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Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression (Review)

Peng L, Min S, Wei K, Ziemann-Gimmel P

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Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression

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ABSTRACT

Background

Depression is a common mental disorder. It affects millions of people worldwide and is considered by the World Health Organization (WHO) to be one of the leading causes of disability. Electroconvulsive therapy (ECT) is a well-established treatment for severe depression. Intravenous anaesthetic medication is used to minimize subjective unpleasantness and adverse side effects of the induced tonic-clonic seizure. The influence of different anaesthetic medications on the successful reduction of depressive symptoms and adverse effects is unclear.

Objectives

This review evaluated the effects of different regimens of intravenous sedatives and hypnotics on anti-depression efficacy, recovery and seizure duration in depressed adults undergoing ECT.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 12); MEDLINE via Ovid SP (from 1966 to 31 December 2012); and EMBASE via Ovid SP (from 1966 to 31 December 2012). We handsearched related journals and applied no language restrictions. We reran the search in February 2017. Four potential new studies of interest were added to a list of 'Studies awaiting Classification' and will be incorporated into the formal review findings during the review update.

Selection criteria

We included randomized controlled trials (RCTs) and cross-over trials evaluating the effects of different intravenous sedatives and hypnotics for ECT. We excluded studies and trials using placebo or inhalational anaesthetics and studies that used no anaesthetic.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. When possible, data were pooled and risk ratios (RRs) and mean differences (MDs), each with 95% confidence intervals (CIs), were computed using the Cochrane Review Manager statistical package (RevMan).

Main results

We included in the review 18 RCTs (599 participants; published between 1994 and 2012). Most of the included trials were at high risk of bias.

We analysed the results of studies comparing six different intravenous anaesthetics.

Only a few studies comparing propofol with methohexital (four studies) and with thiopental (three studies) could be pooled.

No difference was noted in the reduction of depression scores observed in participants treated with propofol compared with methohexital (low-quality evidence). These four studies were not designed to detect differences in depression scores.

The duration of electroencephalograph (EEG) and of motor seizures was shorter in the propofol group compared with the methohexital group (low-quality evidence). No difference was seen in EEG seizure duration when propofol was compared with thiopental (low-quality evidence).

Time to recovery (following commands) was longer among participants after anaesthesia with thiopental compared with propofol (low-quality evidence).

For the remaining comparisons of anaesthetics, only single studies or insufficient data were available. Adverse events were inadequately reported in eligible trials, and none of the included trials reported anaesthesia-related mortality.

Authors' conclusions

Most of the included studies were at high risk of bias, and the quality of evidence was generally low. The studies were not designed to detect clinically relevant differences in depression scores. Anaesthetic agents should be chosen on the basis of adverse effect profile, emergence and how these medications affect seizure duration. If it is difficult to elicit an adequately long seizure, methohexital may be superior to propofol (low-quality evidence). If a patient is slow to recover from anaesthesia, propofol may allow a faster time to follow commands than thiopental (low-quality evidence). A factor of clinical concern that was not addressed by any study was adrenal suppression from etomidate. Optimal dosages of intravenous sedatives or hypnotics have not yet been determined.

Larger well-designed randomized studies are needed to determine which intravenous anaesthetic medication leads to the greatest improvement in depression scores with minimal adverse effects.

PLAIN LANGUAGE SUMMARY

Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression

Depression is a common mental disorder. It can present as loss of interest or pleasure, sadness, disturbed sleep or appetite, feelings of guilt or low self worth. In 2008, the World Health Organization (WHO) estimated that depression was the second leading cause of disability-adjusted life-years among all men and women between 15 and 44 years of age. The treatment of choice for severe and recurrent depression is electroconvulsive therapy (ECT). ECT involves the application of an electrical current to the patient's head. The aim is to induce a controlled convulsion. Patients usually undergo several sessions of ECT.

To minimize adverse events and improve the quality of ECT, patients receive anaesthetic agents such as intravenous sedatives or hypnotics. These agents can influence the effectiveness of ECT but can cause potential adverse effects. It would be helpful to identify which is the best anaesthetic agent for ECT in this group of patients.

This Cochrane review examined whether different types of anaesthetic agents could have an effect on anti-depression therapy and reported on the safety of those agents. The evidence is current to December 2012. We included in this review 18 randomized controlled trials (599 participants). We analysed nine pairs of comparisons: methohexital versus propofol; thiopental versus propofol; etomidate versus propofol; thiopental versus etomidate; etomidate versus methohexital; methohexital versus midazolam; thiopental versus midazolam; midazolam versus propofol; and thiamylal versus propofol.

