of scenarios

Table 12 shows a summary of the treatment therapies that were combined to form the eight scenarios that were analysed by the model.

Results

A Monte Carlo simulation approach was taken by varying the inputs for the successful treatment rates, failure to complete therapy rates, quality of life utility values and treatment costs. Values were selected at random from within the 95% CI, based on a normal distribution (Tables 4 and 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 first, second and third treatment strategies, Table 13 shows the results from the 3000 Monte Carlo simulation runs of different treatment strategies.

Scenario 4 has the cheapest average total cost per patient at £10,592, while scenario 2 is the most expensive with an average total treatment cost of £15,354. Scenario 5 generates the most QALYs (0.539), while scenario 3 generates the fewest with only 0.424 QALYs. However, it should be noted that when considering the 95% CIs for both the average costs and QALYs, there is a high degree of overlap between the scenarios. Scenario 1 was considered as the pharmacological treatment comparator as it is the best 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 owing to the range of values the parameters can take, the 95% CIs do overlap with other pharmacological treatments (not shown).

Scenarios 2, 3 and 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 plus TCA combination as the maintenance therapy and scenario 5 assumes that an SSRI is an effective maintenance treatment to prevent relapse.

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

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

Net benefit
When comparing the cost-effectiveness of two or more treatments a consideration of the incremental net benefit of one treatment over another is required. The net benefit of the treatments combines the health gain and financial consequences. The net benefit can be presented in monetary terms as the net monetary benefit (NMB) or in health outcome terms as the net health benefit (NHB):

\[ \text{NMB} = \lambda E - C \]
\[ \text{NHB} = E - C / \lambda \]

where \( \lambda \) is the amount that one is prepared to pay to gain one unit of health benefit (also called the societal value), in this case a QALY, \( E \) is the effect (or health outcome) and \( C \) is the cost.

For example, 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:

\[ £30,000 \times 2.0 - £15,000 = £45,000 \]

That is, £45,000 is the average NMB of introducing this treatment.

The incremental net benefit (NMB and NHB) of one treatment (\( T_1 \)) over another (\( T_0 \)) is represented by the formulae:

\[ \lambda (\text{QALYs} T_1 - \text{QALYs} T_0) - (\text{Cost} T_1 - \text{Cost} T_0) \]
\[ \text{or } \lambda \Delta E - \Delta C \]

\[ (\text{QALYs} T_1 - \text{QALYs} T_0) - (\text{(Cost} T_1 - \text{Cost} T_0)/\lambda) \]
\[ \text{or } \Delta E - \Delta C / \lambda \]
where \( \lambda \) is the societal value of a QALY, \( \Delta E \) is the difference in effect and \( \Delta C \) is the difference in cost.

The difference between two average net monetary benefits has a useful property in that:

\[
\text{NMB}_1 - \text{NMB}_0 = (\lambda E_1 - C_1) - (\lambda E_0 - C_0) = \lambda (E_1 - E_0) - (C_1 - C_0) = \lambda \Delta E - \Delta C = \Delta \text{NMB}
\]

Therefore, one can formulate the average net benefit for each scenario. The scenario with the highest net benefit is the preferred option and there is no need to worry about an appropriate comparator, as there would be with cost-effective ratios.

Table 14 shows the average NMB for each of the treatment strategies assuming that the societal value of a QALY is £30,000.257

Table 14 shows that scenario 5 would be the preferred strategy as it has the highest average net benefit. If scenario 5 did not exist as a realistic option then scenario 4 would be the preferred strategy. Scenario 2 is the only scenario with a negative average net benefit. The 95% CIs for the average net benefit for each scenario have a high degree of overlap. This shows that one cannot be certain of the rank order of the average net benefit of the scenarios.

### Caveat

The average net benefit analyses were undertaken on the mean cost and mean QALYs of each scenario only. Table 14 shows that there is a high level of overlap in the confidence intervals.

### Sensitivity analysis

This section of the report attempts to evaluate the robustness of the model assumptions and show which variables require further information to increase confidence in the results.

#### QALY sensitivity analysis

The default quality of life utility scores used in the model were derived from the Bennett study.256 However, another study by Revicki and Wood255 presented significantly different QALY scores, especially for severely depressed patients. Table 15 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 13, as these assumptions have not altered. The QALYs gained by each scenario have decreased owing 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 scenario’s cost and QALY results.

An NMB analysis between each of the eight scenarios using the Revicki QALY assumptions is shown in Table 16. Again, it has been assumed that the willingness to pay for one QALY is £30,000.

The results in Table 16 show that scenarios 1 and 4 have changed places in the preferred strategy order.

#### Sensitivity of the cost of ECT

The assumption for the cost of ECT is based on a paper from 1994 and increased for inflation. The following analysis reports the effect 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 17 shows the cost and QALYs for each of the eight scenarios. All of the scenarios that have ECT included as a treatment have reduced their average cost. This reduction in cost varies between

### Table 14

Results of average NMB analysis for the scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Average NMB</th>
<th>95% CI</th>
<th>Rank order</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£3330</td>
<td>£720 to £5723</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>-£1614</td>
<td>-£3866 to £498</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>£1422</td>
<td>-£771 to £3586</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>£3508</td>
<td>£1134 to £5624</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>£5148</td>
<td>£2660 to £7602</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>£731</td>
<td>-£2643 to £3917</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>£1989</td>
<td>-£311 to £4275</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>£272</td>
<td>-£3325 to £3482</td>
<td>7</td>
</tr>
</tbody>
</table>
the scenarios depending on whether ECT is prescribed as a first line therapy and whether maintenance ECT is also given. The confidence intervals of the cost and QALYs still have a high level of overlap between the scenarios.

Analysis of the average NMB does not produce anything surprising. Table 18 shows that although the actual NMBs have changed from the scenarios with the default ECT costs, the preferred strategy order remains the same. Again, there is a large amount of overlap in the confidence intervals of the different scenarios.

Sensitivity analysis was also 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 made little difference to the overall scenario results.

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

**Conclusions**

The model described here is the first known attempt at modelling the cost-effectiveness of ECT in a depressed population. Evidence from published trials was used where possible, but it is 

**TABLE 15** Scenario results based on Revicki QALYs

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cost (95% CI)</th>
<th>QALY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£11,325 (£9,204 to £13,647)</td>
<td>0.346 (0.311 to 0.381)</td>
</tr>
<tr>
<td>2</td>
<td>£15,329 (£13,452 to £17,291)</td>
<td>0.297 (0.261 to 0.333)</td>
</tr>
<tr>
<td>3</td>
<td>£11,205 (£9,206 to £13,405)</td>
<td>0.314 (0.278 to 0.353)</td>
</tr>
<tr>
<td>4</td>
<td>£10,613 (£8,913 to £12,450)</td>
<td>0.314 (0.278 to 0.353)</td>
</tr>
<tr>
<td>5</td>
<td>£10,965 (£8,978 to £13,065)</td>
<td>0.378 (0.338 to 0.419)</td>
</tr>
<tr>
<td>6</td>
<td>£13,946 (£11,201 to £17,061)</td>
<td>0.341 (0.305 to 0.377)</td>
</tr>
<tr>
<td>7</td>
<td>£12,597 (£10,751 to £14,587)</td>
<td>0.329 (0.293 to 0.365)</td>
</tr>
<tr>
<td>8</td>
<td>£14,550 (£11,736 to £17,704)</td>
<td>0.344 (0.309 to 0.381)</td>
</tr>
</tbody>
</table>

**TABLE 16** Average NMB results for each strategy using Revicki QALYs

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Average NMB</th>
<th>95% CI</th>
<th>Rank order</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–£945</td>
<td>–£3441 to £1461</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>–£6419</td>
<td>–£8656 to –£4207</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>–£3375</td>
<td>–£5581 to –£1206</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>–£1193</td>
<td>–£3454 to £196</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>–£375</td>
<td>–£2160 to £2700</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>–£3716</td>
<td>–£7217 to –£707</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>–£2727</td>
<td>–£4868 to –£411</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>–£4230</td>
<td>–£7647 to –£1035</td>
<td>7</td>
</tr>
</tbody>
</table>

**TABLE 17** Scenario results based on reduction of 25% in ECT cost

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cost (95% CI)</th>
<th>QALY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£11,349 (£9,191 to £13,699)</td>
<td>0.490 (0.453 to 0.525)</td>
</tr>
<tr>
<td>2</td>
<td>£12,747 (£11,104 to £14,552)</td>
<td>0.458 (0.424 to 0.492)</td>
</tr>
<tr>
<td>3</td>
<td>£9739 (£7,962 to £11,710)</td>
<td>0.421 (0.388 to 0.456)</td>
</tr>
<tr>
<td>4</td>
<td>£9871 (£8,184 to £11,484)</td>
<td>0.470 (0.432 to 0.509)</td>
</tr>
<tr>
<td>5</td>
<td>£9518 (£7,661 to £11,485)</td>
<td>0.538 (0.499 to 0.580)</td>
</tr>
<tr>
<td>6</td>
<td>£13,568 (£10,876 to £16,760)</td>
<td>0.490 (0.453 to 0.526)</td>
</tr>
<tr>
<td>7</td>
<td>£11,296 (£9,595 to £13,063)</td>
<td>0.486 (0.449 to 0.523)</td>
</tr>
<tr>
<td>8</td>
<td>£13,990 (£11,167 to £17,169)</td>
<td>0.494 (0.457 to 0.531)</td>
</tr>
</tbody>
</table>
accepted that a few assumptions were made based on the authors’ limited knowledge of the area, owing to a lack of available data. The model appears to suggest that ECT treatment provided as a second line therapy (scenario 4) would be the preferred strategy as the average NMB is greater than that of the pharmacological only treatment (scenario 1), assuming a £30,000 willingness to pay threshold. However, this cannot be stated with any great confidence as the sensitivity analysis around the QALYs changes the preferred strategy order. 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.

The economic modelling does not demonstrate that any of the available scenarios has a clear economic benefit over the other available options. Specifically, if ECT should be used, the mode does not indicate whether it should be a first, second, or third line treatment. The main reason for this is that there is a lot of 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 RCTs concerned with ECT in the severely depressed. However, it could also be the nature of depressive illness. The clinical evidence produced by this review suggests that ECT is an effective treatment for depression for some people, whereas for others it could even have a detrimental effect.

Further research

The economic modelling undertaken for depression showed 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, may be useful in identifying key parameters where further research would reduce the uncertainty of the cost-effectiveness estimate.

**Modelling schizophrenia**

**Introduction**

The main schizophrenic population for which ECT is indicated in the APA and RCP guidelines comprises patients resistant to pharmacotherapy. Therefore, the model structure 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: a Canadian study by Oh and colleagues that centred on treating treatment-resistant schizophrenia with clozapine. This was a decision tree model that compared clozapine with a standard treatment using chlorpromazine or haloperidol. Oh and co-workers 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-effectiveness 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 in treatment-resistant schizophrenia from other appropriate studies. This would allow analysis of whether ECT was a cost-effective treatment compared with both clozapine, the standard

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Average NMB</th>
<th>95% CI</th>
<th>Rank order</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£3399</td>
<td>£697 to £5755</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>£67</td>
<td>£67 to £67</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>£2035</td>
<td>£2035 to £2035</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>£3763</td>
<td>£3763 to £3763</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>£5792</td>
<td>£5792 to £5792</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>£888</td>
<td>£888 to £888</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>£2827</td>
<td>£2827 to £2827</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>£628</td>
<td>£628 to £628</td>
<td>7</td>
</tr>
</tbody>
</table>
treatment for patients who are treatment resistant, and chlorpromazine, a neuroleptic which, as stated by Thornley and colleagues, "remains the benchmark treatment for patients with schizophrenia".

**Methodology**

Oh’s 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 1-year. Figure 3 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 in Oh’s study. This meta-analysis was conducted in 1995 and the search concentrated on all RCTs involving clozapine, haloperidol and chlorpromazine compared with placebo or active therapy in treatment-resistant schizophrenia. For ECT the clinical success outcome was based on a study by Chanpattana and colleagues, which was the only study in the clinical effectiveness review that had both clinical outcomes and a treatment-resistant population. The authors state that research on the use of ECT in treatment-resistant schizophrenia 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 patients with treatment-resistant schizophrenia. However, they conclude that the literature suggests 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. Chanpattana and co-workers conclude 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 were derived from Burke and colleagues and suggest that between 18 and 35% of ECT patients do not complete the treatment. For the model it was assumed that these figures are the 95% CI and the mean was calculated as the midpoint.

Table 19 shows the event rates for the three comparators in the treatment of treatment-resistant schizophrenia.

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 their 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 authors whether this is a real reflection of the difference in quality of life between patients with depression and those with schizophrenia.

The resultant utility scores from the Oh study are shown in Table 20.

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

Table 21 shows the dosage and cost assumptions for each of the comparable treatments for treatment-resistant schizophrenia.

The pharmacological treatment costs were taken from the BNF and dosages from Oh and colleagues. The ECT cost is based on the study by Montgomery and colleagues which estimated that the cost of ECT in 1994 was £2055 for six sessions. The estimated cost for ECT has been increased from 1994 to 2001 values using the Hospital and Community Health Services inflation index from the Unit Costs for Health and Social Care 2001. ECT incorporates a neuroleptic, as combined ECT and neuroleptic treatment appears to be more effective than either ECT alone or neuroleptic alone. The neuroleptic chosen is flupenthixol as this was the neuroleptic of choice in the Chanpattana study.
FIGURE 3 One-year treatment-resistant schizophrenia treatment model
Results
Table 22 shows the results from the decision model assuming the central values for each parameter. The results suggest that clozapine is the most cost-effective treatment for patients with treatment-resistant schizophrenia since clozapine dominates the other two strategies as it is cheaper and generates more QALYs. ECT dominates the chlorpromazine/haloperidol strategy. The results show that ECT may be cost-effective compared with the standard treatment of chlorpromazine/haloperidol. These results suggest that ECT for treatment-resistant schizophrenia may be a cost-effective treatment for patients who do not respond to clozapine.

Sensitivity analysis
The sensitivity of the model assumptions was 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.

Results of the analysis are shown in Tables 23 and 24.

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 zero on its own would not alter the results sufficiently without also reducing the cost of inpatient care from £171 to £42. Altering the quality of life utility estimates did not change the results sufficiently to make ECT the preferred option, even if it was assumed that the QALYs of patients following ECT were higher than those for clozapine. For ECT to become the preferred treatment strategy 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

---

**Table 19** Event probabilities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success rate</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.65 (0.04 to 1.0)</td>
</tr>
<tr>
<td>ECT + neuroleptic</td>
<td>0.57 (0.48 to 0.67)</td>
</tr>
<tr>
<td>Chlorpromazine/haloperidol</td>
<td>0.04 (0.01 to 0.08)</td>
</tr>
<tr>
<td>Discontinue rate</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.05 (0.02 to 0.09)</td>
</tr>
<tr>
<td>ECT + neuroleptic</td>
<td>0.26 (0.18 to 0.35)</td>
</tr>
<tr>
<td>Chlorpromazine/haloperidol</td>
<td>0.05 (0.02 to 0.09)</td>
</tr>
<tr>
<td>Discharge if symptoms improve</td>
<td>0.81 (0 to 1)</td>
</tr>
<tr>
<td>Relapse within 1 year</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.16 (0 to 1) within 48 weeks</td>
</tr>
<tr>
<td>ECT + neuroleptic</td>
<td>0.40 within 10 weeks</td>
</tr>
<tr>
<td>Chlorpromazine/haloperidol</td>
<td>0.16 (0 to 1) within 48 weeks</td>
</tr>
</tbody>
</table>

**Table 20** Quality of life utility estimates

<table>
<thead>
<tr>
<th>Description</th>
<th>Average utility rating</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate symptoms: hospitalised patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.91</td>
<td>0.86 to 0.96</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>0.86</td>
<td>0.77 to 0.95</td>
</tr>
<tr>
<td>Mild symptoms: community</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.87</td>
<td>0.82 to 0.92</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>0.84</td>
<td>0.75 to 0.93</td>
</tr>
<tr>
<td>Mild symptoms: hospitalised patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.87</td>
<td>0.82 to 0.92</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>0.84</td>
<td>0.75 to 0.93</td>
</tr>
</tbody>
</table>

**Table 21** Dosage and cost estimates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>500 mg day⁻¹</td>
<td>£9.78 per dose</td>
</tr>
<tr>
<td>Blood test</td>
<td>One per week (18 weeks), one per fortnight thereafter</td>
<td>£25 per test</td>
</tr>
<tr>
<td>ECT acute</td>
<td>Two sessions per week for 4 weeks</td>
<td>£2475 per six sessions</td>
</tr>
<tr>
<td>Flupenthixol</td>
<td>12 mg day⁻¹</td>
<td>£0.60 per dose</td>
</tr>
<tr>
<td>ECT maintenance</td>
<td>One session per fortnight session</td>
<td>£212.12 per session</td>
</tr>
<tr>
<td>Flupenthixol</td>
<td>12 mg day⁻¹</td>
<td>£0.60 per dose</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>20 mg day⁻¹</td>
<td>£0.43 per dose</td>
</tr>
<tr>
<td>Hospital costs</td>
<td></td>
<td>£171 per day</td>
</tr>
<tr>
<td>At-home costs</td>
<td></td>
<td>£275 per year</td>
</tr>
</tbody>
</table>

**Table 22** Cost-effectiveness results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average cost</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>£34,787</td>
<td>0.863</td>
</tr>
<tr>
<td>ECT</td>
<td>£55,267</td>
<td>0.842</td>
</tr>
<tr>
<td>Chlorpromazine/haloperidol</td>
<td>£58,265</td>
<td>0.820</td>
</tr>
</tbody>
</table>
the cost per QALY of clozapine would increase beyond £65,672. The 95% CIs for the probability of clozapine success vary from 4 to 100% based on the meta-analysis undertaken by Oh and colleagues, and 21% lies within these limits.

Conclusions and recommendations
The cost-effective analysis using the model presented here shows that clozapine for treatment-resistant schizophrenia is a cost-effective alternative compared with ECT or chlorpromazine/haloperidol treatment. The results of the model showed that ECT was a cost-effective option compared with chlorpromazine/haloperidol treatment. However, the model shown here is based on limited data owing to a lack of research in this area and cannot be considered as robust. These results suggest that ECT for treatment-resistant schizophrenia could be effective in patients who do not respond well to clozapine.