Our analysis revealed no difference in the reduction of depression scores when methohexital was compared with propofol. Propofol reduced seizure duration to a greater extent than methohexital. No difference in seizure duration was noted when thiopental was compared with propofol. Patients recovered faster from anaesthesia when propofol rather than thiopental was used. Adverse events related to anaesthesia induction agents and to the treatment for depression were not well reported in most trials. We found the quality of the evidence to be low. Larger well-designed randomized controlled trials are needed. More clinically relevant outcomes (such as

remission of depressive symptoms and postanaesthetic adverse events) during a longer follow-up period should be reported in future studies.

We reran the search in February 2017. Four potential new studies of interest were added to a list of 'Studies awaiting Classification' and will be incorporated into the formal review findings during the review update.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Methohexital compared to propofol for depressive patients receiving MECT						
Patient or population: patients with depressive patients receiving MECT Settings: in-patients and outpatients Intervention: methohexital Comparison: propofol						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Propofol	Methohexital				
Change in Hamilton Depression Scale scores Scale of Hamilton Depression scores Follow-up: from start of ECT to 8 weeks after last session of ECT	Mean change in Hamilton depression scores in the control groups was the mean change in HDS before and after MECT treatment	Mean change in Hamilton Depression Scale scores in the intervention groups was 1.10 higher (0.56 lower to 2.77 higher)		165 (4 studies)	⊕⊕○○ low ^{1,3,4,5}	Geretsegger 2007;Fear 1994;Malsch 1994;Kirkby 1995
EEG seizure duration EEG detection and measurement Follow-up: from start of RCT (mean number as 2.5) to 2 months after ECT months	Mean EEG seizure duration in the control groups was 0 average participants (second)	Mean EEG seizure duration in the intervention groups was 7.42 higher (0.39 to 14.4 higher)		119 (2 studies)	⊕⊕○○ low ^{1,2,3,4,5}	Geretsegger 2007;Malsch 1994
Motor seizure duration Direct observation of motor seizure Follow-up: number of ECT sessions (6.6 to 7.	Mean motor seizure duration in the control groups was 0 seconds	Mean motor seizure duration in the intervention groups was 5.87 higher (1.97 to 9.77 higher)		78 (2 studies)	⊕⊕○○ low ^{1,2,3,4,5}	Fear 1994;Malsch 1994

8) per participant

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Length of follow-up period was different among included studies.

²Small samples might render the pooled results imprecise.

³All data were retrieved from published trials and no unpublished data were identified.

⁴The report of all trials was published and no unpublished data were detected.

⁵Heterogeneity might exist in baseline features of included participants.

BACKGROUND

Description of the condition

Depression is a common mental disorder that affects approximately 121 million people worldwide. Depression is considered one of the leading causes of disability (WHO 2008). Treatments for depression are diverse and include pharmacotherapy, cognitive-behavioural therapy and psychotherapy. Electroconvulsive therapy (ECT) is considered for use in patients who are unresponsive to these interventions (refractory depression) (Barbui 2008; Leiknes 2012).

Description of the intervention

ECT was first used to treat schizophrenia and was later found to be clinically effective in the treatment of depression (Berner 1974). Over subsequent decades, ECT was used to treat patients with various mental disorders, including affective disorders, delusion, suicidal intention, dysfunction of the vegetative nervous system, inanition and catatonia (Rasmussen 2001; Thompson 1994). Technical variations of ECT involve the number and placement of electrodes or the energy dose and the electrical waveform of the stimulus. These factors may impact therapeutic outcomes. Current practice delivers a brief-pulse current to induce a seizure (Rudorfer 2003). ECT was originally performed without anaesthesia or sedation. Patients received an electrically induced convulsion or tonic-clonic seizure to bring on remission or palliation of their depressive symptoms. This practice was reported to be associated with risk of cardiovascular events, post-treatment muscle pains, joint injury, electrolyte imbalance and postictal cognitive impairment (Andrade 2003; Andrade 2012). With the introduction of intravenous anaesthetic drugs and muscle relaxants, ECT was performed increasingly with anaesthesia. This approach is termed modified ECT. Modified ECT (mECT) provides the merits of increased safety and patient comfort along with fewer procedure-associated adverse events (Sackeim 1987). Today almost all clinicians regard mECT as the standard practice (Berg 2003; Swartz 2009), and in this review, mECT is referred to as ECT.

How the intervention might work

The exact mechanism of how ECT helps to reduce depressive symptoms is unclear (Merkl 2009). Previous studies have shown that longer seizure duration may be associated with improved anti-depressive efficacy (Sackeim 1993; Weiner 1979), but considerable debate and controversy are ongoing. No consensus has been reached regarding the established association between anti-depression efficacy and seizure duration. Most trials have reported this

outcome as the main index of seizure quality and as a possible surrogate of anti-depression efficacy. This review sought to evaluate both anti-depression scores and seizure duration.