TABLE 23 Threshold analysis for treatment-resistant schizophrenia: ECT as the preferred strategy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline value (95% CI)</th>
<th>Threshold value</th>
<th>Direction of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of clozapine</td>
<td>£9.78</td>
<td>£72.80</td>
<td>If the cost of clozapine rises above £72.80 then ECT would be the preferred strategy. This would require over a seven-fold increase in cost</td>
</tr>
<tr>
<td>Adverse events for clozapine</td>
<td>0.5 (0.02 to 0.09)</td>
<td>0.837</td>
<td>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</td>
</tr>
<tr>
<td>Probability of clozapine success</td>
<td>0.65 (0.04 to 1.0)</td>
<td>0.21</td>
<td>If the probability of clozapine success falls below 21% then ECT would be the preferred strategy. The 95% CI for this variable is large, although 0.21 is towards the lower end</td>
</tr>
</tbody>
</table>

TABLE 24 Threshold analysis for treatment-resistant schizophrenia: ECT as the least preferred option

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline value (95% CI)</th>
<th>Threshold value</th>
<th>Direction of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of ECT</td>
<td>£2475</td>
<td>£5900</td>
<td>If the cost of ECT rises to £5900 then ECT would be the least preferred strategy</td>
</tr>
<tr>
<td>Adverse events for ECT</td>
<td>0.26 (0.18 to 0.35)</td>
<td>0.87</td>
<td>If the adverse events rate for ECT rises above 87% then ECT would be the least preferred strategy. This is well above its 95% CI</td>
</tr>
<tr>
<td>Probability of ECT success</td>
<td>0.57 (0.48 to 0.67)</td>
<td>0.26</td>
<td>If the probability of ECT success falls below 26% then ECT would be the least preferred strategy</td>
</tr>
</tbody>
</table>
Chapter 5

Implications for other parties

Implications for other parties are discussed in Chapter 7.
ECT is an intervention that has been used in the NHS since its formation in 1948. Since 1985, the use of ECT in England has been decreasing. The estimated 65,930 administrations in 1999 compares with 105,466 reported administrations in 1990/91 and 137,940 in 1985.

Most administrations of ECT are provided on an inpatient basis. In contrast, current government policies such as the NSF on mental health advise that the care and treatment of people with psychiatric illness should be provided in community settings.
Summary of main results and discussion

Depressive illness

Real versus sham ECT

The efficacy of real versus sham ECT is unclear. The UK ECT Group\(^5\) found that in the short term, real ECT is more effective than sham ECT when data from all six trials were pooled. The pooled effect size from the UK ECT Group review was –0.91 (95% CI –1.27 to –0.54). An effect size of 0.9 indicates that about 82% of patients treated with ECT would be less depressed at the end of treatment than the average patient treated with sham ECT. The average size of the difference between real and sham ECT on the HRSD was 9.7 points.

The present 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 three 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 homogeneous data from two trials also suggested that real bilateral ECT was not more effective than sham ECT (RR = 1.51, 95% CI 0.94 to 2.49). However, removal of the trial\(^5\) that included one real ECT treatment in the control group, leaving one trial,\(^\) suggests that real bilateral ECT is more effective than sham ECT (RR = 1.98, 95% CI 1.05 to 3.79).

Only four out of nine trials provided sufficient dichotomous data for this analysis, compared with six out of seven providing sufficient continuous data for analysis by the UK ECT Group. This may explain, in part, the differences in the results of the analyses. A further explanation for the difference is the impact of stimulus parameters on the effectiveness of ECT. When all the results are pooled (as in the UK ECT Group analysis\(^5\), real ECT is more effective than sham ECT. However, when the results are analysed separately, real unilateral ECT is not more effective than sham ECT and it is unclear whether bilateral ECT is more effective than sham ECT.

These trials also varied in other aspects of the stimulus parameters used, such as the machine used to administer the stimulus, the number of ECT treatments administered, the dosage and the waveform of the stimulus. Most of the trials were conducted during the 1970s and 1980s, and in all cases, the methods used to administer ECT do not conform to current guidelines set by the RCP\(^1\) or the APA.\(^1\) Five trials specified the machine used to deliver ECT and none was of the type recommended by current guidelines.\(^1\) Two used Duopulse Mk IV machines,\(^9\) two used Ectron Mk IV machines\(^9\) and one used a Transycon machine.\(^9\) Of the seven trials that specified the dosage and waveform of ECT, none used stimulat dose; rather, they gave a fixed dose. Two used sine wave at 150 V\(^9\) one used sine wave but did not specify the dose,\(^9\) one used chopped sine wave (dosage not specified),\(^9\) one used 60% sine wave at 400 V,\(^9\) one used a double-sided unrectified wave at 40 J\(^9\) and only one used brief pulse at 10 J.\(^9\) Seizure threshold has been shown to vary 40-fold between individuals, and to increase over the course of ECT.\(^1\) 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.\(^9\) It has subsequently been shown that the stimulus dose needs to be increased to between five and six times higher than seizure threshold for unilateral ECT to equal bilateral ECT in efficacy.\(^1\)

ECT versus antidepressant pharmacotherapy

Overall, the data suggest that ECT is more effective than pharmacotherapy in the short term, but the data on which this assertion is based are subject to important flaws. The UK ECT Group\(^5\) found that ECT is more effective than drug therapy in the short-term treatment of depression (17 RCTs, 1136 participants). The pooled effect size from the UK ECT Group review\(^5\) was –0.75 (95% CI –1.28 to –0.20), which indicates that about 77% of patients treated with ECT would be less depressed at the end of treatment than the average patient treated with drug therapy. The average size of the difference on the HRSD was 5.2 points. The present analysis of limited data from one trial suggests that ECT is more effective than SSRIs in the short term (RR = 3.41, 95% CI 1.39 to 7.11). The pooled analysis of data from six trials suggests that ECT was also more effective.
than TCAs in the short term (RR = 1.42, 95% CI 1.17 to 1.72).

The analysis conducted by the UK ECT Group pooled data from trials comparing ECT with a number of different antidepressant drugs including SSRIs, TCAs, MAOIs and L-tryptophan. The last two are not considered first line treatments for depression in current clinical practice. The present separate analysis of ECT in comparison to SSRIs and TCAs found ECT to be superior in both cases. However, the results of this analysis need to be interpreted with some degree of caution. Only one trial 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 criterion for a response was defined a priori (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 (50 mg) was therapeutically adequate.

The quality of reporting in the 14 trials was largely inadequate and only six 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 provided data for analysis were of low quality. Only one of the six trials that contributed data for analysis used blinded clinicians to rate outcomes; the remaining five were not blind or the blinding was not clear. This is of particular importance when the method of judging responders is considered. Two trials defined responders using different criteria specified a priori based on scores from quantitative outcome measures, while the remaining four 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 relative risk 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 used a fully adequate therapeutic dose of SSRI (50 mg paroxetine), but none used a fully adequate dose up to 300 mg or equivalent of imipramine. Two trials used 250 mg, one used 220 g, one used 200 mg and four used 150 mg. One trial used 100 mg, the minimum dose shown to be therapeutically effective, while two trials used doses below this level. Two trials did not state the dosage of TCA used. Although most trials used a dose of TCA above the minimally therapeutic dose, none compared ECT to a dose 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 used a fixed dose of 110 V of alternating current, whereas the other two used stimulus dosing at 2.5 times or 60 mC above seizure threshold. One trial used an ECT machine that is in line with current standards.

Trials examining the efficacy of ECT have been criticised for rarely reporting the number of people who were initially screened before 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. A recent study has shown the ECT was less effective in a ‘real-life’ heterogeneous patient sample compared with homogeneous patient samples used in RCTs. None of the trials comparing ECT with pharmacotherapy provided any information regarding the number of people initially screened before 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.
In terms of inclusion criteria, three trials did not specify inclusion criteria and eight did not use explicit diagnostic criteria to diagnose or assess the severity of depression. Six trials used explicit diagnostic criteria for major depression, one used DSM-III, one used DSM-IV, and one used the Feighner criteria and one used the criteria specified by Klein. Four trials specified the severity of depression for inclusion according to the HRSD, with two specifying scores on the 17-item HRSD of less than 17, one specifying a score of less than 20 and one specifying scores of less than 22 on the 21-item HRSD.

Four trials explicitly included people who were treatment resistant to antidepressants. Two did not define treatment resistance. One study defined treatment resistance as failure to respond to a full course of TCAs, defined as at least 150 mg of anitryptaline for at least 4 weeks and failure of HRSD to drop by 40% or at least to fall by 20 points. The other defined treatment resistance as failure to respond to at least two different antidepressants (including at least one TCA) at a dosage of at least 100 g imipramine or equivalent and no improvement for a total period of 8 weeks. These definitions are both different, and are different to that proposed by Nierenberg and Amsterdam, defined as failure to respond to a trial of more than one antidepressant drug in a dose equivalent to 250–300 mg of imipramine given for a duration of 6–8 weeks each. A further five trials 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, or for how long the drugs had been administered. None of the trials included people for whom ECT was indicated as an emergency.

This suggests that nine trials included participants who had severe depression and four included people who were treatment resistant, although none of the participants met the criteria for treatment resistance specified by Nierenberg. None of the trials reported data separately for older people.

Only one trial 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. In contrast, current government policies such as the NSF on mental health advise that the care and treatment of people with psychiatric illness should be provided in community settings.

ECT versus rTMS

Limited data from one trial including 40 participants indicated that ECT is significantly more effective than rTMS in the short term. The WMD was 6.8 points (95% CI 1.41 to 12.19) on the HRSD in favour of ECT.

This treatment is not currently used in routine clinical practice.

Adjunctive pharmacotherapy

Limited data from two separate trials suggest that the efficacy of ECT may be improved by the concomitant use of TCAs during the ECT course. The WMD was –3.00, 95% CI –5.65 to 0.35, n = 52; RR = 0.55, 95% CI 0.33 to 0.90, n = 132) and that the addition of pindolol may increase the speed but not the extent of response to ECT. Limited data suggest that continuing to take TCAs following ECT does not reduce the risk of relapses at 6 months (RR = 0.80, 95% CI 0.55 to 1.15, p = 0.23, n = 100).

Not any of the participants in the 11 included trials 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 trial, nine out of 35 (26%) were treatment resistant. In Arfwidsson, 42% of participants had received antidepressant medication during the current episode, in d’Elia 39% had received antidepressants, and in Lauritzen 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 patients in group B in this trial could reflect the fact that participants had failed to respond to the same class of antidepressant medication before ECT. Mayur and colleagues report that only half of the participants in either group had received an adequate drug trial before participation in the study. Depression was diagnosed according to standardised criteria in three trials, with Lauritzen using DSM-III-R and Shiah and Mayur using DSM-IV. The remaining six trials did not use standardised criteria to diagnose depression in their inclusion criteria.
Only one trial provided usable data to assess the efficacy of continuation pharmacotherapy on relapses and the interpretation of the results was heavily influenced by the inclusion of those who withdrew from the trial in the analysis. Eighteen people dropped out from the treatment group compared with seven in the control and assuming that they all relapsed, this resulted in a non-statistically significant difference in relapse rates between the treatment arms. Given the high rates of dropout in this study, these results should be interpreted with caution.

Continuation pharmacotherapy
Limited data suggest that continuation pharmacotherapy with tricyclic antidepressants does not reduce the relapse rate in those who have successfully responded to ECT (RR = 0.73, 95% CI 0.53 to 1.01, \( p = 0.06, n = 56 \)). However, when TCAs were augmented with lithium there was a statistically significant reduction on the rate of relapses compared with placebo (RR = 0.58, 95% CI 0.39 to 0.86).

Electrode placement
In the short term, bilateral ECT is more effective than unilateral ECT (27 RCTs, 1367 participants). The pooled effect size from the UK ECT Group review was –0.29 (95% CI –0.43 to –0.15), which indicates that about 62% of patients treated with bilateral ECT would be less depressed at the end of treatment than the average patient treated with unilateral ECT. The average size of the difference on the HRSD was 3.4 points.

Dosage and frequency of administration
Higher dose ECT was more effective than lower dose ECT (seven RCTs, 342 patients). The pooled effect size from the UK ECT Group review was –0.73 (95% CI –0.41 to –1.08), which indicates that about 77% of patients treated with higher dose ECT would be less depressed at the end of treatment than the average patient treated with lower dose ECT. The average size of the difference on the HRSD was 5.2 points. Although the trials differed in the precise doses used, there was a consistent benefit for higher dose treatment. There was no different in effectiveness between twice weekly and three times weekly ECT (six RCTs, 210 patients).

Schizophrenia
Real versus sham ECT
The Cochrane Schizophrenia Group ECT review found a non-significant trend towards real ECT being 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. The UK ECT Group found that real ECT was no more effective than sham ECT.

ECT versus antipsychotic drugs
The Cochrane Schizophrenia Group ECT review 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 suggested an advantage of ECT antipsychotic combination, but only in relation to mental state as measured by the BPRS. The UK ECT Group found no advantage of ECT over antipsychotic medication either alone or in combination with antipsychotic medication.

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

Continuation ECT
Both reviews 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 responded to a course of ECT by strict criteria. The Cochrane Schizophrenia Group ECT review suggested that the NNT to prevent a relapse in this population was two (95% CI 1.5 to 2.5).

Electrode placement
Neither review found evidence for a difference between unilateral and bilateral ECT.

Dosage and frequency
The Cochrane Schizophrenia Group ECT review found limited data from one trial that suggested that higher doses resulted in a faster rate of improvement, but had no impact on the extent of improvement compared with lower doses. No conclusions can be drawn from the limited evidence on the impact of the frequency of ECT.

Generalisability of the trial evidence in schizophrenia
The Cochrane Schizophrenia Group ECT review 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 recommends 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 a recent onset. Similarly, the RCP advises that the practical usefulness of ECT in schizophrenia is limited to acute catatonic states, schizoaffective disorders, acute paranoid syndromes and people with type 1 schizophrenia who are either intolerant of or unresponsive to a dose of a neuroleptic equivalent to 500 mg of chlorpromazine daily.

The Cochrane Schizophrenia Group ECT review 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-IIIR, DSM-IV, Feighner’s criteria, Present State Examination (PSE) and CATEG Research Diagnostic Criteria, and the Chinese Medical Council Clinical Diagnostic Criteria. Ungvari and Petho classified participants based on the classification of Langfeldt into systematic and unsystematic schizophrenia, a classification similar to the process and reactive or non-process classification of Langfeldt. Two trials included people with homogenous clinical subtypes of schizophrenia, namely chronic catatonic schizophrenia and paranoid schizophrenia. One trial included only young males with schizopreniform disorder (a diagnosis made when the symptoms of schizophrenia have been present for less than the 6 months required for the diagnosis of schizophrenia. If the symptoms persist beyond 6 months this provisional diagnosis is changed to schizophrenia). One trial 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 which clinicians currently use ECT, according to a recent survey.

The Cochrane Schizophrenia Group ECT review found little homogeneity between trials in the duration of the disorder, with seven trials stipulating a duration of less than 2 years, of which Abrams included participants with onset of disorder less than 3 months and Sarkar and colleagues less than 2 months. Seven trials included participants who had been ill for more than 2 years and two of these trials included individuals with chronic illness hospitalised for 10 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 1 month to 32 years. From the reports of Bagadia and colleagues and Baker, it was unclear for how long the participants had been ill.

In terms of past history of response to antipsychotic drugs, the Cochrane Schizophrenia Group ECT review found three trials that specifically included people with treatment-resistant schizophrenia that fulfilled modified criteria for treatment-resistant schizophrenia. A further three trials also included participants who had failed to respond to antipsychotics, although it is uncertain how many would meet stringent criteria for treatment resistance. The review also reports that other trials included people with varying degrees of non-response to conventional antipsychotics, although Abrams, Sarkar and colleagues and possibly Ungvari and Petho included people who were acutely ill and hence unlikely to be resistant to treatment. One trial predominantly included people with catatonia and one included only people with paranoid schizophrenia.

The Cochrane Schizophrenia Group ECT review 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 reported that five trials stated that brief-pulse ECT devices were used; the remainder appear to have used sine-wave machines. The review 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 the adequacy of treatments with ECT. Two studies titrated individual thresholds for participants and monitored seizures with the cuff method and EEG recordings. Two studies used supra-threshold stimuli and monitored motor and electrical seizure activity as above. One study 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, with reference to the use of stimulus dosing and brief-pulse stimuli.

**Mania**
The UK ECT Group review found very limited evidence of the efficacy of ECT in mania. They were unable to draw any firm conclusions on the use of ECT in this group.

**Catatonia**
Limited subgroup analyses by the Cochrane Schizophrenia Group ECT review suggested that ECT had no significant benefits in people with catatonia. The poor quality of randomised evidence does not allow firm conclusions to be drawn regarding the relative efficacy of ECT in this group.

**Children and adolescents**
The use of ECT in adolescents and children is rare. This explains, in part, why there are no RCTs of the efficacy of ECT in this group. The non-randomised evidence did not allow firm conclusions to be drawn regarding the efficacy of ECT compared with 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.

**Older people**
The UK ECT Group could not conduct reliable subgroup analyses of the use of ECT in this group and older people were not well represented in the RCTs. The trials reviewed by the present group, comparing real versus sham ECT and ECT versus 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.

**Pregnancy**
There was no randomised evidence relating to the use of ECT 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 because of the poor reporting in the studies.

**Long-term efficacy of ECT**
Very few of the trials included in the UK ECT Group review and the Cochrane Schizophrenia Group ECT review assessed the efficacy of ECT beyond the end of the course of ECT. It is therefore not possible to determine for how long the short-term benefits of ECT are maintained. Evidence from the SURE review suggests that there is a negative relationship between the length of time since ECT and satisfaction with outcome, such that satisfaction with treatment is reduced in the longer term.

**Adverse events: mortality**
Trials in the UK ECT Group review did not suggest that there was an increased risk of death due to ECT. The short-term nature of the trials meant that they did not provide any evidence of the long-term impact ECT on mortality rates. In the trials included by the Cochrane Schizophrenia Group ECT review on schizophrenia, none of the 779 participants died during or immediately after a course of ECT. The non-randomised evidence from the UK ECT Group review produced inconsistent results and did not provide clear evidence that ECT either increased or decreased death rates.

**Adverse events: cognitive functioning**
The Cochrane Schizophrenia Group ECT review found limited evidence to suggest that greater cognitive impairment occurs at the end of a course of ECT than for antipsychotics in people with schizophrenia. The UK ECT Group found it difficult to summarise the data on the cognitive effects of ECT. They included trials that measured different aspects of cognitive functioning often using instruments that had not been psychometrically validated. Parallel forms of the tests were rarely used and there was little consistency in the types of instrument used across studies. The trials also varied in the stimulus parameters of ECT or did not report them, making it very difficult to compare results across studies.

Cognitive testing was often used in the trials in an ad hoc way and as a result lacked a consistent theoretical underpinning to predict and interpret findings. Owing to the small sample sizes of many trials, confounding factors were dealt with inadequately and between-group comparisons rarely controlled for baseline differences in cognitive functioning. The analyses often used multiple testing without provision with a high risk of type I errors.
As a result, no quantitative summary of the findings on cognitive functioning could be performed. Despite this, a number of conclusions could be drawn from the findings of the UK ECT Group review. Cognitive impairments following ECT mostly reflect memory impairment. On the whole, bilateral ECT resulted in greater memory impairment than unilateral ECT, a higher dose of ECT produced more impairment than lower doses and administration of ECT three times a week resulted in greater memory impairment than twice a week.

This suggests that the stimulus parameters of ECT have an important impact on cognitive impairment following ECT. Limited evidence from the UK ECT Group suggests that these impairments do not last beyond 6 months. The trials included in the UK ECT Group review rarely measured cognitive functioning beyond the course of ECT and no trials assessed cognitive functioning 12 months post-ECT.

Evidence from the SURE review suggested that a significant proportion of people who receive ECT report memory loss that persists for longer than 6 months. This review suggested a number of reasons for the mismatch between patient and clinical perspectives on memory loss as a result of ECT. First, objective tests used in RCTs rarely capture the type of memory problems that occur most frequently in the subjective reports of participants, such as personal autobiographical memories. Second, patients and clinicians interpret memory loss in different ways. Patients see memory loss as an important side-effect of ECT, whereas clinicians may attribute memory loss to other factors such as age and the symptoms of depression. The extent to which trials attempted to handle or discuss the interactions between impairments in cognitive functioning as a direct result of ECT, improvements in cognitive functioning as a result of improvements in depression and decreases in cognitive functioning as a result of age is unclear from the evidence presented in the UK ECT Group or Cochrane Schizophrenia Group ECT review.

**Adverse effects: brain damage**

The UK ECT Group review found no evidence from structural brain imaging studies that ECT causes brain damage. Where moderate abnormalities were detected at higher rates, they were likely to be due to clinical factors such as severity of illness.

**Patient acceptability in choice**

None of the RCTs included in the reviews conducted by the Cochrane Schizophrenia Group and the UK ECT Group explored the impact of patient acceptability or choice on the outcomes of ECT. The rate of discontinuations was generally similar between ECT and other comparison interventions.

Evidence from the SURE review suggests that estimates of the perceived benefit of ECT are influenced by the timing and methods used to obtain this information. Studies that interview consumers shortly after ECT are likely to overestimate the perceived benefit, especially if the interviews are conducted by a clinician in a hospital setting using a brief set of questions. The SURE review also suggests that perceived benefit of ECT from the patient’s perspective is not unidimensional but complex. Patients make trade-offs between the benefits and risks of ECT that are not the same for each individual. The review also argues that the patient’s perspective of the perceived benefit of ECT are not adequately captured by clinical measures assessing signs and symptoms. A reduction in severity of symptoms on a depression rating scale is not the same as subjective relief from depression. These clinical measures may also be subject to bias in people reporting that they are better in order to avoid further ECT, although this has not been explored systematically.

The SURE review found mixed results regarding the relationship between patient choice and satisfaction with ECT. The review did not find any studies that explored the impact of patient choice on the perceived benefit of ECT.

**Patient information and consent**

Evidence from the SURE review suggests that at least 50% of users feel that they have inadequate information before ECT and between 7 and 16% were judged to have adequate objective knowledge about the procedure of ECT. They also found that between one-quarter and one-third of people who sign a consent form to ECT do so under pressure, in the belief that they cannot refuse.

Limited data from one small and one larger trial 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.
or mean knowledge score following the intervention. However, the results of these trials should be interpreted with caution. The sample size in one trial was small and included no baseline assessment of knowledge, and in both trial the instrument used to measure knowledge had not been psychometrically tested.

Assumptions, limitations and uncertainties

Comprehensiveness of the review
The present searches of the randomised evidence and those included in the three good systematic reviews were exhaustive and the authors are confident that they have not missed any important RCTs of ECT. They are less certain that their searches of the non-randomised literature were as comprehensive. They did not review evidence concerning the different types of anaesthesia or the impact of pretreatment with caffeine on the efficacy of ECT. They also did not examine adjunctive or post-treatments that aimed to reduce the cognitive side-effects of ECT.

Cost effectiveness modelling for schizophrenia
This report includes the first attempt, to the authors’ knowledge, of modelling the cost-effectiveness of ECT for schizophrenia. The robustness of the model was constrained by a lack of data in this field. As such, the conclusions should be interpreted with caution.

Need for further research

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

There is currently no randomised evidence comparing ECT with, or in addition to, newer antipsychotic drugs (e.g. clozapine and risperidone) and antidepressants (e.g. venlafaxine) that are currently used in clinical practice. Further work is needed in these areas. More research is also needed to compare ECT with rTMS, especially in people with schizophrenia. Again, there is a need for further, high-quality RCTs comparing the use of ECT with these treatments.

More research is needed to examine the long-term efficacy of ECT and the effectiveness of post-ECT pharmacotherapy. There is only limited evidence regarding the efficacy of supplementing ECT with pharmacotherapy in people with depression and the continuation of pharmacotherapy following successful response to ECT to prevent relapses. In most trials, the aftercare 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 patients’ perspectives on the impact of ECT into future RCTs. Consideration should be given to the use of both quantitative and qualitative methods. The outcome measures used should reflect both clinical and patient perspectives on the impact of ECT.

There is also little good quality 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 patients’ 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-up within RCTs to explore the impact of ECT 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 into 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 Consolidated Standards of Reporting Trials (CONSORT) recommendations.

**Cost-effectiveness**

Further economic analysis, such as expected value of perfect information, may 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 to make the decision on whether ECT is a cost-effective treatment.
Chapter 8
Conclusions

Clinical effectiveness

The results of this review largely relate to the use of ECT within well-developed health services. 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 suggest TCAs may improve the antidepressant effect of ECT during the course of ECT, and that continuation pharmacotherapy with TCAs combined with lithium in people who have responded to ECT reduces the rate of relapses. Overall, gains in the efficacy of the intervention depending on the stimulus parameters of ECT are achieved only at the expense of an increased risk of cognitive side-effects. Limited evidence suggests that these effects do not last beyond 6 months, but there is no evidence examining the longer term cognitive effects of ECT. There is little evidence of the long-term efficacy of ECT, much less evidence regarding the efficacy of ECT in schizophrenia and mania, 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 mania or catatonia, older people, younger people and women, or the impact of ECT on all-cause mortality. There was limited non-randomised evidence regarding the impact of patient acceptability and choice on the outcomes of ECT, and this produced mixed results.

Cost-effectiveness

Depression

No previous analysis has been undertaken on the cost-effectiveness of ECT in depression. The model described here attempted to reflect the possible treatment protocols that could be used 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 first, second, or third line therapy, have been compared with a pharmacological-only therapy.

The results from the model are not conclusive regarding the cost-effectiveness of ECT. Based on the default assumptions the economic modelling results suggest that ECT provided as a second line therapy is the preferred treatment strategy. However, the confidence intervals around the results are large, primarily because of the large confidence intervals around the inputs due to a lack of good 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. ECT needs to be followed by pharmacological treatment or maintenance ECT 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 that if an effective treatment could be found that reduces the relapse rates of patients following ECT even with maintenance therapy, ECT would become a cost-effective treatment in hospitalised, severely depressed people.

Schizophrenia

No previous analysis has been undertaken of the cost-effectiveness of ECT in schizophrenia. The economic model constructed for schizophrenia was based on a pharmacological model constructed by Oh and colleagues which was the only cost-utility study identified in the treatment of schizophrenia. This model analysed the cost-effectiveness of clozapine compared with haloperidol/chlorpromazine treatment in treatment-resistant schizophrenia. The results of the adapted model including ECT suggest that clozapine is a cost-effective treatment compared with ECT. However, for patients who fail to respond to clozapine, ECT may be preferred to the comparative treatment of haloperidol/chlorpromazine. However, the clinical evidence underpinning the ECT assumptions in the model is weak.
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Contributions of authors
Joanne Greenhalgh and Daniel Hind carried out the review of clinical effectiveness. Chris Knight carried out the review of cost-effectiveness. Catherine Beverley carried out the electronic searches. Stephen Walters provided statistical advice. Joanne Greenhalgh is responsible for the report as lead author.

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163. Cronholm B, Ottoffson JO. Ultrabrief stimulus techniques in electroconvulsive therapy. II. Comparative studies of therapeutic effects and memory disturbances in treatment of endogenous depression with the Elther ES electroshock apparatus and Siemens Konvulsator III. *Journal of Nervous and Mental Disease* 1963;137:208–76.


References


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249. Royal Pharmaceutical Society of Great Britain. BNF42. WeBNF No. 42; 2002.


### Appendix 1

**Electronic bibliographic databases searched**

<table>
<thead>
<tr>
<th>Biological Abstracts</th>
<th>Health Technology Assessment (HTA) Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>CINAHL</td>
<td>MEDLINE</td>
</tr>
<tr>
<td>Cochrane Controlled Trials Register (CCTR)</td>
<td>NHS Economic Evaluations Database (NHS EED)</td>
</tr>
<tr>
<td>Cochrane Database of Systematic Reviews (CDSR)</td>
<td>Office of Health Economics Health Economic Evaluations Database (OHE HEED)</td>
</tr>
<tr>
<td>Cochrane Schizophrenia Group Trials Register</td>
<td>PreMEDLINE</td>
</tr>
<tr>
<td>Database of Abstracts of Reviews of Effectiveness (DARE)</td>
<td>PsycINFO</td>
</tr>
<tr>
<td>EBM Reviews</td>
<td>Science Citation Index (SCI)</td>
</tr>
<tr>
<td>EMBASE</td>
<td>Social Sciences Citation Index (SSCI)</td>
</tr>
<tr>
<td>Health Management Information Consortium (HMIC)</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2

Other sources consulted

Agency for Healthcare Research and Quality (AHRQ)
Aggressive Research Intelligence Facility (ARIF)
AltaVista
Association of British Health Care Industries
Bandolier
Canadian Co-ordinating Centre for Health Technology Assessment (CCOHTA)
CenterWatch Trials Register
Centre for Health Economics, University of York
Copernic
Current Controlled Trials (CCT)
Current Research in Britain (CRiB)
Dantec Electronics Ltd
Department of Health
Ectron Ltd
eGuidelines
Health Evidence Bulletins, Wales
Index to Theses
International Network of Agencies for Health Technology Assessment (INAHTA) Clearinghouse
Medical Research Council (MRC) Funded Projects Database
Mental Health Foundation
MIND

National Assembly for Wales
National Coordinating Centre for Health Technology Assessment (NCCHTA)
National Guideline Clearinghouse (NGC)
National Research Register (NRR)
Organising Medical Networked Information (OMNI)
Research Findings Register (ReFeR)
Royal College of Anaesthetists
Royal College of Nursing
Royal College of Psychiatrists
ScHARR Library Catalogue
Schizophrenia Association of Great Britain
Scottish InterCollegiate Guideline Network (SIGN)
The Association of Anaesthetists of Great Britain and Ireland
The Mental Health Act Commission
Trent Working Group on Acute Purchasing
Turning Research into Practice (TRIP) Database
Wessex Development and Evaluation Committee (DEC) Reports
West Midlands Development and Evaluation Services (DES) Reports
World Health Organization (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 electroconvulsive 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

CDSR and CCTR
2001 Issue 4
The Cochrane Library, Update Software (CD-ROM version)
Search undertaken December 2001

#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 SCHIZOPHRENIA*
#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 schizophrenia/
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

Centre for Reviews and Dissemination (CRD) databases (NHS DARE, EED and HTA)
CRD website – 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 electroconvsive 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-psychois' / 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

OHE HEED
CD-ROM version
Search undertaken December 2001

Search terms
- ect or electroconvulsive or electro convulsive or electroshock or electro shock

Fields searched
- Abstract
- All data
- Article title
- Book title
- Keywords
- Technology assessed

HMIC
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$. stimulation.tw
8 or/1-7
9 depression/
10 exp schizophrenia/
11 schizophrenia$.tw
12 catatonia/
13 catatonia$.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

SCI and SSCI
1981–2001
Web of Science
Search undertaken December 2001

#1 ect
#2 electroconvulsive therap*
#3 electro convulsive therap*
#4 #1 or #2 or #3
Title=(ect or electroconvulsive therapy or electroconvulsive therapy or electroshock therapy or electro shock therapy) and (depression or schizophrenia* 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 not 12

Randomised 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$)).ti, ab
11 placebo/
12 placebos.ti, ab
13 random.ti, ab
14 research design/
15 or/7-14
16 comparative study/
17 exp evaluation studies/
18 follow up studies/
19 (control$ 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 thirty six or sf thirty six or short form 36 or short form thirty six or short form thirty six 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
Appendix 4

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 25  Systematic reviews of the clinical effectiveness and safety of ECT in depression, schizophrenia and mania

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion/exclusion criteria</th>
<th>Search strategies</th>
<th>Data quality</th>
<th>Data synthesis methods</th>
</tr>
</thead>
</table>
| UK ECT Group, 2003<sup>51</sup> | **Interventions**: ECT: electrode placement (bilateral vs unilateral), dosage, waveform, frequency of administration, number of ECT sessions  
**Comparators**: no ECT, sham ECT, pharmacotherapy and/or psychotherapy  
**Populations**: same diagnosis of depression, schizophrenia and mania, according to explicit criteria  
**Outcomes**: Primary: symptoms: change on a continuous scale at the end of a course of ECT and at 6 months' follow-up; mortality: all cause and cause specific, including suicide; cognitive functioning: orientation, retrograde memory, anterograde memory, subjective distress immediately after ECT, at end of treatment and at 6 months; quality of life; duration of hospital admission; functional impairment; structural brain changes  
**Study types**: effectiveness: RCTs; safety: case–control and cohort studies | **Electronic databases**: CDSR, DARE, Cochrane Collaboration Depression Anxiety and Neurosis (Group) Controlled Trial Register (CCDANCTR), Cochrane Schizophrenia Group Register (CSGCTR), February 2001; Biological Abstracts, CINAHL, EMBASE, LILACS, MEDLINE, PsycINFO and SIGLE, March 2001; CCTR, June 2001  
**Other**: checked reference lists of the ECT guidelines issued by the APA (2001) and RCP (1995); handsearched specialist textbooks on ECT by Fink<sup>271</sup> and Abrams<sup>272</sup>; citation tracking of included studies and systematic reviews; contacted experts in the field and manufacturers of ECT machines for unpublished studies | **Blinded assessment**: no  
**Study quality rating**: no. RCTs: allocation concealment, blinding, loss to follow up and length of follow-up; cohort studies: measurement bias, handling of confounding factors, number of cases and loss to follow-up; case–control studies: measurement bias, handling of confounding factors and number of cases  
**Methods**: two independent reviewers | **Meta-analysis**: full random effects model  
**Heterogeneity**: conducted but methods not reported  
**Sensitivity analysis**: conducted excluding studies of inferior quality  
**Subgroup analyses**: defined a priori psychotic depression, retarded depression, age, treatment resistance, gender and severity at entry to the trial, but not conducted owing to limited data  
**Publication bias**: assessed by funnel plots  
**Continuous data**: standardised effect size  
**Dichotomous data**: odds ratios and absolute risk differences  
**Confidence intervals**: yes |

*continued*
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion/exclusion criteria</th>
<th>Search strategies</th>
<th>Data quality</th>
<th>Data synthesis methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tharyan and Adams, 2002&lt;sup&gt;50&lt;/sup&gt;</td>
<td><strong>Interventions</strong>: ECT (modified or unmodified), electrode placement (bilateral vs unilateral), dosage, waveform, frequency of administration, number of ECT sessions</td>
<td><strong>Electronic databases</strong>: Biological Abstracts, 1966–1996; EMBASE, 1980–1996; MEDLINE, 1966–2001; PsycLIT, 1974–1996; Cochrane Schizophrenia Group Register up to 2001</td>
<td><strong>Blinded assessment</strong>: not reported</td>
<td><strong>Meta-analysis</strong>: fixed then random effects</td>
</tr>
<tr>
<td></td>
<td><strong>Comparators</strong>: placebo, sham ECT, pharmacological interventions, non-pharmacological interventions</td>
<td><strong>Other</strong>: citations of included studies were checked for additional trials and the first author of each trial published since 1980 was contacted for additional references and unpublished trials, manufacturers of ECT machines and the editorial board of the journal Convulsive Therapy were contacted for additional studies</td>
<td><strong>Study quality rating</strong>: Cochrane Collaboration Handbook categories A and B</td>
<td><strong>Heterogeneity</strong>: Mantel–Haenszel test, significance level &lt;0.10 = evidence of heterogeneity. If remained following use of random effects model, results were not pooled and sensitivity analysis was undertaken</td>
</tr>
<tr>
<td></td>
<td><strong>Populations</strong>: people with schizophrenia, schizoaffective disorder or chronic mental disorder (non-affective)</td>
<td><strong>Methods</strong>: two independent reviewers</td>
<td><strong>Sensitivity analysis</strong>: conducted where there was evidence of heterogeneity and to test the effect of including studies with high attrition rates</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Outcomes</strong>: <strong>Primary</strong>: clinically meaningful benefits in overall functioning, hospitalisation status, changes in mental state, behaviour, social and occupational functioning, remission of symptoms in the short term (&lt;6 weeks), medium term (6 weeks to 6 months) and long term (&gt;6 months). <strong>Secondary</strong>: premature withdrawal from trial by decision of either researcher or investigators and adverse events such as cognitive side-effects and mortality. Continuous data excluded if &gt;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</td>
<td><strong>Publication bias</strong>: funnel plot</td>
<td><strong>Subgroup analyses</strong>: defined a priori and tested for method of schizophrenia diagnosis, symptom profile, duration of illness and trial size</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Study types</strong>: all relevant RCTs with quality rating A or B according to the Cochrane Handbook</td>
<td><strong>Continuous data</strong>: pooled WMD</td>
<td><strong>Dichotomous data</strong>: relative risk, NNT, NNH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Confidence intervals</strong>: yes</td>
<td></td>
<td></td>
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</table>
TABLE 26  Systematic reviews of non-randomised evidence: patient acceptability and choice