Why it is important to do this review

Anaesthetics and hypnotics possess anticonvulsant properties that could modify seizure activity and duration (Sackheim 1991). The range of intravenous sedatives and hypnotics is large, but the most commonly used and widely studied anaesthetic agents are methohexital, propofol and etomidate (Hooten 2008). The influence of different types of anaesthetic medications on the successful reduction of depressive symptoms, on adverse effects or on seizure duration of ECT is unclear.

OBJECTIVES

This review evaluated the effects of different regimens of intravenous sedatives and hypnotics on anti-depression efficacy, recovery and seizure duration in depressed adults undergoing ECT.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs) that met the following inclusion criteria: trials that evaluated different regimens of intravenous sedatives and hypnotics during general anaesthesia for ECT and their effects on remission of depression, cognitive recovery and safety of the anaesthesia. We included cross-over trials. We included studies irrespective of language and publication status.

We excluded:

1. prospective cohort studies and quasi-randomized studies;
2. trials reported as ECT without the use of any anaesthetic; and
3. RCTs that compared placebo or inhalation anaesthetic agents with intravenous sedatives and hypnotics.

Types of participants

We included adult participants (16 years of age or older) with major depressive disorder and depressive episodes of bipolar disorder according to the *Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV/DSM-III* and equivalent diagnoses of the *International Classification of Diseases (ICD)-10/ICD-9* (American

[Psychiatric Association 2000](#)) who were eligible for ECT under general anaesthetic management.

Participants received intravenous sedatives or hypnotics with or without other types of anaesthetic medications (except for inhalational agents) during the induction phase.

Types of interventions

We included all RCTs that compared different types of intravenous sedatives or hypnotics used as induction agents for ECT, including:

1. intravenous sedative or hypnotic (treatment group) versus another intravenous sedative or hypnotic;
2. intravenous sedative or hypnotic combined with a muscle relaxant versus another intravenous sedative or hypnotic combined with the same muscle relaxant;
3. intravenous sedative or hypnotic combined with an analgesic versus another intravenous sedative or hypnotic combined with the same analgesic; or
4. intravenous sedative or hypnotic combined with an analgesic and a muscle relaxant versus another intravenous sedative or hypnotic combined with the same analgesic and muscle relaxant.

Because ketamine was not an established intravenous sedative or hypnotic for both its excitatory and inhibitory effects on the central nervous system (CNS) ([Duncan 2013](#)), it was excluded from the scope of this review.

Types of outcome measures

Primary outcomes

1. Remission of depressive symptoms (risk and score reduction) (using validated international scales for measures of depressive symptoms) (see [Table 1](#)).
2. ECT-induced seizure electroencephalogram (EEG) duration (time in seconds).
3. ECT-induced seizure motor duration (time in seconds) (muscular contractions observed and measured by stopwatch-hand/limb-cuff method).
4. Anaesthesia-related mortality and morbidity (lung aspiration, cardiac arrest, severe allergy).

Secondary outcomes

1. Recovery time (time to emergence and time to recovery).
2. Rate of postanaesthetic cognitive adverse events (confusion/delirium/agitation).
3. Postanaesthetic nausea and vomiting.
4. Injury to and adverse events of systems other than those mentioned above.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, issue 12); MEDLINE via Ovid SP (from 1966 to 31 December 2012); and EMBASE via Ovid SP (from 1966 to 31 December 2012). We searched as well the World Health Organization International Clinical Trials Registry Platform (ICTRP) (up to 31 December 2012) and [clinicaltrials.gov](#) (up to 31 December 2012).

We combined the sensitive strategies described in Section 6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) to search for RCTs in MEDLINE and EMBASE. We used the free text and associated exploded MeSH terms found in [Appendix 1](#) in combination with the RCT sensitive search strategy. We incorporated into the search strategy any new terms that were identified. We adapted our MEDLINE search strategy for searching in CENTRAL (see [Appendix 2](#)), and we searched EMBASE using the terms found in [Appendix 3](#). We reported the modified search strategy in full in this review.

We applied no language restrictions.

We reran the search in February 2017. We will deal with the potential studies of interest when we update the review.

Searching other resources

We screened the reference lists of all eligible trials and reviews. We intended to contact experts to identify any unpublished research and trials still under way. However, all potentially eligible trials were already published.

We searched the following databases for ongoing trials: MetaRegister of Controlled Trials and the National Research Register. Free text terms were used in all databases and in combination with subject headings when these were components of a database (see [Appendix 1](#), [Appendix 2](#) and [Appendix 3](#)).

We searched international conference and consortium articles for finished or ongoing trials of potential value.

1. Annual Conference of American Society of Anaesthesiologists (2000 to 2012).
2. Annual Conference of American Psychiatric Association (2000 to 2012).
3. Annual European Congress of Psychiatry (2000 to 2012).

We also searched the following related journals.

1. *Journal of Electric Convulsive Therapy* (1990 to 2012).
2. *American Journal of Psychiatry* (1990 to 2012).
3. *Anesthesia and Analgesia* (1990 to 2012).
4. *Anesthesiology* (1990 to 2012).

Data collection and analysis

Selection of studies

Two review authors (Peng Lihua and Wei Ke) independently screened all titles and abstracts for eligibility according to the study inclusion criteria (see [Criteria for considering studies for this review](#)). We included eligible cross-over trials. We contacted the first author of the relevant trial if further information was required to make a decision about including a trial. We resolved disagreements by discussion. If we were unable to reach a consensus, we consulted with a third review author (Min Su). We based our decision for including or excluding a study on the full text of the study, if available. We recorded data from included studies on a specially developed form (see [Appendix 4](#)).

Data extraction and management

Two review authors (Min Su and Wei Ke) independently extracted and reported data on specially designed forms (see [Appendix 4](#)). We assessed methodological quality using predefined criteria (see [Appendix 5](#)). Data extraction was checked by a third review author (Peng Lihua). We resolved disagreements concerning data extraction by consensus with two review authors, based on the above predefined criteria. For detailed information on the included trials and their outcomes in uniform tables, see [Appendix 6](#) and [Appendix 7](#). We double-checked our data entry into [RevMan 5.1](#). In the case of further disagreement, we consulted a third review author (Peng Lihua).

Assessment of risk of bias in included studies

Two review authors (Wei Ke and Peng Lihua) independently assessed the risk of bias of all eligible trials. We resolved disagreements by discussion, and if we could not reach a consensus, a third review author (Min Su) arbitrated.

We performed risk of bias assessment using the 'Risk of bias' tool described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A copy of the form that we used will be found in [Appendix 5](#).

We assessed each trial according to the quality domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases.

1. Random sequence generation: adequate (random numbers generated by a computer or similar) or inadequate (other methods or not described).
2. Allocation concealment: adequate (sealed envelopes or similar) or inadequate (not described, open table of random numbers or similar).
3. Blinding: indexed as adequate (investigator who assessed clinical outcomes did not know whether the participant undertook the intervention or similar) or inadequate (not performed or similar).
4. Intention-to treat (ITT): ITT considered adequate if all dropouts or withdrawals were accounted for; ITT considered

inadequate if the number of dropouts or withdrawals was not stated, or if the reasons for any dropouts or withdrawals were not stated.

We considered a trial as having a low risk of bias if all domains were assessed as adequate. We considered a trial as having a high risk of bias if one or more domains were assessed as inadequate or unclear.

We reported the 'Risk of bias' table as part of the table [Characteristics of included studies](#) and presented a 'Risk of bias summary' figure, which detailed all of the judgements made for all included studies in the review.

Measures of treatment effect

We performed all analyses according to the ITT principle, including all randomly assigned participants. We presented categorical and dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs) when meta-analysis was possible. The absolute harm or benefit was calculated in the summary of finding (SOF) tables using a standard calculation formula as absolute differences. For continuous outcomes such as seizure duration, we used means and standard deviations (SDs) to summarize and analyse the value in each group.

Unit of analysis issues

If continuous data were appropriately reported (mean with standard deviation or standard error, or mean difference), we combined cross-over studies with RCTs in the meta-analysis and performed a sensitivity analysis. If multiple treatment arms existed, we combined groups to create a single pair-wise comparison. Outcomes assessed during and after the ECT procedure were analysed separately. If pair-wise data for before and after are reported for each participant or for each arm, we reported change scores using recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; 16.1.3.2).

Dealing with missing data

We contacted the original investigators to obtain missing data when possible. If we were unable to contact the original investigators or to obtain missing data, we used mean values. We then performed sensitivity analyses to assess how sensitive the results were to reasonable changes in assumptions made. In the discussion section of the review, we addressed the potential impact of missing data on the findings of the review.

Assessment of heterogeneity

We assessed the clinical heterogeneity of the included studies according to their clinical diversity (e.g. gender, position and number of stimulation electrodes, premedication or no premedication)

and as methodological diversity (risk of bias assessment). We assessed statistical heterogeneity using the I^2 statistic, thereby estimating the percentage of total variance across studies that is due to heterogeneity rather than to chance (Higgins 2002). We considered an I^2 value greater than 50% as statistically significant. If significant heterogeneity was found, we again checked that data were correct and explored the reasons for the heterogeneity. When heterogeneity could not be explained readily, we conducted a meta-analysis using the random-effects model.

Assessment of reporting biases

We performed comprehensive searches for studies that met our eligibility criteria, including, when possible, unpublished studies and trial registries. We used funnel plots to assess reporting biases. We tested for funnel plot asymmetry if more than 10 studies were included in the meta-analysis.