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion/exclusion criteria</th>
<th>Search strategies</th>
<th>Data quality</th>
<th>Data synthesis methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURE, 2003^53</td>
<td><strong>Interventions/populations:</strong> research participants and all patients who provided testimonies that they had received ECT</td>
<td><strong>Electronic databases:</strong> psycINFO, MEDLINE, Web of Science and the King’s fund database, 1975–2001, Proquest newspaper database, Mental Health Media Testimony archive, searches of the Internet, e-mail forums and chat rooms</td>
<td><strong>Blinded assessment:</strong> not reported</td>
<td>Research studies: when research studies using a range of methodologies produced the same results, findings were presented in terms of ‘at least X% of patients’ experience Y’</td>
</tr>
<tr>
<td></td>
<td><strong>Outcomes:</strong> long-term memory loss, information and consent, felt compulsion to have ECT, perceived benefit and satisfaction with ECT</td>
<td><strong>Other:</strong> handsearches and contacting patient groups to identify unpublished literature</td>
<td><strong>Study quality rating:</strong> no</td>
<td>Testimonies: analysed using a mixture of content and discourse analysis; inter-rater reliability of allocating testimonies to categories was 83%; illustrative quotations presented to represent themes</td>
</tr>
<tr>
<td></td>
<td><strong>Study types:</strong> all forms of evidence from research studies and patient testimonies in which patients’ views about ECT were ascertained directly</td>
<td></td>
<td><strong>Methods:</strong> described a number of key methodological issues identified influencing the ability of the studies to reflect adequately and accurately patients’ views of ECT. These include the setting in which attitudes to ECT were elicited, who conducted the interview; the source of the sample included in the study; the interval since ECT; the depth and complexity of the questions asked, the degree to which the questions were value laden and the different scales</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 27  Systematic reviews of non-randomised evidence: children and adolescents

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion/exclusion criteria</th>
<th>Search strategies</th>
<th>Data quality</th>
<th>Data synthesis methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey and Walter, 1997^70, Walter et al., 1999^71</td>
<td><strong>Intervention:</strong> ECT</td>
<td><strong>Electronic databases:</strong> medical and psychological database (names not stated) up to March 1996</td>
<td><strong>Blinded assessment:</strong> yes</td>
<td>Meta-analysis: no</td>
</tr>
<tr>
<td></td>
<td><strong>Population:</strong> people aged ≤ 18 years who received ECT</td>
<td><strong>Other:</strong> manual searches to identify studies that assessed the effectiveness of ECT in people under the age of 18</td>
<td><strong>Study quality rating:</strong> yes</td>
<td>Other methods: data on outcome summarised by adding case series and reports together to produce an overall percentage of those with a good outcome after ECT (ITT) and at 6 months (not ITT) by diagnosis. Qualitative overview of data on adverse effects</td>
</tr>
<tr>
<td></td>
<td><strong>Outcomes:</strong> 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</td>
<td></td>
<td><strong>Methods:</strong> two independent raters rated study quality on several variables to obtain a quality score</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Study types:</strong> included if data on diagnosis and individual outcomes were provided, in all languages, all study types</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 28 Systematic reviews of non-randomised evidence: catatonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion/exclusion criteria</th>
<th>Search strategies</th>
<th>Data quality</th>
<th>Data synthesis methods</th>
</tr>
</thead>
</table>
| Hawkins et al., 1995<sup>78</sup> | **Interventions**: any intervention to treat catatonia, including ECT combined with pharmacotherapy and ECT alone  
**Populations**: studies providing 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 rated retrospectively by reviewers on a three-point scale: none, partial and complete  
**Study types**: all study types, written in English | **Electronic databases**: paperchase medical literature search system, 1985–1994  
**Other**: citation tracking from included studies | **Blinded assessment**: no  
**Study quality rating**: no | **Meta-analysis**: no  
**Other methods**: descriptive statistics of percentage of cases with each outcome by treatment type |

### TABLE 29 Systematic review of non-randomised evidence: use of ECT in pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion/exclusion criteria</th>
<th>Search strategies</th>
<th>Data quality</th>
<th>Data synthesis methods</th>
</tr>
</thead>
</table>
| Miller, 1994<sup>81</sup> | **Intervention**: ECT  
**Population**: pregnant women  
**Outcomes**: physiological effects of ECT during pregnancy, risk of ECT  
**Study types**: all | **Electronic databases**: MEDLINE, dates not reported  
**Other**: not reported | **Blinded assessment**: no  
**Study quality rating**: no | **Meta-analysis**: no  
**Other methods**: results summarised in terms of the percentage of cases reporting each complication |
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gregory et al., 1985</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: met MRC (1965) criteria for depression of &gt;1 month in duration and were right-handed</td>
<td>Comparison: real ECT vs sham ECT ECT: either unilateral or bilateral ECT at waveform 1 of the duopulse Mk IV machine twice weekly, number of treatments determined by clinical team in charge of the patient’s care. Right unilateral ECT in the tempoparietal position; bilateral in the bifrontotemporal position. Monitored using the cuff method and length of fits timed with a stopwatch</td>
<td>Continuous: MADRS, HRSD, PIRS, PSE (unusable, graph or mean change scores only, no mean or SD)</td>
<td>N randomised: 69, n completed: 48</td>
</tr>
<tr>
<td></td>
<td>Blinding: double-blind</td>
<td>Exclusion: severe physical illness or had already received ECT for current episode of illness</td>
<td>Comparator: sham ECT twice weekly as treatment group but with no electricity, number of ECTs determined by clinical team in charge of the patient’s care</td>
<td>Dichotomous: none</td>
<td>Length of follow-up: until end of ECT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: not specified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: not specified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>History: not specified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blinding: double-blind</td>
<td>Age: real ECT: mean (SD), 52 (11.1) (range 35–78) years; sham ECT: 53.3 (22.9) (26–82) years</td>
<td>Comparator: sham ECT: received anaesthesia as treatment group but no electricity twice a week for 3 weeks</td>
<td>Dichotomous: none</td>
<td>Length of follow-up: 3 weeks: until end of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: real ECT: 6 M, 5F; sham ECT: 7M, 4F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>History: all patients given 50 mg amitryptaline at night during the study. All had depression severe enough to warrant ECT and all had suicidal ideas. 16 had previously had unipolar illness and two had bipolar illness. No information on previous ECTs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^4]: Source information needed
### Table 30: RCTs of real versus sham ECT: depression (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
</table>
| Jagadeesh et al., 1992 | **Allocation**: B, unclear  
**Blinding**: double-blind | **Inclusion**: aged between 20 and 60 years, diagnosis of major depression endogenous subtype on Research Diagnostic Criteria. Present depressive episode untreated with ECT, antidepressants or antipsychotics, informed consent  
**Exclusion**: organic factors contraindicating ECT, current suicide attempt or suicide score >3 on HRSD  
**Age**: six real ECT: mean (SD) 39.92 (8.39) years; five sham ECT: 31.92 (6.34) (range 22–52) years  
**Gender**: real ECT: 5 M, 7 F; sham ECT: 5 M, 7 F  
**History**: first episode for 5/12 patients in real ECT and 2/12 in sham ECT group. Mean duration of current episode 2.91 months in real ECT and 1.92 months in sham ECT group. Mean initial HRSD score was 26.83 for real ECT and 26.17 for sham ECT | **Comparison**: six real vs one real + five sham ECT  
**ECT**: six real ECT: bifrontotemporal bilateral ECT, sine wave 120–150 V for 0.5–0.8 s three times per week for 2 weeks. Seizure monitored using the cuff method  
**Comparator**: one real + five sham received initial real ECT as for treatment group, plus five sham ECT where received anaesthesia but no electricity | **Continuous**: HRSD, GRSD  
**Dichotomous**: responder: a score of ≤2 on GRSD at end of treatment | **N randomised**: 24  
**n completed**: 23  
**Length of follow-up**: 2 weeks |

continued
### Table 30: RCTs of real versus sham ECT: depression (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
</table>
| Lambourn and Gill, 1978⁵⁵ | Allocation: C, quasi-randomised  
Blinding: double-blind | **Inclusion:** right-handed, diagnosis of depressive illness referred for ECT  
**Exclusion:** another psychiatric or organic disorder or received ECT within the previous 3 months  
**Age:** real ECT: mean 54.4 (range 36–69) years; sham ECT: mean 53.4 (37–66) years  
**Gender:** real ECT: 7 M, 9 F; sham ECT: 7 M, 9 F  
**History:** all ECT group inpatients, two sham ECT group outpatients. Eight real ECT and six sham ECT had previous failed courses of antidepressants. 11/16 in real ECT and 10/16 in sham ECT group had received at least one course of ECT in the past. Mean HRSD score was 25 for real ECT and 27 for sham ECT | **Comparison:** real ECT vs sham ECT  
ECT: unilateral right tempoparietal brief-pulse ECT at 10 J from Ectron Duopulse Mk IV three times a week for 2 weeks  
**Comparator:** sham ECT three times a week for 2 weeks, received anaesthesia but no electricity | **Continuous:** HRSD (15 item) (unusable, mean change only reported)  
**Dichotomous:** individual data presented, a priori decision by reviewer of a 50% reduction on HRSD | *N* randomised: 32  
*n* completed: 26  
Length of follow-up: 2 weeks |
TABLE 30 RCTs of real versus sham ECT: depression (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeman et al., 1978*</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: inpatients, aged 20–78 years, clinical diagnosis of depression and a minimum score of 15 on both the BDI and HRSD</td>
<td>Comparison: real ECT vs sham ECT</td>
<td>Continuous: HRSD, Wakefield Scale, BDI, VAS (usable, graph only)</td>
<td>N randomised: 40</td>
</tr>
<tr>
<td></td>
<td>Blinding: double-blind</td>
<td>Exclusion: depression secondary to other psychiatric illnesses such as schizophrenia, major or progressive physical illness, organic brain disease or received ECT in past 6 months</td>
<td>ECT: bilateral twice a week with bidirectional 60% sine-wave current of 400 V for a peak of 1.5 s from Ectron Mk IV machine. Number of ECTs titrated against treatment outcome, and number ranged from three to 12 ECTs</td>
<td>Dichotomous: clinical judgement of a 'satisfactory response'</td>
<td>n completed: 38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: real ECT: mean 51 years; sham ECT: mean 50.5 years</td>
<td>Comparator: sham ECT: first two treatments were sham ECTs where patients received anaesthesia but no electric current; remaining ECTs were real, as above</td>
<td>Length of follow-up: not specified, but outcome measurement occurred after last ECT</td>
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<tr>
<td></td>
<td></td>
<td>Gender: real ECT: 6 M, 14 F; sham ECT: 5 M, 15 F</td>
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<tr>
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<td>History: 50% of real ECT and 60% of sham ECT had received ECT before, and 14 real and 14 sham ECT had one or more previous episodes of depression. Seven real and 11 sham ECT were taking some sort of antidepressant medication. 25% in each group had had previous manic illness</td>
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<tr>
<td>Study</td>
<td>Methods</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Number and follow-up</td>
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</table>
| Johnstone et al., 1980 | Allocation: B, unclear  
Blinding: double-blind | **Inclusion:** aged 30–69 years, met MRC criteria for depressive illness, Feighner criteria for primary depressive illness, Newcastle criteria for endogenous depressive illness, Newcastle criteria for predicting a good outcome to ECT  
**Exclusion:** poor anaesthetic risk  
**Age:** mean 49.4 years  
**Gender:** 18 M, 52 F  
**History:** 46 had definite previous episodes of depressive illness and seven had definite previous episodes of mania. 15 patients had received ECT for a previous episode (21%). 49 patients had had antidepressant prescribed for the index episode before the trial | **Comparison:** real ECT vs sham ECT  
**ECT:** eight treatments of twice-weekly bifrontal ECT using Duopulse waveform 1 at 150 V for 3 s over 4 weeks. Confirmation that a convulsion had taken place was done using the cuff method  
**Comparator:** sham ECT: received anaesthesia and muscle relaxants, but no electricity was passed | **Continuous:** HRSD, HAD (then the ‘Leeds Scale’), memory tests, Bunney and Hamburg NRS (unusable, graph only)  
**Dichotomous:** HRSD 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 |

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**TABLE 30 RCTs of real versus sham ECT: depression (cont’d)**

continued
### TABLE 30: RCTs of real versus sham ECT: depression (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
</table>
| Brandon et al., 1984¹⁰ | Allocation: A, concealed  
Blinding: double-blind | **Inclusion**: all patients prescribed for inpatient ECT (n = 219). 186 interviewed and 48 refused treatment; of remaining patients, 95 had depression and 43 had no depressive diagnoses. Total of 138 entered trial  
**Age**: real ECT: mean 55.4 years; sham ECT: mean: 53 years  
**Gender**: real ECT: 21 M, 32 F; sham ECT: 13 M, 29 F  
**History**: mean number of previous admissions 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 before the trial. 55% in the real and 65% in the sham ECT group had received ECT before | **Comparison**: real ECT vs sham ECT  
ECT: bilateral using chopped sine-wave current from Ectron Mk IV machine on setting I twice a week for 4 weeks. Received a maximum of eight but clinician could withdraw patient if deterioration occurred. Patient carefully observed to ensure fit took place  
**Comparator**: sham ECT: received ECT procedure as for control group, but without electricity | **Continuous**: HRSD (unable, graphs only) |  
N randomised: 95  
n completed: 77  
Length of follow-up: until end of treatment |

M, male; F, Female; PIRS, Psychological Impairments Scale; NRS, Nurses’ Rating Scale; GRSD, Global Rating Scale for Depression; VAS, visual analogue scale; HAD, Hospital Anxiety and Depression scale.
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinan and Barry, 1989</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: fulfilled DSM-II for major depression; score &gt;20 on HDRS; Newcastle endogenicity score &gt;5</td>
<td>Comparison: ECT vs TCA + lithium</td>
<td>Continuous: HRSD</td>
<td>N randomised: 30</td>
</tr>
<tr>
<td></td>
<td>Blinding: clinician</td>
<td></td>
<td>ECT: bilateral, six treatments over 3 weeks, other stimulus parameters not specified (n = 15)</td>
<td>Dichotomous: unclear, no a priori definition, independent clinician unclear</td>
<td>n completed: 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclusion: not on any other medication</td>
<td>Comparator: TCA + lithium: remained on prestudy dose of TCA with lithium added initially at a dose of 600 or 800 mg and dose adjusted to obtain serum lithium between 0.5 and 0.7 mEq ††</td>
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<td>Length of follow-up: 3 weeks</td>
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<td>Age: 29–77 years</td>
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<td>Gender: 10 M, 20 F</td>
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<td></td>
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<td>History: all had failed to respond to a full course of TCAs, defined as ≥150 mg of anitryptaline for ≥4 weeks and failure of HRSD to drop by 40%, or at least to fall by 20 points. 11 had previously received ECT and 28 had a previous history of depression. Mean duration of current episode was 6.1 months in lithium group and 7.7 in ECT group</td>
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<tr>
<td>Study</td>
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<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
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<tr>
<td>Folkerts et al., 1997</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: fulfil ICD-10 criteria for major depression; score of ≥ 22 on the HDRS 21-item version; relative therapy resistance, defined as at least two different antidepressants (including at least one TCA) at a dosage of ≥ 100 g imipramine or equivalent and no improvement for a total period of 8 weeks</td>
<td><strong>Comparison</strong>: ECT vs SSRI</td>
<td>Continuous: HRSD (21 item)</td>
<td>N randomised: 43</td>
</tr>
<tr>
<td></td>
<td>Blinding: unclear</td>
<td>Exclusion: Major depressive disorder with psychotic features, pronounced suicidal tendencies, severe physical illness or history of substance abuse; previous paroxetine or ECT for current episode; aged &gt; 80 years</td>
<td><strong>ECT</strong>: right unilateral at 2.5 supratreshold, brief pulse (1 ms, 0.9 A) performed with a Thymatron-DGx three times per week. Mean number of ECTs received: 7.2 (n = 21)</td>
<td>Dichotomous: responder defined as reduction of ≥ 50% on HRSD 21-item version</td>
<td>n completed: 39</td>
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<tr>
<td></td>
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<td>Age: ECT group: mean (SD) 47.6 (14.7) years; paroxetine group: 52.3 (15.7) years</td>
<td><strong>Comparator</strong>: paroxetine (SSRI): starting dose 20 mg day⁻¹, 40 mg within 7 days with a maximum of 50 mg. Mean end dose 44 mg day⁻¹</td>
<td>Length of follow-up: until end of ECT or 4 weeks</td>
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<td></td>
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<td>Gender: 18 M, 21 F; gender of dropout not specified</td>
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<td>History: all treatment resistant with a mean of 4–5 previous antidepressant trials. Baseline HRSD was 31.1 in ECT group and 32.6 in paroxetine group. Current episode lasted for a mean of 59.8 weeks in ECT group and 75.2 in paroxetine group</td>
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</table>
### TABLE 31  RCTs of ECT versus pharmacotherapy: depression (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herrington et al., 1974</td>
<td>Allocation: B, unclear Blinding: none</td>
<td>Inclusion: physically healthy adults aged 25–69 years with a primary diagnosis of depression. The severity of their illness was such that immediate admission to hospital and ECT were considered appropriate Age: ECT: 54.8 years; l-tryptophan: 52.7 years Gender: ECT: 6 M, 15 F; l-tryptophan: 7 M, 15 F History: mean duration of current episode: ECT: 4.1 months; l-tryptophan: 6.1 months; mean number of previous episodes ECT: 2.4; l-tryptophan 1.6</td>
<td>Comparison: ECT vs l-tryptophan ECT: administered twice a week, for a total of six to eight treatments. Option for cross-over if no success after 2 weeks Comparator: l-tryptophan, 6 g day⁻¹ for first 2 weeks and 8 g day⁻¹ for the second 2 weeks. Option for cross-over if no success after 2 weeks</td>
<td>Continuous: MRC depression scale, HRSD, BDI, Taylor Manifest Anxiety Scale (unusable, graphs only) Dichotomous: clinical opinion of response, not defined</td>
<td>N randomised: 40 n completed: 38 Length of follow-up: 6 months</td>
</tr>
<tr>
<td>Bruce et al., 1960</td>
<td>Allocation: B, unclear Blinding: not blind</td>
<td>Inclusion: suffering from depression, considered to be sufficiently ill to require ECT. 49/50 had endogenous depression (no details on the remaining patient) Exclusion: not recorded Age: no data Gender: no data History: no data</td>
<td>Comparison: ECT vs TCA ECT: average 6.1 treatments in first month Comparator: imipramine (Tofranil, TCA) rising to 75 mg t.d.s. or less if patient was responding well</td>
<td>Continuous: none Dichotomous: clinical opinion as responder (not defined)</td>
<td>N randomised: 50 n completed: 49 Length of follow-up: 1 month and 3 months</td>
</tr>
</tbody>
</table>
### Table 31: RCTs of ECT versus pharmacotherapy: depression (cont'd)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner et al., 1978&lt;sup&gt;107&lt;/sup&gt;</td>
<td>Allocation: A, concealed</td>
<td>Inclusion: met criteria for endogenomorphic depression as defined by Klein&lt;sup&gt;265&lt;/sup&gt;</td>
<td>Comparison: ECT vs TCA + placebo vs TCA + L-triiodothyronine</td>
<td>Continuous: personal data inventory, CGI, HRSD, Side-Effect Symptom Scale</td>
<td>N randomised: 12 n completed: 12</td>
</tr>
<tr>
<td>Blinding: not blind</td>
<td>Exclusion: known endocrine or cardiovascular disorders, CNS disorders including brain trauma or convulsive disorders, drug addiction or mental deficiency and treated with ECT at any time in the past 6 months</td>
<td>ECT: bilateral twice a week until improvement was noticed, but no more than ten treatments allowed. Waveform, dosage and machine not specified</td>
<td>Dichotomous: responder defined as moderate or marked improvement on CGI and a total score on HRSD of ≤10 (50% reduction in HRSD also gives same result)</td>
<td>Length of follow-up: 5 weeks</td>
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<tr>
<td></td>
<td>Age: mean 55.5 (range 30–60) years</td>
<td>Comparator: (1) imipramine 150 g plus placebo for 5 weeks; (2) imipramine 150 mg plus L-triodothyronine</td>
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<tr>
<td></td>
<td>Gender: all F</td>
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<tr>
<td></td>
<td>History: mean number of previous episodes of depression 2.4, and a family history of depression in four patients. All had been currently depressed for 6 weeks and had been unsuccessfully treated in an outpatient treatment trial (definition not specified)</td>
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<tr>
<td>Greenblatt and Grosser, 1964&lt;sup&gt;113&lt;/sup&gt;</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: all patients admitted with a symptomatology of severe depression, regardless of dynamics or specific diagnostic category. The major diagnostic categories comprised psychoneurosis, manic depression, involution, schizophrenic reactions, schizoaffective type and a mixed category of character</td>
<td>Comparison: ECT vs TCA vs MAOI</td>
<td>Continuous: none</td>
<td>N randomised: 281 n completed: 281</td>
</tr>
<tr>
<td>Blinding: unclear</td>
<td>Exclusion: patients with severe organic brain syndromes, chronic alcoholism or drug addiction</td>
<td>ECT: three times per week</td>
<td>Dichotomous: clinician opinion of 'marked improvement': the patient is practically symptom free and capable of functioning in the community</td>
<td>Length of follow-up: until end of treatment</td>
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<tr>
<td></td>
<td>Age: M 46.8 years, F 45.4 years</td>
<td>Comparator: imipramine (Tofranil, TCA) 200 mg + optional 50 mg, phenelzine (Nardil, MAOI) 60 mg + optional 15 mg, or isocarboxazid (Marplan, MAOI) 40 mg + optional 10 mg</td>
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</table>
## TABLE 31 RCTs of ECT versus pharmacotherapy: depression (cont'd)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
</table>
| Gangadhar et al., 1982110  | Allocation: B, unclear | Inclusion: fulfilled criteria for major depressive episode according to ICD-10 as judged independently by two psychiatrists. Two had bipolar depression, the others had either single or recurrent major depression | **Comparison:** ECT vs TCA  
ECT: modified bilateral using 150–250 mg of thiopentone, 20–30 mg of succinylcholine and 0.65 mg of atropine. Six ECTs on alternate days for the first 2 weeks and one ECT each week in the next 2 weeks. Three maintenance ECTs were administered in the next 8 weeks during weeks 6, 8 and 12 of the trial period  
Comparator: Imipramine (TCA) (25 mg) three per day week 1, six per day weeks 2–11 and three per day during week 12 | Continuous: HRSD, social dysfunction and organic brain dysfunction battery, side-effects checklist (unusable, medians, no SD) | N randomised: 32  
n completed: 24  
Length of follow-up: 6–12 months |
|                            | Blinding: double-blind | Exclusion: patients treated with any psychopharmacological agents except for benzodiazepines in the past month, those who had received ECT for the current depressive episode and patients who had major physical illnesses | Age: ECT: mean (SD) 46.06 (11.80) years, imipramine: 42.19 (12.66) years  
Gender: ECT 9 M, 7 F; imipramine: 5 M, 11 F  
History: past history of affective illness: ECT: depression 3, mania 3, both 1; imipramine: depression 2, mania 1. Family history of affective illness: ECT: 0; imipramine: 3. Duration of illness: ECT: <3 months 10, >3 months 6; imipramine: <3 months 7, >3 months 9 | **Dichotomous:** none |
TABLE 31 RCTs of ECT versus pharmacotherapy: depression (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald et al., 1966</td>
<td><strong>Allocation:</strong> B, unclear</td>
<td><strong>Inclusion:</strong> all new admissions eligible to receive ECT; <strong>Exclusion:</strong> organic complications to contraindicate drugs or ECT, antidepressants in past 2 weeks, unable to speak English</td>
<td><strong>Comparison:</strong> ECT vs TCA vs sham ECT</td>
<td><strong>Continuous:</strong> MMPI, WBIS, BGT, unvalidated depression scale (unsuitable, no SD)</td>
<td>N randomised: 30 n completed: 30 Length of follow-up: until end of treatment</td>
</tr>
<tr>
<td></td>
<td><strong>Blinding:</strong> double-blind</td>
<td><strong>Age:</strong> 20–65 years</td>
<td><strong>ECT:</strong> electrode placement unclear; minimum of eight treatments, three times a week</td>
<td><strong>Dichotomous:</strong> none</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Gender:</strong> 11 M, 19 F</td>
<td><strong>Comparator:</strong> amitriptyline (TCA) 20 mg i.m. for 3 days, 50 mg orally for remainder of 1-month trial period. Sham ECT was delivered while the patient was unconscious through injection of thiopental sodium (Pentothal, barbiturate)</td>
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<tr>
<td></td>
<td></td>
<td><strong>History:</strong> none (new admissions)</td>
<td>Continuous ECT and non-ECT</td>
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</table>

Janakiramaiah et al., 2000 | **Allocation:** B, unclear | **Inclusion:** patients with DSM-IV melancholic depression who were never treated for the current episode, medically fit, HRSD ≥ 17 | **Comparison:** ECT vs TCA vs yoga | **Continuous:** BDI, HRSD (17 item) | N randomised: 45 n completed: 45 Length of follow-up: 4 weeks |
| | **Blinding:** not blind | **Age:** ECT: mean (SD) 36.7 (2.5) years; imipramine: 43.4 (11.9) years; Yoga: 36.0 (7.8) years | **ECT:** bilateral, three times a week. The stimulus was set 60 mC above threshold (determined on the first and seventh ECT). Mean (SD) number of ECT sessions 8.9 (3.3). Seizures of 25 s on EEG or 15 s on motor were ensured in all sessions | **Dichotomous:** remitters defined as HRSD 17-item score <8 | |
| | | **Gender:** ECT: 6 M, 9 F; imipramine: 10 M, 5 F; yoga: 9 M, 6 F | **Comparator:** imipramine (Tofranil, TCA) 150 mg once daily for 4 weeks, no other psychotropic drugs; or Sudarshan Kriya yoga for 45 minutes; 6 days a week, mean (SD) number of sessions 20.3 (2.8) | | |
| | | **History:** duration of current episode: mean (SD) ECT: 4.8 (3.3) months; imipramine: 5.4 (3.5) months; yoga: 3.8 (2.8) months. Recurrent: ECT: 3; imipramine 2; yoga: 4 | | |
### TABLE 31 RCTs of ECT versus pharamotherapy: depression (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
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</thead>
<tbody>
<tr>
<td>Wilson et al., 1963&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Allocation: B, unclear, Blinding: unclear</td>
<td>Inclusion: all women aged 40–59 years admitted to a psychiatric hospital with depressive symptoms</td>
<td>Comparison: ECT + TCA vs ECT + placebo vs sham ECT + imipramine</td>
<td>Continuous: HRSD, MMPI-D (unusable, graph or mean change only reported)</td>
<td>N randomised: 24, n completed: 22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclusion: schizophrenia and organic brain disorder</td>
<td>ECT: two treatments per week for a total of six treatments, electrode placement, dosage waveform and machine not specified</td>
<td>Dichotomous: none</td>
<td>Length of follow-up: 5 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: 40–59 years</td>
<td>Comparator: imipramine: mean dose 150 g in the first and last thirds of the study, 220 g in the middle third of the study</td>
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<td></td>
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<td>Gender: all F</td>
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<tr>
<td></td>
<td></td>
<td>History: not specified</td>
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<tr>
<td>Shepherd, 1965&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Allocation: B, unclear, Blinding: unclear</td>
<td>Inclusion: aged 40–69 years, previous duration of illness &lt;18 months, depressive illness</td>
<td>Comparison: ECT vs TCA vs MAOI vs placebo</td>
<td>Continuous: physician’s rating on 15 symptoms (unvalidated) (unusable, no SD)</td>
<td>N randomised: 269, n completed: 250</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclusion: treatment during past 6 months with either ECT or adequate trial of pharamotherapy, depression secondary to other psychiatric illness such as schizophrenia or an obsessional state, physical disease such as malignancy, organic cerebral disease</td>
<td>ECT: four to eight treatments within first 3.5 weeks of trial, according to physician’s judgement</td>
<td>Dichotomous: clinical opinion of wholly or almost without symptoms</td>
<td>Length of follow-up: 4, 8, 12 and 24 weeks and immediately postdischarge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: ECT: mean 55.4 years; imipramine: 54.8 years; phenelzine: 54.7 years; placebo: 56.3 years</td>
<td>Comparator: 50 mg of imipramine, 15 mg of phenelzine or 15 mg of placebo, with two tablets on day 1, three on day 2, four on days 3–28, four on days 29–56, two on days 57–84 and one on days 85 and 112</td>
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<td></td>
<td></td>
<td>Gender: completers: ECT: 24 M, 42 F; imipramine: 22 M, 41 F; phenelzine: 18 M, 43 F; placebo: 17 M, 44 F</td>
<td>Comparator: 50 mg of imipramine, 15 mg of phenelzine or 15 mg of placebo, with two tablets on day 1, three on day 2, four on days 3–28, four on days 29–56, two on days 57–84 and one on days 85 and 112</td>
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<tr>
<td></td>
<td></td>
<td>History: number rated severely ill: ECT: 35/65; imipramine: 27/63; phenelzine: 20/61; placebo: 16/65</td>
<td>Comparator: 50 mg of imipramine, 15 mg of phenelzine or 15 mg of placebo, with two tablets on day 1, three on day 2, four on days 3–28, four on days 29–56, two on days 57–84 and one on days 85 and 112</td>
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continued
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanley and Fleming, 1962</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: patient suffering from depression and where ECT was normally indicated</td>
<td>Comparison: ECT vs MAOI</td>
<td>Continuous: nine 'depressive scales' found to be valid by Foulds and Caine (unusable, no SD)</td>
<td>N randomised: 47</td>
</tr>
<tr>
<td></td>
<td>Blinding: clinician</td>
<td>Exclusion: not reported</td>
<td>ECT: three times a week; total number of treatments determined by response, usually six to eight</td>
<td></td>
<td>n completed: 38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: ECT: mean 43.8 years; phenelzine 51.3 years</td>
<td>Comparator: phenelzine (MAOI)</td>
<td></td>
<td>Length of follow-up: 1 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: all F</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>History: acute admissions</td>
<td></td>
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<tr>
<td>MacSweeney, 1975</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: not reported</td>
<td>Comparison: ECT vs L-tryptophan</td>
<td>Continuous: BDI (unusable, no SD)</td>
<td>N randomised: 27</td>
</tr>
<tr>
<td></td>
<td>Blinding: not blind</td>
<td>Exclusion: not reported</td>
<td>ECT: unilateral ECT administered twice weekly</td>
<td>Dichotomous: none</td>
<td>n completed: 25</td>
</tr>
<tr>
<td>Kendrick et al., 1965</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: elderly patients admitted to Bethem Royal Hospital suffering from affective disorder</td>
<td>Comparison: ECT vs TCA + TCA</td>
<td>Continuous: MILL HILL VOCABULARY SCALE, RAVEN'S COLOURED PROGRESSIVE MATRICES, WAIS, SYNONYM LEARNING TEST, ING'S PAIRED ASSOCIATE LEARNING TEST, DIGIT COPYING TEST (unusable, no symptom scales reported)</td>
<td>N randomised: 69</td>
</tr>
<tr>
<td></td>
<td>Blinding: unclear</td>
<td>Exclusion: not reported</td>
<td>ECT: not reported</td>
<td></td>
<td>n completed: 68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: elderly, but age not reported</td>
<td>Comparator: imipramine andTrofranil</td>
<td></td>
<td>Length of follow-up: not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: 32 M, 34 W</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>History: not reported</td>
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</table>

**TABLE 31 RCTs of ECT versus pharmacotherapy: depression (cont’d)**
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davidson et al., 1978</td>
<td>Allocation: A, concealed Blinding: clinician</td>
<td>Inclusion: unipolar depression or depression secondary to anxiety or character disorder as defined by the Feighner criteria and therapy resistant (no definition given)</td>
<td>Comparison: ECT vs TCA + MAOI</td>
<td>Continuous: HRSD, BDI, State Trait Anxiety (mean and SE)</td>
<td>N randomised: 19 n completed: 17 Length of follow-up: unclear: 3–5 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: ECT mean 40.7 years; pharmacotherapy 41.5 years</td>
<td>ECT: bilateral, minimum of four and maximum of ten, three times per week, with the mean number of ECTs received 5.4. Dosage, waveform and machine not specified</td>
<td>Dichotomous: none</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Gender: ECT: 2M, 7 F; pharmacotherapy: 3 M, 5 F</td>
<td>Comparator: combination of MAOI (phenelzine) and TCA (amitryptaline): initiated with amitryptaline up to 100 mg for 5–7 days with addition of 15 mg of phenelzine up to a maximum of 45 mg for a minimum of 3 weeks. Mean daily dose was 34 mg of MAOI and 71 mg of TCA</td>
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<td></td>
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<td>History: all were treatment resistant to conventional psychotropic drugs in clinically adequate doses. Baseline mean HRSD scores were 26.5 in ECT group and 22.8 in pharmacotherapy group. The pharmacotherapy group had a greater mean number of previous illnesses (2.5) than the ECT group (1.1)</td>
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<tr>
<td>Bagadia et al., 1981</td>
<td>Allocation: B, unclear Blinding: double-blind</td>
<td>Inclusion: aged 18–65 years, clear depression of non-organic cause, score ≥ 16 on HRSD (17-item version), score of ≥ 12 on BDI Exclusion: treatment with antidepressant or antipsychotic drugs within the previous 3 weeks, with ECT or insulin therapy within the previous 8 weeks, organic brain syndrome, convulsive disorder and physical illness Age: actual age of participants not reported Gender: both, numbers not reported History: not reported</td>
<td>Comparison: ECT + placebo vs TCA + sham ECT</td>
<td>Continuous: HRSD, BDI, BPRS, Clinical Global Assessment, cognitive test battery (usable, HRSD not reported)</td>
<td>N randomised: 35 n completed: 20 Length of follow-up: until end of ECT course</td>
</tr>
<tr>
<td></td>
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<td>ECT: bilateral with stimulus of 110 V a.c. for approx. 0.5 s. One person received eight ECTs, the others received six ECTs. Three ECTs were given in the first week and two in the following week. Comparator: imipramine 25 mg with an initial dose of two tablets a day increased to six tablets a day, up to 150 mg. Placebo was calcium lactate 300 mg</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson and Smedberg, 1963</td>
<td>Allocation: A, concealed</td>
<td>Inclusion: not specified</td>
<td>Comparison: ECT vs TCA vs MAOI</td>
<td>Continuous: unvalidated depression scale (unsuitable, no SD)</td>
<td>N randomised: 200</td>
</tr>
<tr>
<td></td>
<td>Blinding: patient</td>
<td>Exclusion: not specified</td>
<td>ECT: no description given</td>
<td></td>
<td>n completed: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: not specified</td>
<td>Comparator: imipramine up to 250 mg day⁻¹; parstelin one tablet t.d.s.; amitryptaline up to 75 mg t.d.s; pheniprazine 12 mg day⁻¹; phenelzine 15 mg t.d.s.; chloropropothixene 120 mg day⁻¹ up to 180 mg day⁻¹. 25 people in each group, except for imipramine (n = 50)</td>
<td>Dichotomous: none</td>
<td>Length of follow-up: 3 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: all F</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>History: not specified</td>
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</tr>
<tr>
<td>Robin and Harris, 1962</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: not specified</td>
<td>Comparison: ECT + placebo vs TCA + sham ECT</td>
<td>Continuous: Immobility Index, Clinical Item score, HRSD, Behaviour Score (unsuitable; not reported)</td>
<td>N randomised: 31</td>
</tr>
<tr>
<td></td>
<td>Blinding: clinician</td>
<td>Exclusion: not specified</td>
<td>ECT: ECT plus placebo biweekly</td>
<td></td>
<td>n completed: 31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: not specified</td>
<td>Comparator: imipramine (TCA) + anaesthesia biweekly</td>
<td>Dichotomous: clinical opinion of marked or moderate improvement</td>
<td>Length of follow-up: 3 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: not specified</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>History: not specified</td>
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</table>