Data synthesis

We used the fixed-effect model in the meta-analyses if no obvious heterogeneity was found. However, when heterogeneity was detected that could not be explained readily, we conducted a meta-analysis using the random-effects model. We performed all analyses according to the ITT principle. For trials reported with multiple intervention groups, we combined groups to create a single pair-wise comparison. This method is suitable for trials reporting several independent comparisons and making multiple pair-wise comparisons.

For dichotomous outcomes, both the sample size and the number of participants across groups were summed. For continuous outcomes, weighted mean differences were combined using the formula in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; see Table 7.7.a). We assessed heterogeneity using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We analysed the association between different kinds and dosages of experimental interventions and intervention effects.

We planned to perform subgroup analyses for subgroups of participants and for subgroups of interventions when data were available.

Subgroups of participants

1. Sex.
2. Age over 60 years.
3. Disease stage (newly diagnosed, disease relapsed).
4. Major depression or bipolar disorder.
5. Number and sites of electrode positioning.
6. Energy of electric stimulus.

Sensitivity analysis

To test whether included trials with variations in methodological design or trials with only abstracts available could bias the results of the meta-analysis, we performed sensitivity analyses of trials labelled as having low risk or high risk of bias. A random-effects estimate was calculated when significant heterogeneity was found for each outcome variable. We initially included all studies and then eliminated studies of moderate or poor quality, as well as those published only as an abstract, one at a time to see if this approach altered the results. Finally, the analysis was performed with data from studies of good methodological quality; thus the sensitivity analyses were done in a multiple-step way. In the case of missing data, we planned to use best case/worst case imputation of missing data. We excluded and re-included any study that appeared to have a large effect size (often the largest or earliest study) to assess its impact on the meta-analysis. If large variations in the control group event rate were noted, we also subjected these data to sensitivity analysis.

RESULTS

Description of studies

See Figure 1.

Figure 1. Study flow diagram.

After screening 425 articles related to the topic, we included 18 trials in this review. One study (Godfrey 2011) is ongoing (see Characteristics of ongoing studies).

All 18 trials were published between 1994 and 2012, and a total of 599 participants were included in the analysis. Two trials reported identical groups of participants with different endpoints (Rosa 2008a; Rosa 2008b). These participants were counted only once. The average number of ECT sessions varied from three to 11.3 for each participant. Two trials reported significantly unequal numbers of ECT sessions between two interventions. The remaining eligible trials reported equal or balanced numbers of ECT sessions. Follow-up assessment ranged from after the first ETC session up to eight weeks after the last treatment.

The number of enrolled participants in each study ranged from 10 to 90 (median 28). The age range was 18 to 81 years.

We found nine pairs of comparisons for different sedatives or hypnotics in these trials

We reran the literature research in February 2017, 1076 articles were found and four studies were potential new studies of interest. These four studies were added to a list of 'Studies awaiting Classification' and will be incorporated into the formal review findings during the review update.'

Propofol versus

1. Methohexital (Avramov 1995; Fear 1994; Fredman 1994; Geretsegger 2007; Kirkby 1995; Malsch 1994; Matters 1995).
2. Thiopental (Bauer 2009; Butterfield 2004; Kumar 2012; Rosa 2008a; Rosa 2008b; Shah 2010).
3. Etomidate (Avramov 1995; Erdil 2009; Grati 2005; Rosa 2008a;

Rosa 2008b).

4. Thiamylal (Sakamoto 1999).

5. Midazolam (Shah 2010).

Methohexital versus

6. Etomidate (Avramov 1995).

7. Midazolam (Auriacombe 1995).

Thiopental versus

8. Etomidate (Abdollahi 2012; Rosa 2008a; Rosa 2008b).

9. Midazolam (Shah 2010).

The different sedatives or hypnotics were used in combination with succinylcholine.

The dose of propofol ranged from 0.75 to 2.5 mg/kg; methohexital 0.75 to 1.5 mg/kg; thiopental 2 to 5 mg/kg; etomidate 0.15 to 0.3 mg/kg; midazolam 0.1 to 0.2 mg/kg; thiamylal 1 mg/kg; and succinylcholine 0.4 to 1.5 mg/kg (see Table 2).

Ten trials reported the change in depression scores before and after ECT.

Sixteen trials reported motor seizure duration. Twelve included trials reported time to recovery.

None of the included trials reported anaesthesia-related mortality. Only three trials reported postanaesthetic adverse events.

The only studies that showed a low risk of bias were Bauer 2009, and Geretsegger 2007. The remaining studies showed a high risk of bias. For detailed information on the risk of bias, see Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Abdollahi 2012	?	?	+	+	?	+	+
Auriacombe 1995	?	?	+	+	?	-	+
Avramov 1995	?	?	+	-	?	?	?
Bauer 2009	+	+	+	+	?	-	+
Butterfield 2004	?	?	+	+	?	?	?
Erdil 2009	+	?	+	-	?	?	?
Fear 1994	?	?	+	-	?	?	?
Fredman 1994	?	?	+	-	?	?	?
Geretsegger 2007	+	+	+	+	?	+	+
Grati 2005	?	?	+	-	?	?	?
Kirkby 1995	?	?	+	-	?	?	?
Kumar 2012	?	?	+	-	?	-	+
Malsch 1994	?	?	+	-	?	?	+
Matters 1995	?	?	+	+	?	-	+
Rosa 2008a	?	?	+	-	?	+	+
Rosa 2008b	?	?	+	-	?	+	+
Sakamoto 1999	?	?	+	-	?	?	?
Shah 2010	+	?	+	+	?	?	?

For additional methodological details, please see [Characteristics of included studies](#).

Results of the search

See above section (description of study).

Included studies

See [Characteristics of included studies](#).

1. Methohexital versus midazolam ([Auriacombe 1995](#)).
2. Methohexital versus propofol ([Avramov 1995](#); [Fear 1994](#); [Fredman 1994](#); [Geretsegger 2007](#); [Kirkby 1995](#); [Malsch 1994](#)).
3. Thiopental versus propofol ([Bauer 2009](#); [Butterfield 2004](#); [Kumar 2012](#); [Rosa 2008a](#); [Rosa 2008b](#); [Shah 2010](#)).
4. Etomidate versus propofol ([Avramov 1995](#); [Erdil 2009](#); [Grati 2005](#); [Rosa 2008a](#); [Rosa 2008b](#)).
5. Thiopental versus etomidate ([Abdollahi 2012](#)).
6. Thiamylal versus propofol ([Sakamoto 1999](#)).
7. Thiopental versus midazolam ([Shah 2010](#)).
8. Midazolam versus propofol ([Shah 2010](#)).
9. Methohexital versus midazolam ([Auriacombe 1995](#)).

The different sedatives or hypnotics were used in combination with muscle relaxants (succinylcholine).

The dose of propofol ranged from 0.75 to 2.5 mg/kg; methohexital 0.75 to 1.5 mg/kg; thiopental 2 to 5 mg/kg; etomidate 0.15 to 0.3 mg/kg; midazolam 0.1 to 0.2 mg/kg; thiamylal 1 mg/kg; and succinylcholine 0.4 to 1.5 mg/kg (see [Table 2](#)).

None of the eligible trials used analgesics.

Outcomes

Primary outcomes

Efficacy of anti-depression (change in depression score before and after ECT)

Ten trials reported the change in depression score before and after ECT ([Abdollahi 2012](#); [Auriacombe 1995](#); [Bauer 2009](#); [Fear 1994](#); [Geretsegger 2007](#); [Kirkby 1995](#); [Kumar 2012](#); [Malsch 1994](#); [Rosa 2008a](#); [Rosa 2008b](#)).

Seizure quality (EEG or motor seizure duration)

All included trials reported motor seizure duration. EEG seizure duration was not reported in two trials ([Abdollahi 2012](#); [Auriacombe 1995](#)).

Four trials reported use of the cuff method for assessing motor seizure duration ([Auriacombe 1995](#); [Avramov 1995](#); [Butterfield](#)

[2004](#); [Erdil 2009](#)), Six trials reported visual observation of motor seizure duration ([Bauer 2009](#); [Fear 1994](#); [Malsch 1994](#); [Fredman 1994](#); [Kirkby 1995](#); [Matters 1995](#)) and the rest of the eligible trials did not report methods of assessing motor seizure duration.

Anaesthesia-related mortality

No included trials reported anaesthesia-related mortality.

Secondary outcomes

Recovery time

Twelve included trials reported time to recovery ([Avramov 1995](#); [Bauer 2009](#); [Butterfield 2004](#); [Erdil 2009](#); [Fredman 1994](#); [Geretsegger 2007](#); [Kumar 2012](#); [Matters 1995](#); [Rosa 2008a](#); [Rosa 2008b](#); [Sakamoto 1999](#); [Shah 2010](#)).

Postanaesthetic adverse events

Only three trials reported postanaesthetic adverse events ([Abdollahi 2012](#); [Grati 2005](#); [Kumar 2012](#)).

Excluded studies

We excluded 17 articles for the reasons detailed in the [Characteristics of excluded studies](#) tables. These reasons included the following.