CGI, Clinical Global Impression; MMPI, Minnesota Multiphasic Personality Inventory; BGT, Bender Gestalt Test; WAIS, Weschler Adult Intelligence Scale.
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pridmore, 2000&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Allocation: A, concealed Blinding: clinician</td>
<td>Inclusion: medication-resistant major depressive episode, diagnosis of MDD (DSM-IV) Exclusion: not recorded Age: ECT alone: median 48 (range 25–70) years; ECT + rTMS: median 46 (26–58) years Gender: ECT alone: 5 M, 6 F; ECT + rTMS: 6 M, 5 F History: not recorded</td>
<td>Comparison: ECT vs ECT + rTMS ECT: non-dominant hemisphere unilateral; three times a week for 2 weeks; number of treatments and dosage according to age-based protocol in instruction manual (percentage of 504 mC equivalent to the patient’s age) Comparator: rTMS (Magstim Super Rapid stimulator) and Magstim 70 mm double coil; intensity 100%, frequency 20 Hz, train length 2 s, number of trains 30, intertrain interval 20 s</td>
<td>Clinical response defined as MADRS of ≤ 12 and HRDS of ≤ 8; VAS one-item scale, GAF; side-effects: six-item subjective side-effects questionnaire derived from Gomez&lt;sup&gt;276&lt;/sup&gt;</td>
<td>N: 23</td>
</tr>
<tr>
<td>Grunhaus et al., 2000&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Allocation: B, unclear Blinding: patient</td>
<td>Inclusion: aged 18+ years, DSM-IV diagnosis of MDD, 17-item HRSD score of ≥ 18, no personal or first degree relative history of seizure, no medical, neurological or neurosurgical disorder that would preclude the administration of ECT or rTMS Exclusion: additional DSM-IV axis I diagnoses Age: ECT: mean (SD) 63.6 (15.0) years; ECT + rTMS: 58.4 (15.7) years Gender: ECT: F 14, M 6; RTMS: F 12, M 8 History: duration of episode: ECT: mean (SD) 6.9 (7.9) months; rTMS: 8.3 (7.4) months; previous episodes: ECT: 2.4 (3.05) months; rTMS: 2.3 (2.85) months; previous ECT: ECT: 9/20; rTMS: 14/20</td>
<td>Comparison: ECT vs rTMS ECT: non-dominant unilateral, switched to bilateral electrode placement if no improvement. Waveform brief-pulse bidirectional current. Mean number of treatments 9.6 (range 7–14) Comparator: 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)</td>
<td>HRSD, BPRS, GAF, GRSD, PSQI</td>
<td>N: 40</td>
</tr>
<tr>
<td>Study</td>
<td>Methods</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Number and follow-up</td>
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</table>
| Mayur et al.,    | Allocation: B, unclear Blinding: unclear                                     | Inclusion: DSM-IV major depression                                             | Comparison: ECT + TCA/SSRI vs ECT + placebo                                | Continuous: HRSD (17 item), MADRS, UKU subscales 1–3                     | N randomised: 30  
| 2000<sup>56</sup> |           | Exclusion: neurological and cardiological disorders                          | ECT: non-dominant d’Elia unilateral ECT<sup>118</sup> three times a week: machine waveform; dosage 30 mC upwards in steps to threshold stimulus dose (at least 25 s of EEG seizure) (n = 15) | Dichotomous: relapses defined as HRSD > 7                                | n completed: 30      |
|                  |           | Age: group 1: mean (SD) 33.8 (8.0) years; group 2: 34.6 (11.9) years         | Comparator: TCA (n = 26), fluoxetine (SSRI) (n = 4)                           |                                                                           | Length of follow-up: 2 weeks                                           |
|                  |           | Gender: group 1: 6 M, 9 F; group 2: 8 M, 7 F                                |                                                                             |                                                                           |                       |
|                  |           | History: previously on antidepressant drugs with or without psychotropics; previous ECT use unclear. Group 1: episode number: mean (SD) 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 (56%) had an adequate drug trial |                                                                             |                                                                           |                       |
|                  |           |                                                                             |                                                                             |                                                                           |                       |
| Shiah et al.,    | Allocation: B, unclear Blinding: unclear                                     | Inclusion: people routinely referred for ECT because of treatment-resistant depression, depression characterised by psychotic features or acute suicidality | Comparison: ECT + pindolol vs ECT + placebo                                  | Continuous: HRSD (29 item), CGI                                           | N randomised: 20  
| 2000<sup>57</sup> |           | Exclusion: other DSM-IV axis I diagnoses, past alcohol or substance abuse, contraindications to the use of β-blockers, received fluoxetine within 5 weeks or MAOIs within 2 weeks | ECT: Stimulus delivered at just above threshold for bilateral ECT and three times above threshold for unilateral ECT, three times a week for 2 weeks | Dichotomous: responder defined as HRSD (29 item) score of ≤ 12 after sixth treatment | n completed: 15      |
|                  |           | Age: completers: ECT plus pindolol: mean (SD) 50 (9.3) years; ECT plus placebo: 45.8 (6.3) years | Comparator: pindolol: 2.5 mg orally, three times a day; placebo: 2.5 mg orally, three times a day |                                                                           | Length of follow-up: 2 weeks                                           |
|                  |           | Gender: completers: 5 M, 10 F                                               |                                                                             |                                                                           |                       |
|                  |           | History: five in Pindolol and four in placebo group were treatment resistant |                                                                             |                                                                           |                       |

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
</table>
| Shiah et al.,    | Allocation: B, unclear Blinding: unclear                                     | Inclusion: people routinely referred for ECT because of treatment-resistant depression, depression characterised by psychotic features or acute suicidality | Comparison: ECT + pindolol vs ECT + placebo                                  | Continuous: HRSD (29 item), CGI                                           | N randomised: 20  
| 2000<sup>57</sup> |           | Exclusion: other DSM-IV axis I diagnoses, past alcohol or substance abuse, contraindications to the use of β-blockers, received fluoxetine within 5 weeks or MAOIs within 2 weeks | ECT: Stimulus delivered at just above threshold for bilateral ECT and three times above threshold for unilateral ECT, three times a week for 2 weeks | Dichotomous: responder defined as HRSD (29 item) score of ≤ 12 after sixth treatment | n completed: 15      |
|                  |           | Age: completers: ECT plus pindolol: mean (SD) 50 (9.3) years; ECT plus placebo: 45.8 (6.3) years | Comparator: pindolol: 2.5 mg orally, three times a day; placebo: 2.5 mg orally, three times a day |                                                                           | Length of follow-up: 2 weeks                                           |
|                  |           | Gender: completers: 5 M, 10 F                                               |                                                                             |                                                                           |                       |
|                  |           | History: five in Pindolol and four in placebo group were treatment resistant |                                                                             |                                                                           |                       |

continued
### TABLE 33 RCTs of ECT plus pharmacotherapy versus ECT plus placebo/pharmacotherapy only: depression (cont’d)

<table>
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<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
</table>
| D’Elia et al., 1977    | Allocation: B, unclear       | 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 tendencies and diurnal rhythm with amelioration of symptoms in the evening. Aetiological, endogenous symptoms. Severity severe enough that ECT considered the treatment of choice by doctor responsible. Exclusion: patients aged > 65 years, somatic disease that could have a relation to the depressive period, pregnant patients or patients given ECT in the past 3 months. Age: ECT + placebo: mean (SD) 46.1 (12.7) years; ECT + L-tryptophan 48.3 (12.4) years. Gender: ECT + placebo: 12 M, 18 F; ECT + L-tryptophan: 11 M, 20 F. History: previous treatment: 40/61 antidepressants in previous periods; 24/61 antidepressants in present period. 24/61 had had previous ECT courses. Duration of present period: 0.5–6.5 months. | Comparison: ECT + L-tryptophan vs ECT + placebo. ECT: unilateral stimulation on the non-dominant hemisphere. Number of treatments: individual: mean (SD) ECT + placebo 6.1 (2.1); ECT + L-tryptophan: 6.3 (2.5). Frequency not clear, may be available from d'Elia. Machine waveform not clear (n = 30). Comparator: ECT as above plus: L-tryptophan, class unknown, dosage 6 g daily, initiated at least 1 day before first ECT and terminated 4 days after last ECT. | Continuous: CODS, NRS, HRSD (unusable, no SD) | N randomised: 61  
 n completed: 57  
 Length of follow-up: 1 month |
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arfwidsson et al., 1973</td>
<td>Allocation: B,</td>
<td>Inclusion: endogenous or mixed endogenous depression</td>
<td>Comparison: ECT + C.ATP vs ECT + C.placebo</td>
<td>Continuous: CODS (unusable, no SD)</td>
<td>N randomised: 57</td>
</tr>
<tr>
<td></td>
<td>unclear</td>
<td>Exclusion: aged ≥ 65 years</td>
<td>ECT: bifrontotemporal electrodes, threshold stimulation with unidirectional stimuli. Initially three times a week, later two or one treatment(s) determined by clinical effect</td>
<td>Dichotomous: clinical opinion of recovered or much improved (responder), or slightly improved or resistant (non-responder)</td>
<td>n completed: 57</td>
</tr>
<tr>
<td></td>
<td>Blinding: patient</td>
<td>Age: chlorpromazine: mean 45.7 (range 19–64) years; placebo: 47.5 (22–63) years</td>
<td>Comparator: chlorpromazine 50–150 mg for 32 days with augmented daily dose 106 mg</td>
<td>Length of follow-up: 4–5 days after end of treatment</td>
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<tr>
<td></td>
<td></td>
<td>Gender: chlorpromazine: 11 M, 17 F; placebo: 14 M, 14 F</td>
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<tr>
<td></td>
<td></td>
<td>History: 24/57 had received ECT previously; 31/57 had received antidepressant medication during the current episode</td>
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<tr>
<td>Kirkegaard et al., 1978</td>
<td>Allocation: B,</td>
<td>Inclusion: not recorded</td>
<td>Comparison: ECT + L-tryptophan vs ECT + placebo</td>
<td>Continuous: HRSD (17 item) (unusable, graph only)</td>
<td>N randomised: 20</td>
</tr>
<tr>
<td></td>
<td>unclear</td>
<td>Exclusion: not recorded</td>
<td>ECT: unilateral (side unclear); number of treatments unclear; twice a week; machine waveform unclear, dosage unclear</td>
<td>Dichotomous: none</td>
<td>n completed: 20</td>
</tr>
<tr>
<td></td>
<td>Blinding: double-blind</td>
<td>Age: both groups: mean 63 years</td>
<td></td>
<td></td>
<td>Length of follow-up: until end of ECT course</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: both groups: 3 M; 7 F</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>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 phasic course, changes in psychomotor activity, exacerbation of the symptoms during morning hours and unfounded changes in self-esteem. Treatment resistance not recorded</td>
<td>Comparator: L-tryptophan in isotonic saline, class unknown, dosage 1 ml kg⁻¹ body weight of a 10 mg ml⁻¹ solution, length of time taken unknown, change in dosage unknown</td>
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C.ATP, continuation therapy with antipsychotic drugs; C.placebo, continuation therapy with placebo; CODS, Cronholme and Ottoson Depression Scale.
TABLE 34 RCTs of ECT plus pharmacotherapy/placebo versus continuation pharmacotherapy: depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imlah et al., 1965</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: suffering from depressive illness of sufficient degree to warrant use of ECT</td>
<td>Comparison: ECT + C.MAOI vs ECT + C.TCA vs ECT + C.placebo</td>
<td>Continuous: none</td>
<td>N randomised: 150</td>
</tr>
<tr>
<td></td>
<td>Blinding: unclear</td>
<td>Age: 32% aged &lt;40, 63% aged 40–60 and 5% aged &gt;60 years</td>
<td>ECT: twice weekly, discontinued when two observers agreed that the patient had reached a maximal response and discontinued after 12 weeks in those who had residual symptoms</td>
<td>Dichotomous: clinical opinion of relapse (not defined)</td>
<td>n completed: 111</td>
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<td></td>
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<td>Gender: 53 M, 97 F</td>
<td>Comparator: placebo: one tablet; imipramine: 25 mg t.d.s.; phenelzine: 15 mg t.d.s.</td>
<td>Length of follow-up: 6 months</td>
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<td>History: 54% had duration of illness &lt;6 months, 26% 6–12 months and 20% &gt;12 months</td>
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<tr>
<td>Kay et al., 1970</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: affective disorders</td>
<td>Comparison: ECT + TCA vs ECT + diazepam</td>
<td>Continuous: Mood rating, HRSD, BDI, Lubin (unusable, no SD)</td>
<td>N randomised: 132</td>
</tr>
<tr>
<td></td>
<td>Blinding: double-blind</td>
<td>Exclusion: organic brain disease, schizophrenia or subnormality</td>
<td>ECT: no details; 1-month trial</td>
<td>Dichotomous: clinical failure defined as removal from trial owing to relapse, unsatisfactory progress, side-effects, taking an overdose</td>
<td>n completed: 53</td>
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<td>Age: overall age range 20–75 years, with &gt;50% 40–59. Age differences between groups were 'non-significant'</td>
<td>Comparator: amitriptyline (TCA): 25 mg, three tablets at start (two to six tablets) daily at doctor’s discretion, 1-month trial. Diazepam (benzodiazepine): 2 mg, three tablets at start (two to six tablets) daily at doctor’s discretion, 1-month trial</td>
<td>Length of follow-up: 3 months</td>
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<td>Gender: 48 M; 84 F. Gender differences between groups were non-significant</td>
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<td>History: mostly inpatients, none with ECT over the past 6 months, no restriction on prior drug therapy</td>
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<td>Study</td>
<td>Methods</td>
<td>Participants</td>
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<tr>
<td>Seager and Bird, 1962</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: inpatients suffering from a depressive illness of moderate to severe intensity, with retardation or agitation, feelings of hopelessness and pessimism, warranting electrical treatment</td>
<td><strong>Comparison:</strong> ECT + C.TCA vs ECT + C.placebo</td>
<td>Continuous: none</td>
<td>N randomised: 43</td>
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<td></td>
<td>Blinding: double-blind</td>
<td><strong>ECT:</strong> modified ECT twice a week using an Ecton machine (1-s duration shock), number of treatments based on clinical opinion; no information on electrode placement</td>
<td><strong>Dichotomous:</strong> clinical opinion of a satisfactory response or a relapse (not defined)</td>
<td>n completed: 28</td>
<td>Length of follow-up: 6 months</td>
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<td><strong>Age:</strong> ECT + imipramine: mean 47.9 (range 28–71) years; ECT + placebo: 49 (30–70) years</td>
<td><strong>Comparator:</strong> imipramine: 25 mg t.d.s. for 3 days increased to 50 mg for hospital and first month after treatment, then reduced to 25 mg; placebo: identical in appearance</td>
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<td>Study</td>
<td>Methods</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Number and follow-up</td>
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<tr>
<td>Lauritzen et al., 1996</td>
<td>Allocation: B, unclear Blinding: patient</td>
<td>Inclusion: major depressive episode in accordance with DSM-III-R, HRSD score of $\geq 18$, age $\geq 18$ years, ability to understand oral and written information about the trial and giving informed consent Exclusion: severe cardiovascular disease within the preceding 6 months, including intraventricular conduction abnormalities, severe unstable somatic diseases, untreated glaucoma, dementia, schizophrenia, chronic alcohol/drug abuse, treatment with irreversible MAOIs within the preceding 14 days, pregnancy/nursing mothers, epilepsy, prophylactic lithium treatment Group A: Age: paroxetine: mean (SD) 71.4 (8.5) years; placebo: 73.0 (8.5) years Gender: paroxetine: 7 M, 11 F; placebo: 4 M, 13 F 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: mean (SD) 19.1 (9.5) weeks; placebo: 22.4 (24.9) weeks. Received treatment for current episode: paroxetine: 90%; placebo: 76% Group B: Age: paroxetine: mean (SD) 55.9 (12.7) years; imipramine: 63.3 (11.5) years Gender: paroxetine: 3 M, 24 F; imipramine: 9 M, 16 F 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: mean (SD) 17.2 (13.5) weeks; imipramine: 12.8 (8.3) weeks. Received treatment for current episode: paroxetine: 92%; imipramine 84%</td>
<td>Comparison: group A: ECT + C.SSR vs ECT + placebo; group B: ECT + C.SSR vs ECT + C.TCA</td>
<td>Continuous: HRSD, Newcastle scale, Melancholia scale Dichotomous: no data</td>
<td>Group A: N randomised: 35 n completed: 33 Group B: N randomised: 52 n completed: 45 All: Length of follow-up: 6 months</td>
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C.MAOI, continuation therapy with monoamine oxidase inhibitors; C.TCA, continuation therapy with tricyclic antidepressants; C.S.SRI, continuation therapy with selective serotonin reuptake inhibitors.
<table>
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<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
</tr>
</thead>
</table>
| Coppen et al., 1981<sup>66</sup> | Allocation: B, unclear   | Inclusion: MDD with HRSD scores of ≥ 16                                       | **Comparison**: continuation lithium vs C placebo  
**ECT**: not described  
**Comparator**: lithium carbonate (Priadel, Delandale: antimanic drugs). Lithium plasma maintained throughout between 0.8 and 1.2 mmol l<sup>−1</sup>  
**Continuous**: HRSD (unusable graph only), no weeks with depression  
**Dichotomous**: none  
**Length of follow-up**: 1 year | N randomised: 38  
N completed: 38 |                                                                   |
|                              | Blinding: double-blind   | Exclusion: not recorded                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                           |                       |
|                              |                          | Age: placebo: mean (SD) 54.0 (2.8) years; lithium: 56.2 (3.0) years          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                           |                       |
|                              |                          | Gender: placebo: 8 M, 12 F; lithium: 6 M, 12 F                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                           |                       |
|                              |                          | History: for 12 patients this was the first episode of depression. No history of mania. Number of previous episodes: placebo: mean (SD) 2.2 (0.5); lithium: 1.6 (0.4) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                           |                       |
| Grunhaus et al., 2001<sup>67</sup> | Allocation: B, unclear   | Inclusion: successfully responded to a course of ECT (post-HRSD 17-item ≤ 10 maintained for 1 week) | **Comparison**: C SSRI vs C SSRI + melatonin  
**ECT**: started on unilateral but switched to bilateral if not achieved decrease of 30% in baseline HRSD scores by sixth treatment. Seizure threshold determined by method of limits and second treatment delivered at 2.5 times threshold; at following sessions electrical parameters were set to deliver seizures of > 25 s  
**Comparator**: fluoxetine + melatonin: 7 days post-ECT 20 mg fluoxetine daily plus 5 mg slow-release melatonin 3 h before bedtime. Following 3 months received 20–40 mg fluoxetine plus 5 or 10 mg melatonin. Fluoxetine + placebo: 7 days post-ECT 20 mg fluoxetine daily plus 5 mg placebo 3 h before bedtime. Following 3 months received 20–40 mg fluoxetine plus 5 or 10 mg placebo  
**Continuous**: HRSD, BPRS, GRSD, MMSE, PSQI  
**Dichotomous**: relapse defined as return of five or more DSM-IV symptoms of major depression and HRSD of ≥ 16  
**Length of follow-up**: 3 months | N randomised: 39  
N completed: 35 |                                                                   |
|                              | Blinding: double-blind   | Age: fluoxetine + melatonin: mean (SD) 61.1 (10.7) years; fluoxetine + placebo: 59.6 (14.1) years |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                           |                       |
|                              |                          | History: duration of illness: fluoxetine + melatonin: mean (SD) of 6.6 (8.3 months); fluoxetine + placebo: 8.7 (7.6 months). Referred to ECT because of medication resistance, presence of delusions or hallucinations and/or very severe depressive illness |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                           |                       |