1. Non-eligible groups of patients.
2. Non-randomized controlled trials.
3. Anaesthesia agents used as premedication, not as induction agents ([Mizrak 2009](#)).
4. Ketamine considered to have pharmacological effects related not only to sedation; therefore trials involving the use of ketamine excluded ([Abdallah 2012](#); [Erdogan 2012](#); [Wang 2012](#); [Yalcin 2012](#)).

Studies awaiting classification

We reran the search in February 2017. There are four studies awaiting classification ([Canbek 2015](#); [Jarineshin 2016](#); [Mir 2017](#); [Purtuloğlu 2013](#)). For further details see [Characteristics of studies awaiting classification](#).

Ongoing studies

We identified one ongoing study ([Godfrey 2011](#)). For further details see [Characteristics of ongoing studies](#)

Risk of bias in included studies

For general information on the risk of bias in all included trials, please refer to [Figure 2](#) and [Figure 3](#).

For additional methodological details, please see [Characteristics of included studies](#).

Allocation

All trials were reported to be randomized. Methods of randomization (sequence generation) were described in four trials ([Bauer 2009](#); [Erdil 2009](#); [Geretsegger 2007](#); [Shah 2010](#)). Two studies ([Bauer 2009](#); [Geretsegger 2007](#)) reported details of allocation concealment and were counted as 'low risk'; the remaining included studies were classified as 'unclear risk' associated with moderate to high risk of selection bias.

Blinding

Nine studies reported the use of blinding for outcome assessment and were assessed as 'low risk' of bias ([Abdollahi 2012](#); [Auriacombe 1995](#); [Bauer 2009](#); [Geretsegger 2007](#); [Kumar 2012](#); [Malsch 1994](#); [Matters 1995](#); [Rosa 2008a](#); [Rosa 2008b](#)). The remaining included studies did not describe blinding of rater (evaluator) or participants and were classified as 'unclear risk' of bias associated with moderate to high risk of performance and detection bias. No study evaluated the success of blinding of rater or participants.

Incomplete outcome data

In the outcome reporting, five studies reported early dropout or exclusion of enrolled participants for various reasons.

1. One participant withdrew consent and another was excluded for delirium during the first ECT provided in the midazolam group ([Auriacombe 1995](#)).
2. Two participants were excluded for protocol violation (different medications administered for anaesthesia) and one participant declined ECT ([Bauer 2009](#)).
3. Two participants were excluded for early discontinuation of ECT unrelated to the study: one for incorrect use of intravenous lidocaine and another for emergence delirium under the use of both thiopental and propofol ([Butterfield 2004](#)).
4. Five participants were excluded for incomplete data collection ([Kirkby 1995](#)).
5. Four participants were excluded for personal or family refusal of ECT, three participants for referred psychiatrist refusal of ECT, one participant for incorrect use of anti-depressant medication and another three participants for stimulus energy not in accordance with the protocol (five in the propofol group and six in the methohexital group) ([Malsch 1994](#)).

Dropout rates between these interventional groups are comparable, and no statistical difference was found; other trials included all eligible participants in the data analysis.

These trials were still rated as 'high risk'. The remaining 13 trials stated that all enrolled participants were included in the analysis and that no dropouts were found; therefore we rated them as 'low risk' of bias.

Selective reporting

Efficacy of anti-depression, seizure quality, recovery time and postanaesthetic adverse events are the focus of the analysis. None of the trials lacked one or more reported results on all outcomes. The most common outcome was absence of reporting of adverse events.

We also found absence of reporting of anti-depression efficacy in eight of the included trials.

Time to recovery was not reported in six of the included trials. We rated trials missing recording of postanaesthetic cognitive evaluation as 'high risk' for reporting bias.

Other potential sources of bias

No description of other potential sources of bias was included in all 18 included studies.

Effects of interventions

See: [Summary of findings for the main comparison Methohexital compared with propofol for depressive patients receiving MECT](#); [Summary of findings 2 Thiopental compared with propofol for patients receiving ECT](#)

Change in depression scores

Four trials including 165 participants compared propofol versus methohexital ([Fear 1994](#); [Geretsegger 2007](#); [Kirkby 1995](#); [Malsch 1994](#)) and reported the change in Hamilton Depression Scale (HDS) scores. No difference in the change in HDS (mean difference [MD] = baseline score minus post-treatment score) was noted among participants who underwent anaesthesia with methohexital compared with propofol ([Analysis 1.1](#)) (see [Figure 4](#)). Electrode placement (unilateral vs bilateral) did not influence the results ([Analysis 1.1](#)). Two studies used unilateral electrode placement ([Geretsegger 2007](#); [Kirkby 1995](#)), one study switched from unilateral electrode placement to bilateral ([Malsch 1994](#)) and another study used bilateral electrode placement in all participants ([Fear 1994](#)). These studies were not designed to determine differences in HDS scores and showed higher baseline and post-treatment HDS scores in the methohexital group ([Analysis 1.2](#); [Analysis 1.3](#)).