*continued*
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<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
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</thead>
<tbody>
<tr>
<td>Sackeim et al., 2001</td>
<td>Allocation: B, unclear</td>
<td>Inclusion: ECT remitters (improvement of &gt;60% reduction in HRSD score) randomised to three continuation pharmacotherapy groups, stratified by classification of the index episode as psychotic depression, medication-resistant non-psychotic depression and non-psychotic depression without medication resistance. Exclusion: history of bipolar disorder, schizophrenia, schizoaffective disorder, non-mood 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</td>
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<td></td>
<td>Blinding: double-blind</td>
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<td>Age: placebo: mean (SD) 55.8 (13.6) years; nortriptyline + placebo: 57.2 (19.8) years; nortriptyline + lithium: 59.2 (18.3) years</td>
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<td>Gender: placebo: 31.0% M, 69.0% F; nortriptyline + placebo: 29.5% M, 70.4% F; nortriptyline + lithium: 39.3% M, 60.7% F</td>
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<td>History: psychotic: placebo 44.8%; nortriptyline + placebo: 37.0%; nortriptyline + lithium: 42.9%. Medication resistant: placebo: 48.3%; nortriptyline + placebo: 44.4%; nortriptyline + lithium: 50.0%</td>
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<td>Comparator: C.TCA vs C.TCA + lithium vs C.placebo</td>
<td>Comparison: C.TCA vs C.TCA + lithium vs C.placebo</td>
<td>Continuous: HRSD, CGI, GAF</td>
<td>N randomised: 84</td>
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<td>ECT: based on clinical judgement: either unilateral or bilateral ECT using the d’Elia or bifrontotemporal placement respectively. Three times per week. Seizure threshold calculated at first treatment using empirical titration; minimal duration 20 s of motor/25 s EEG. Length of ECT course determined on clinical grounds</td>
<td>Dichotomous: relapse defined as mean HRSD (continuous rater and study psychiatrist) of ≥16 that was maintained for ≥1 week</td>
<td>Length of follow-up: 24 weeks</td>
<td>n completed: 73</td>
</tr>
<tr>
<td>Study</td>
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<td>Battersby et al., 1993&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Allocation: B, unclear, Blinding: not blind</td>
<td><strong>Inclusion</strong>: not reported, <strong>Exclusion</strong>: acute or chronic brain disorder, dysfunction or distress to limit participation. Patients about to have ECT were excluded</td>
<td><strong>Comparison</strong>: video vs no video, <strong>ECT</strong>: no ECT involved, <strong>Video</strong>: watched a video of a psychiatrist interviewing a depressed elderly inpatient before receiving ECT. Interspersed 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 dissatisfaction with ECT or had a negative outcome with ECT</td>
<td>Continuous: knowledge, behavioural intent, fear, Dichotomous: none</td>
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<tr>
<td>Westreich et al., 1995&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Allocation: A, concealed, Blinding: not blind</td>
<td><strong>Inclusion</strong>: drawn from geropsychiatric inpatient unit and two general psychiatry inpatient units, English speaking, <strong>Exclusion</strong>: non-English speaking, <strong>Age</strong>: video: median 63 years; no video: 65 years, <strong>Gender</strong>: not reported, <strong>History</strong>: number of past ECT courses: video: mean (SD) 2.57 (3.95), no video: 1.00 (1.34), Score on BPRS: video: 34.71 (7.32); no video: 40.00 (5.04)</td>
<td><strong>Comparison</strong>: video vs no video, <strong>ECT</strong>: no ECT involved, <strong>Video + written consent</strong>: received information video on ECT and written consent form before giving consent to ECT, <strong>Written consent alone</strong>: received written consent form only before giving consent to ECT</td>
<td>Continuous: MMSE and BPRS as measures of illness severity, eight item knowledge questionnaire, Dichotomous: none</td>
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<tr>
<td>Study</td>
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<td>Participants</td>
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</table>
| Manly et al., 2000⁷⁵          | Design: cohort (retrospective)  
**Quality assessment:** some control of confounding by matching and blinding; comparison treatments and length of follow-up not reported | **ECT:** patients aged ≥75 years, diagnosed with major depression, who had received ECT between 1987 and 1993; 3 M, 36 F  
**Comparison:** patients aged ≥75 years treated pharmacologically, computer matched by age, gender and discharge diagnosis | **ECT:** administered two or three times per week using a brief-pulse device (Mecta SRI). 19 patients received bilateral ECT, nine right unilateral, nine both bilateral and unilateral, and in two patients it was not noted  
**Pharmacotherapy:** no information provided on drugs received by the pharmacology group | Response to treatment (good, moderate, poor), complications including falls, CVD, confusion, gastrointestinal, pulmonary, metabolic and total complications |
| Kroessler and Fogel, 1993³⁶   | 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 aged >80 years when admitted and who had a discharge diagnosis of MDD according to either DSM-II or ICD-9 or 8, and were treated with ECT or pharmacotherapy. Some patients from the pharmacotherapy group were recruited from another hospital | **ECT:** mean number of ECTs received was 7.9 (SD 2.9). No information on electrode placement, dosage or waveform used. Two patients had only two ECTs, one patient withdrew consent and one developed congestive heart failure and died before treatment could be continued  
**Pharmacotherapy:** TCAs (n = 20), benzodiazepines (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, rehospitalisation, additional ECT and residence following hospitalisation |
### TABLE 37 Non-randomised evidence of efficacy of ECT in older people with depression (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
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<tbody>
<tr>
<td>Philibert et al., 1995</td>
<td>Design: cohort (retrospective) Quality assessment: no control of confounding factors, unblinded outcome assessment</td>
<td>All patients aged &gt;65 years and admitted to hospital meeting the DSM-III criteria for unipolar depression between 1980 and 1987, identified by computerised search</td>
<td>ECT: mean (SD) number of ECTs 10.7 (4.1). ECT administered three times per week; both unilateral and bilateral ECT was used, but no information is provided on the numbers receiving either treatment</td>
<td>Global improvement and all-cause mortality</td>
<td>N: 192 Lost to follow-up: unclear</td>
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<td>Pharmacotherapy: no information provided on treatment received by those not receiving ECT</td>
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<td>Rubin et al., 1991, 1993</td>
<td>Design: cohort (prospective) Quality assessment: some control over confounding variables using statistical analyses and exclusions, unblinded outcome assessment but loss to follow-up reported</td>
<td>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 aged &gt;65 years</td>
<td>ECT: three times per week at a moderately suprathreshold dose using a Mecta SRI brief-pulse device. 36 patients received bilateral ECT, six received unilateral ECT using the d’Elia placement and six received both. Seizures were monitored using electroencephalography. The mean (SD) number of treatments was 9.3 (3)</td>
<td>GDS, BDI, MMSE and length of stay</td>
<td>N: 103 Lost to follow-up: 7/48 in ECT group; 8/55 in control group</td>
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<td>Pharmacotherapy: both the non-ECT group and the ECT group received pharmacotherapy, and the type and dose of treatment including TCAs, antipsychotics, lithium and antianxiety agents, were determined by the treating physician</td>
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### TABLE 38  Non-randomised evidence: children and adolescents

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<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Number and follow-up</th>
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<tr>
<td>Cohen et al., 2000&lt;sup&gt;72&lt;/sup&gt;</td>
<td><strong>Design:</strong> case–control (retrospective)</td>
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<td><strong>Quality assessment:</strong> large loss to follow-up, no control of confounding variables, unblinded outcome assessment</td>
<td>20 adolescents treated with ECT for a mood disorder before the age of 19 in three adolescent units and three adult clinics in Paris between 1987 and 1996; only ten were included in the study (six women, four men). Five had major depression with psychotic features, three had manic depression with psychotic features and two had mixed depression with psychotic features. Ten matched controls had never received ECT</td>
<td>ECT: bilateral ECT between 2 and 9 years before interviews. Received a mean of 9.8 ECTs</td>
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<td><strong>Comparison:</strong> no information on treatment received</td>
<td>Clinical judgement of improvement, relapses and various cognitive test including MMSE, WMS and California Verbal Learning Test. Perceptions of the adequacy of ECT information and of the perceived benefit of ECT</td>
<td><strong>Test to follow-up:</strong> 10</td>
</tr>
<tr>
<td>Study</td>
<td>Methods</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
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<tr>
<td>Bush et al., 1996</td>
<td>Design: case series (prospective)</td>
<td>Those treated with ECT were those who failed to respond to lorazepam (5/28): 3/5 had mania, three were women, two were men and the mean duration of catatonia was 11 days (SD 12.1)</td>
<td>ECT: in five patients the symptoms of catatonia resolved 2 days before treatment; two 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 resolution of catatonic symptoms. The five non-responders were treated with ECT; one refused consent</td>
<td>BFCRS scores</td>
<td>N = 5 4 treated, 1 refused consent</td>
</tr>
<tr>
<td>Malur et al., 2001</td>
<td>Design: case series (prospective)</td>
<td>Case 1: aged 24 years, female, no known medical or psychiatric history, seven catatonic signs with a duration of 14 weeks before ECT, BFCRS score of 19, probable NMS, respiratory acidosis and cardiac asystole</td>
<td>ECT: case 1: lorazepam max. 12 mg day$^{-1}$ for 5.5 weeks, resulting in a BFCRS score of 15, followed by 15 bilateral ECTs over a 6-week period; case 2: lorazepam max. 4 mg day$^{-1}$ for 10 weeks, resulting in a BFCRS score of 10, followed by 14 bilateral ECTs over 5 weeks; case 3: lorazepam max. 16 mg day$^{-1}$ for 3 weeks, resulting in a BFCRS score of 10, followed by 22 bilateral ECTs over 3 months. All ECTs were administered using a Thymatron DG device with bidirectional brief-pulse square current three times per week. Initial stimulus intensity was 50% in case 1, 20% in case 2 and 40% in case 3</td>
<td>BFCRS</td>
<td>N: 3</td>
</tr>
<tr>
<td>Study</td>
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<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
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<tr>
<td>Bhatia et al., 1999[^2]</td>
<td>Design: case series (prospective)</td>
<td><strong>Case 1</strong>: aged 26 years, white primagravida at 35 weeks of gestation, uncomplicated pregnancy. Current episode treated with desipramine (150 g day⁻¹) and lorazepam (0.5 mg t.d.s.) <strong>Case 2</strong>: aged 23 years, white gravida at 27 weeks of gestation. Pregnancy complicated by generalised anxiety disorder with panic attacks and depression resulting in weight loss and an episode of threatened abortion. Failed to respond to desipramine 400 mg/day⁻¹, oxazepam 15 mg q.d.s. and tryptophan 1 g every bedtime</td>
<td><strong>ECT</strong>: case 1: bilateral ECT three times per week for six treatments in delivery room; case 2: bilateral ECT, five treatments, one on day 1, two on day 2 and two on day 3</td>
<td>Clinical opinion on efficacy, complications</td>
<td>N: 2</td>
</tr>
<tr>
<td>Moreno et al., 1998[^3]</td>
<td>Design: case report (prospective)</td>
<td>Aged 25 years, 8 weeks of gestation. Diagnosed with severe depression with psychotic symptoms. Initially treated with levopromazine (25 mg i.m.) and haloperidol (5 mg) then changed to amitryptaline (75 mg), haloperidol (10 mg) and carbamazepine (1,200 mg). Treatment with amitryptaline and carbamazepine was stopped when a second pregnancy test was positive</td>
<td><strong>ECT</strong>: bilateral ECT with sine wave of 2.5-s duration at an intensity of 0.7 A for nine treatments</td>
<td>Clinical opinion on efficacy, adverse events</td>
<td>N: 1</td>
</tr>
<tr>
<td>Polster and Wisner, 1999[^4]</td>
<td>Design: case report</td>
<td>Aged 29 years, white, in week 23 of pregnancy. History of paranoid schizophrenia and depression. Current episode became catatonic and suicidal. Did not respond to risperidone (3 mg b.d.), loxapine (75 mg b.d.), lorazepam (1 mg t.d.s.) or nortriptyline (50 mg)</td>
<td><strong>ECT</strong>: unilateral ECT, pulse width 1.2 ms, frequency 50 Hz, current 0.6 A and seizure length 89 s for eight treatments followed by bilateral ECT three times per week for 3.5 weeks</td>
<td>Clinical improvement, adverse events</td>
<td>N: 1</td>
</tr>
</tbody>
</table>
Appendix 6

Results of meta-analyses
Comparison: 01 Real bilateral ECT vs sham ECT
Outcome: 01 Improvement (all studies)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Real ECT n/N</th>
<th>Sham ECT n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeman et al. 96</td>
<td>16/20</td>
<td>20/20</td>
<td>37.66</td>
<td>0.80</td>
<td>0.64 to 1.00</td>
</tr>
<tr>
<td>Johnstone et al. 97</td>
<td>20/37</td>
<td>9/33</td>
<td>29.36</td>
<td>1.98</td>
<td>1.05 to 3.73</td>
</tr>
<tr>
<td>Jagadeesh et al. 52</td>
<td>10/12</td>
<td>8/12</td>
<td>32.98</td>
<td>1.25</td>
<td>0.78 to 2.01</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>69</td>
<td>65</td>
<td>100.00</td>
<td>1.21</td>
<td>0.61 to 2.40</td>
</tr>
</tbody>
</table>

Total events: 46 (real ECT), 37 (sham ECT)
Test for heterogeneity: $\chi^2 = 15.42$, df = 2 ($p = 0.0004$)
Test for overall effect: $Z = 0.55$ ($p = 0.59$)

FIGURE 4a

Comparison: 01 Real bilateral ECT vs sham ECT
Outcome: 02 Improvement excluding Freeman et al. (1978) 96

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Real ECT n/N</th>
<th>Sham ECT n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnstone et al. 97</td>
<td>20/37</td>
<td>9/33</td>
<td>41.44</td>
<td>1.98</td>
<td>1.05 to 3.73</td>
</tr>
<tr>
<td>Jagadeesh et al. 52</td>
<td>10/12</td>
<td>8/12</td>
<td>58.56</td>
<td>1.25</td>
<td>0.78 to 2.01</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>49</td>
<td>45</td>
<td>100.00</td>
<td>1.51</td>
<td>0.92 to 2.49</td>
</tr>
</tbody>
</table>

Total events: 30 (real ECT), 17 (sham ECT)
Test for heterogeneity: $\chi^2 = 1.64$, df = 1 ($p = 0.20$)
Test for overall effect: $Z = 1.63$ ($p = 0.10$)

FIGURE 4b
### Comparison: 01 Real bilateral ECT vs sham ECT

**Outcome:** 03 Improvement: all trials that did not give real bilateral ECT to the control arm

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Real ECT n/N</th>
<th>Sham ECT n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnstone et al.97</td>
<td>20/37</td>
<td>9/33</td>
<td>1.98 (1.05 to 3.73)</td>
<td>100.00</td>
<td>1.98 (1.05 to 3.73)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>37</td>
<td>33</td>
<td>100.00</td>
<td>1.98</td>
<td>1.98 (1.05 to 3.73)</td>
</tr>
<tr>
<td>Total events: 20 (real ECT), 9 (sham ECT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.12 (p = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 4c**

### Comparison: 02 Real unilateral ECT vs sham ECT

**Outcome:** 01 Improvement (clinical opinion)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Unilateral ECT n/N</th>
<th>Sham ECT n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambourn and Gill95</td>
<td>9/16</td>
<td>9/16</td>
<td>1.00 (0.54 to 1.84)</td>
<td>100.00</td>
<td>1.00 (0.54 to 1.84)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>16</td>
<td>16</td>
<td>100.00</td>
<td>1.00</td>
<td>1.00 (0.54 to 1.84)</td>
</tr>
<tr>
<td>Total events: 9 (unilateral ECT), 9 (sham ECT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.00 (p = 1.00)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 5**
Comparison: 03 ECT vs TCAs
Outcome: 01 Marked or moderate improvement (all studies)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT</th>
<th>TCA</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruce et al. 104</td>
<td>21/23</td>
<td>16/27</td>
<td>21.27 1.54 (1.10 to 2.16)</td>
<td>21.56</td>
<td>1.27 (0.91 to 1.78)</td>
</tr>
<tr>
<td>Robin and Harris 115</td>
<td>12/15</td>
<td>3/16</td>
<td>3.09 4.27 (1.49 to 12.20)</td>
<td>115</td>
<td>4.27 (1.49 to 12.20)</td>
</tr>
<tr>
<td>Greenblatt and Grosser 113</td>
<td>46/63</td>
<td>36/73</td>
<td>21.65 1.20 (0.86 to 1.67)</td>
<td>21.27</td>
<td>1.54 (1.10 to 2.16)</td>
</tr>
<tr>
<td>Shepherd 100</td>
<td>4/15</td>
<td>3/4</td>
<td>5.16 1.00 (0.45 to 2.23)</td>
<td>115</td>
<td>4.27 (1.49 to 12.20)</td>
</tr>
<tr>
<td>Steiner et al. 107</td>
<td>3/4</td>
<td>3/4</td>
<td>21.56 1.27 (0.91 to 1.78)</td>
<td>100.00</td>
<td>1.40 (1.16 to 1.69)</td>
</tr>
<tr>
<td>Janakiramaiah et al. 103</td>
<td>14/15</td>
<td>11/15</td>
<td>21.56 1.27 (0.91 to 1.78)</td>
<td>115</td>
<td>4.27 (1.49 to 12.20)</td>
</tr>
</tbody>
</table>

Total (95% CI) 194 200
Total events: 137 (ECT), 99 (TCAs)
Test for heterogeneity: $\chi^2 = 6.79$, df = 5 ($p = 0.24$)
Test for overall effect: $Z = 3.47$ ($p = 0.0005$)

FIGURE 6a
### Comparison: 03 ECT vs TCAs
### Outcome: 02 No improvement (all studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>ECT</th>
<th>TCAs</th>
<th>RR (random)</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruce et al.¹⁰⁴</td>
<td>2/23</td>
<td>11/27</td>
<td>8.02</td>
<td>8.02</td>
<td>0.21 (0.05 to 0.87)</td>
</tr>
<tr>
<td>Robin and Harris¹¹⁵</td>
<td>2/15</td>
<td>7/16</td>
<td>7.97</td>
<td>7.97</td>
<td>0.30 (0.07 to 1.24)</td>
</tr>
<tr>
<td>Greenblatt and Grosser¹¹³</td>
<td>6/63</td>
<td>19/63</td>
<td>21.83</td>
<td>21.83</td>
<td>0.32 (0.14 to 0.74)</td>
</tr>
<tr>
<td>Shepherd¹⁰⁰</td>
<td>17/74</td>
<td>23/65</td>
<td>55.78</td>
<td>55.78</td>
<td>0.65 (0.38 to 1.10)</td>
</tr>
<tr>
<td>Steiner et al.¹⁰⁷</td>
<td>1/4</td>
<td>1/4</td>
<td>2.73</td>
<td>2.73</td>
<td>1.00 (0.09 to 1.03)</td>
</tr>
<tr>
<td>Janakiramaiah et al.¹⁰³</td>
<td>1/15</td>
<td>4/15</td>
<td>3.67</td>
<td>3.67</td>
<td>0.25 (0.03 to 1.98)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>194</td>
<td>190</td>
<td>100.00</td>
<td>100.00</td>
<td>0.47 (0.31 to 0.69)</td>
</tr>
</tbody>
</table>

Total events: 29 (ECT), 65 (TCAs)

Test for heterogeneity: $\chi^2 = 4.75$, df = 5 ($p = 0.45$)

Test for overall effect: $Z = 3.77$ ($p = 0.0002$)

**FIGURE 6b**
## Comparison: 03 ECT vs TCAs
### Outcome: 03 Improvement (clinical opinion only)

<table>
<thead>
<tr>
<th>Study</th>
<th>ECT</th>
<th>TCAs</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruce et al.104</td>
<td>21/23</td>
<td>16/27</td>
<td>1.54 (1.10 to 2.16)</td>
<td>28.98</td>
<td>1.54 (1.10 to 2.16)</td>
</tr>
<tr>
<td>Robin and Harris115</td>
<td>12/15</td>
<td>3/16</td>
<td>4.27 (1.49 to 12.20)</td>
<td>6.67</td>
<td>4.27 (1.49 to 12.20)</td>
</tr>
<tr>
<td>Greenblatt and Grosser113</td>
<td>48/53</td>
<td>36/73</td>
<td>1.84 (1.43 to 2.35)</td>
<td>34.88</td>
<td>1.84 (1.43 to 2.35)</td>
</tr>
<tr>
<td>Shepherd100</td>
<td>41/74</td>
<td>30/65</td>
<td>1.20 (0.86 to 1.67)</td>
<td>29.27</td>
<td>1.20 (0.86 to 1.67)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>165</td>
<td>181</td>
<td>1.63 (1.21 to 2.20)</td>
<td>100.00</td>
<td>1.63 (1.21 to 2.20)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 7.44, df = 3 (p = 0.06)$
Test for overall effect: $Z = 3.22 (p = 0.001)$

**FIGURE 6c**

## Comparison: 03 ECT vs TCAs
### Outcome: 04 Improvement (quantitative definition)

<table>
<thead>
<tr>
<th>Study</th>
<th>ECT</th>
<th>TCAs</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner et al.107</td>
<td>3/4</td>
<td>3/4</td>
<td>1.00 (0.45 to 2.23)</td>
<td>14.82</td>
<td>1.00 (0.45 to 2.23)</td>
</tr>
<tr>
<td>Janakiramaiah et al.103</td>
<td>14/15</td>
<td>11/15</td>
<td>1.27 (0.91 to 1.78)</td>
<td>85.18</td>
<td>1.27 (0.91 to 1.78)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>19</td>
<td>19</td>
<td>1.23 (0.90 to 1.67)</td>
<td>100.00</td>
<td>1.23 (0.90 to 1.67)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 0.30, df = 1 (p = 0.58)$
Test for overall effect: $Z = 1.31 (p = 0.19)$

**FIGURE 6d**
### FIGURE 7

**Comparison:** 04 ECT vs rTMS  
**Outcome:** 01 Improvement (HRSD)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT</th>
<th>rTMS</th>
<th>WMD (random)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Grunhaus et al.</td>
<td>20</td>
<td>17.20 (9.72)</td>
<td>20</td>
<td>10.40 (7.54)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>20</td>
<td>17.20 (9.72)</td>
<td>20</td>
<td>10.40 (7.54)</td>
</tr>
</tbody>
</table>
| Test for heterogeneity: not applicable  
Test for overall effect: $Z = 2.47 \ (p = 0.01)$

### FIGURE 8a

**Comparison:** 05 ECT plus chlorpromazine vs ECT plus placebo  
**Outcome:** 01 Improvement at end of ECT course (clinical opinion)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + chlorpromazine</th>
<th>ECT + placebo</th>
<th>RR (random)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
</tr>
<tr>
<td>Arfwidsson et al.</td>
<td>24/28</td>
<td>22/29</td>
<td>1.13 (0.88 to 1.46)</td>
<td>100.00</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>28</td>
<td>29</td>
<td>1.13 (0.88 to 1.46)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
| Total events: 46 (ECT + chlorpromazine), 44 (ECT + placebo)  
Test for heterogeneity: not applicable  
Test for overall effect: $Z = 0.94 \ (p = 0.35)$
### Comparison: 05 ECT plus chlorpromazine vs ECT plus placebo

**Outcome:** 02 Relapse at three months

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + chlorpromazine n/N</th>
<th>ECT + diazepam n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arfwidsson et al.⁵⁸</td>
<td>18/28</td>
<td>16/29</td>
<td>100.00</td>
<td>1.17 (0.76 to 1.79)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>28</td>
<td>29</td>
<td>100.00</td>
<td>1.17 (0.76 to 1.79)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 18 (ECT + chlorpromazine), 16 (ECT + diazepam)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.70 (p = 0.48)

**FIGURE 8b**

### Comparison: 06 ECT + pindolol vs ECT + placebo

**Outcome:** 01 Improvement at end of ECT course

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + pindolol n/N</th>
<th>ECT + placebo n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiah et al.⁵⁷</td>
<td>4/9</td>
<td>0/11</td>
<td>100.00</td>
<td>10.80 (0.66 to 177.36)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>9</td>
<td>11</td>
<td>100.00</td>
<td>10.80 (0.66 to 177.36)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 4 (ECT + pindolol), 0 (ECT + placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.67 (p = 0.10)

**FIGURE 9a**
Comparison: 06 ECT + pindolol vs ECT + placebo
Outcome: 02 Improvement at end of ECT course (HRSD)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + pindolol Mean (SD)</th>
<th>ECT + placebo Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah et al.57</td>
<td>8 11.80 (8.40)</td>
<td>7 20.90 (5.20)</td>
<td>-9.10 (-16.08 to -2.12)</td>
<td>100.00</td>
<td>-9.10 (-16.08 to -2.12)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>8</td>
<td>7</td>
<td>-9.10 (-16.08 to -2.12)</td>
<td>100.00</td>
<td>-9.10 (-16.08 to -2.12)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: Z = 2.56 (p = 0.01)

FIGURE 9b

Comparison: 07 ECT + L-tryptophan vs ECT + placebo
Outcome: 01 Improvement at end of ECT course (clinical opinion)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + L-tryptophan n/N</th>
<th>ECT + placebo n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>d’Elia et al.60</td>
<td>29/31</td>
<td>27/30</td>
<td>1.04 (0.89 to 1.21)</td>
<td>100.00</td>
<td>1.04 (0.89 to 1.21)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>31</td>
<td>30</td>
<td>1.04 (0.89 to 1.21)</td>
<td>100.00</td>
<td>1.04 (0.89 to 1.21)</td>
</tr>
</tbody>
</table>

Total events: 29 (ECT + L-tryptophan), 27 (ECT + placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.50 (p = 0.62)

FIGURE 10
### Comparison: 09 ECT vs SSRIs
#### Outcome: 01 Improvement (HRSD scores)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT</th>
<th>Paroxetine</th>
<th>WMD (random)</th>
<th>Weight</th>
<th>WMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
<td>95% CI</td>
<td>%</td>
</tr>
<tr>
<td>Folkerts et al.</td>
<td>21</td>
<td>12.50 (3.90)</td>
<td>22</td>
<td>23.00 (10.40)</td>
<td>100.00</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>21</td>
<td>22</td>
<td>100.00</td>
<td>-10.50 (-15.15 to -5.85)</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: $Z = 4.42 (p = 0.00001)$

**FIGURE 11a**

### Comparison: 09 ECT vs SSRIs
#### Outcome: 02 Improvement (50% reduction in HRSD)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT</th>
<th>Paroxetine</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>95% CI</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>Folkerts et al.</td>
<td>15/21</td>
<td>5/22</td>
<td>3.14 (1.39 to 7.11)</td>
<td>100.00</td>
<td>3.14 (1.39 to 7.11)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>21</td>
<td>22</td>
<td>100.00</td>
<td>3.14 (1.39 to 7.11)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 15 (ECT), 5 (paroxetine)
Test for heterogeneity: not applicable
Test for overall effect: $Z = 2.75 (p = 0.006)$

**FIGURE 11b**
Comparison: 10 ECT + TCA vs ECT + diazepam
Outcome: 01 Relapse by end of ECT course

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + amitryptaline n/N</th>
<th>ECT + diazepam n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kay et al.(^6)</td>
<td>15/59</td>
<td>34/73</td>
<td></td>
<td>100.00</td>
<td>0.55 (0.33 to 0.90)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>59</td>
<td></td>
<td>100.00</td>
<td>0.55 (0.33 to 0.90)</td>
</tr>
<tr>
<td>Total events: 15 (ECT + amitryptaline), 34 (ECT + diazepam)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.37 (p = 0.02)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

FIGURE 12

Comparison: 11 ECT + SSRI vs ECT + placebo
Outcome: 01 Improvement at end of ECT course (HRSD)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + paroxetine n N</th>
<th>ECT + placebo n N</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauritzen et al.(^6)</td>
<td>18 8.90 (4.70)</td>
<td>17 9.20 (3.40)</td>
<td></td>
<td>100.00</td>
<td>-0.30 (–3.01 to 2.41)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>18</td>
<td>17</td>
<td></td>
<td>100.00</td>
<td>-0.30 (–3.01 to 2.41)</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.22 (p = 0.83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 13
### Comparison: 12 ECT + TCA vs ECT + SSRI
#### Outcome: Improvement at end of ECT course (HRSD)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + imipramine</th>
<th>ECT + paroxetine</th>
<th>WMD (random)</th>
<th>Weight %</th>
<th>WMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Lauritzen et al.⁶⁴</td>
<td>25</td>
<td>6.60 (4.10)</td>
<td>27</td>
<td>9.60 (5.60)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>25</td>
<td>6.60 (4.10)</td>
<td>27</td>
<td>9.60 (5.60)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: Z = 2.22 (p = 0.03)

#### FIGURE 14

### Comparison: 13 ECT + lithium vs ECT + placebo
#### Outcome: Number of weeks spent depressed during 6 months following ECT

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + lithium</th>
<th>ECT + placebo</th>
<th>WMD (fixed)</th>
<th>Weight %</th>
<th>WMD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Coppen et al.⁶⁶</td>
<td>18</td>
<td>1.50 (0.80)</td>
<td>20</td>
<td>2.40 (1.10)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>18</td>
<td>1.50 (0.80)</td>
<td>20</td>
<td>2.40 (1.10)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: Z = 2.90 (p = 0.004)

#### FIGURE 15
Comparison: 14 ECT + TCA vs ECT + placebo
Outcome: 01 Relapse at 6 months (ITT)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + imipramine n/N</th>
<th>ECT + placebo n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imlah et al.62</td>
<td>24/50</td>
<td>30/50</td>
<td></td>
<td>100.00</td>
<td>0.80 (0.55 to 1.15)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>50</td>
<td>50</td>
<td></td>
<td>100.00</td>
<td>0.80 (0.55 to 1.15)</td>
</tr>
<tr>
<td>Total events:</td>
<td>24 (ECT + imipramine), 30 (ECT + placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.19 (p = 0.23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 1.19 (p = 0.23)

FIGURE 16a

Comparison: 14 ECT + TCA vs ECT + placebo
Outcome: 02 Relapse at 6 months (non-ITT)

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>ECT + imipramine n/N</th>
<th>ECT + placebo n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imlah et al.62</td>
<td>7/50</td>
<td>21/50</td>
<td></td>
<td>100.00</td>
<td>0.33 (0.16 to 0.71)</td>
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<tr>
<td>Total (95% CI)</td>
<td>50</td>
<td>50</td>
<td></td>
<td>100.00</td>
<td>0.33 (0.16 to 0.71)</td>
</tr>
<tr>
<td>Total events:</td>
<td>7 (ECT + imipramine), 21 (ECT + placebo)</td>
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<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
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<tr>
<td>Test for overall effect: Z = 2.83 (p = 0.005)</td>
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<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 2.83 (p = 0.005)

FIGURE 16b
### Appendix 6

#### FIGURE 17

**Comparison:** Continuation TCA vs continuation placebo  
**Outcome:** Relapse at 6 months

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Nortriptyline n/N</th>
<th>Placebo n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sackeim et al.</td>
<td>17/27</td>
<td>25/29</td>
<td>0.73 (0.53 to 1.01)</td>
<td>100.00</td>
<td>0.73 (0.53 to 1.01)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>0.73 (0.53 to 1.01)</td>
</tr>
<tr>
<td>Total events:</td>
<td>17 (nortriptyline), 25 (placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.90 (p = 0.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### FIGURE 18

**Comparison:** Continuation TCA + lithium vs continuation placebo  
**Outcome:** Relapse at 6 months

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Nortriptyline + lithium n/N</th>
<th>Placebo n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sackeim et al.</td>
<td>14/28</td>
<td>25/29</td>
<td>0.58 (0.39 to 0.86)</td>
<td>100.00</td>
<td>0.58 (0.39 to 0.86)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>0.58 (0.39 to 0.86)</td>
</tr>
<tr>
<td>Total events:</td>
<td>14 (nortriptyline + lithium), 25 (placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.68 (p = 0.007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Comparison: 17 Continuation SSRI + melatonin vs continuation SSRI
Outcome: 01 Relapse at 3 months

Study or subcategory | SSRI + melatonin | SSRI | RR (random) 95% CI | Weight % | RR (random) 95% CI
--- | --- | --- | --- | --- | ---
Grunhaus et al. | 6/20 | 9/20 | 0.67 (0.29 to 1.52) | 100.00 | 0.67 (0.29 to 1.52)
Total (95% CI) | 20 | 20 | 100.00 | 0.67 (0.29 to 1.52)

Test for heterogeneity: not applicable
Test for overall effect: $Z = 0.96 \ (p = 0.34)$

FIGURE 19

Comparison: 18 Information video in patients about to have ECT
Outcome: 01 Knowledge of ECT

Study or subcategory | Information video | No information video | WMD (random) 95% CI | Weight % | WMD (random) 95% CI
--- | --- | --- | --- | --- | ---
Westreich et al. | 11 | 7 | -0.81 (-1.86 to 0.24) | 100.00 | -0.81 (-1.86 to 0.24)
Total (95% CI) | 11 | 7 | 100.00 | -0.81 (-1.86 to 0.24)

Test for heterogeneity: not applicable
Test for overall effect: $Z = 1.51 \ (p = 0.13)$

FIGURE 20
Comparison: Information video in general psychiatric patients
Outcome: Knowledge about ECT

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Information video</th>
<th>No information video</th>
<th>WMD (random)</th>
<th>Weight %</th>
<th>WMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Battersby et al.</td>
<td>35</td>
<td>12.63 (2.98)</td>
<td>34</td>
<td>11.35 (3.39)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>35</td>
<td>12.63 (2.98)</td>
<td>34</td>
<td>11.35 (3.39)</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: Z = 1.66 (p = 0.10)

**FIGURE 21**
# Health Technology Assessment Programme

## Prioritisation Strategy Group

<table>
<thead>
<tr>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chair,</strong> Professor Tom Walley, Director, NHS HTA Programme, Department of Pharmacology &amp; Therapeutics, University of Liverpool</td>
</tr>
<tr>
<td>Professor Bruce Campbell, Consultant Vascular &amp; General Surgeon, Royal Devon &amp; Exeter Hospital</td>
</tr>
<tr>
<td><strong>Chair,</strong> Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol</td>
</tr>
<tr>
<td><strong>Programme Director,</strong> Professor Tom Walley, Director, NHS HTA Programme, Department of Pharmacology &amp; Therapeutics, University of Liverpool</td>
</tr>
<tr>
<td><strong>Chair,</strong> Professor Shah Ebrahim, Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol</td>
</tr>
<tr>
<td><strong>Deputy Chair,</strong> Professor Jenny Hewison, Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine</td>
</tr>
<tr>
<td>Dr Jeffrey Aronson, Reader in Clinical Pharmacology, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford</td>
</tr>
<tr>
<td>Professor Ann Bowling, Professor of Health Services Research, Primary Care and Population Studies, University College London</td>
</tr>
<tr>
<td>Professor Andrew Bradbury, Professor of Vascular Surgery, Department of Vascular Surgery, Birmingham Heartlands Hospital</td>
</tr>
<tr>
<td>Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health &amp; Related Research, University of Sheffield</td>
</tr>
<tr>
<td>Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford</td>
</tr>
<tr>
<td>Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York</td>
</tr>
<tr>
<td>Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford</td>
</tr>
<tr>
<td>Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen</td>
</tr>
<tr>
<td>Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen</td>
</tr>
<tr>
<td>Professor F D Richard Hobbs, Professor of Primary Care &amp; General Practice, Department of Primary Care &amp; General Practice, University of Birmingham</td>
</tr>
<tr>
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<tr>
<td>Professor Peter Jones, Head of Department, University of Cambridge</td>
</tr>
<tr>
<td>Professor Sallie Lamb, Research Director, Interdisciplinary Research Centre in Health, Coventry University</td>
</tr>
<tr>
<td>Professor Julian Little, Professor of Epidemiology, Department of Medicine and Therapeutics, University of Aberdeen</td>
</tr>
<tr>
<td>Professor Stuart Logan, Director of Health &amp; Social Care Research, The Peninsula Medical School, Universities of Exeter &amp; Plymouth</td>
</tr>
<tr>
<td>Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol</td>
</tr>
<tr>
<td>Professor Ian Roberts, Professor of Epidemiology &amp; Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine</td>
</tr>
<tr>
<td>Professor Peter Sandrock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh</td>
</tr>
</tbody>
</table>

## HTA Commissioning Board

<table>
<thead>
<tr>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Programme Director,</strong> Professor Tom Walley, Director, NHS HTA Programme, Department of Pharmacology &amp; Therapeutics, University of Liverpool</td>
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</tr>
<tr>
<td>Professor Peter Sandrock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh</td>
</tr>
</tbody>
</table>

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Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London  
Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London  
Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool  
Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry  
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J Greenhalgh, C Knight, D Hind, C Beverley and S Walters

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