Figure 4. Forest plot of comparison: I Methohexital versus propofol, outcome: I.1 Change in Hamilton Depression Scale (HDS) score.

Multiple orphan trials compared depression scores using different scales at different time points after completion of ECT (Abdollahi 2012; Bauer 2009; Fear 1994; Kumar 2012). No difference in the reduction in depression scores was noted when methohexital was compared with propofol or midazolam (Auriacombe 1995; Fear 1994). Propofol and etomidate showed greater reduction in depression scores when compared with thiopental, but no difference in the number of participants achieving clinical improvement was noted (> 50% reduction in HDS scores or HDS < 10) (Abdollahi 2012; Bauer 2009; Geretsegger 2007; Kumar 2012). In one study, unilateral electrode placement was changed to bilateral electrode placement if participants did not show satisfactory clinical improvement (Malsch 1994). It is interesting to note that more participants in the methohexital group required this intervention compared with those in the propofol group (12/29 vs 4/29; P value 0.038).

No data were available or only single trials compared the remaining comparisons (Summary of findings for the main comparison) (see Appendix 8, Appendix 9, Appendix 10 and Appendix 11).

EEG seizure duration

Two trials including 108 participants compared propofol with methohexital (Geretsegger 2007; Malsch 1994), and two trials including 90 participants compared propofol with thiopental (Bauer 2009; Kumar 2012).

Propofol showed a significant reduction in EEG seizure duration compared with methohexital (P value 0.04) (Analysis 1.4) (see Figure 5). No difference in EEG seizure duration was seen when propofol was compared with thiopental (P value 0.83) (Analysis 2.1).

Figure 5. Forest plot of comparison: I Methohexital versus propofol, outcome: I.4 EEG seizure duration (seconds).

No data were available or only single trials compared the remaining intravenous anaesthetics; see Summary of findings 2 and Appendix 9, Appendix 12, Appendix 13 and Appendix 14.

Motor seizure duration

Two trials including 78 participants compared propofol with methohexital (Fear 1994; Malsch 1994).

Participants treated with propofol showed a significantly shorter motor seizure duration than participants treated with methohexital (P value 0.003) (Analysis 1.5) (see Figure 6). No data were available or only single trials compared the remaining comparisons.

Figure 6. Forest plot of comparison: I Methohexital versus propofol, outcome: 1.5 Motor seizure duration (seconds).

In single trials, no difference in motor seizure duration was noted when methohexital was compared with propofol (Matters 1995) or with midazolam (Auriacombe 1995). Motor seizure duration was longer when thiopental was compared with propofol or with midazolam (Shah 2010). Participants treated with etomidate showed a longer motor seizure duration than those treated with methohexital (Avramov 1995; Grati 2005). A single cross-over study reported no difference in motor seizure duration when etomidate was compared with propofol (Erdil 2009). See Summary of findings for the main comparison and Summary of findings 2; also see Appendix 9, Appendix 11, and Appendix 13 to Appendix 17.

Time to recovery (following commands)

Two trials including 48 participants compared propofol versus thiopental (Kumar 2012; Rosa 2008a). After anaesthesia, participants with thiopental recovered more slowly than those given propofol (P value 0.006) (Analysis 2.2). Time to eye opening was reported in multiple studies, but this endpoint is potentially influenced by ambient noise. These data were not included. No data were available or only single trials performed the remaining comparisons.

Multiple orphan trials reported time to recovery. Participants after anaesthesia given propofol recovered more quickly than those given etomidate or thiopental (Avramov 1995; Butterfield 2004; Rosa 2008a). No difference in time to recovery was noted when etomidate was compared with thiopental (Rosa 2008a) or with methohexital (Avramov 1995), and no difference was observed when propofol was compared with thiamylal (Sakamoto 1999). A single cross-over study reported no difference in time to recovery when etomidate was compared with propofol (Erdil 2009); see Appendix 9, Appendix 10, Appendix 12 to Appendix 14 and Appendix 18.

Adverse events

Data were insufficient for pooling, and outcome was reported in single studies. Observed adverse events did not differ between propofol, thiopental, etomidate and midazolam. No study reported cognitive adverse events (see Appendix 19 to Appendix 21). Most studies showed a great degree of heterogeneity. After very low-quality trials were excluded, the sensitivity analysis did not significantly change the statistical results.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Propofol versus thiopental					
Patient or population: patients with major depression treated with ECT Settings: in-patients Intervention: thiopental Comparison: propofol					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Propofol	Thiopental			
Mean EEG seizure duration	0 second	2.26 seconds (-18.35 to 22.87)		90 (2 studies)	⊕⊕○○ low ^{1,2,3}
Mean time to recovery Time to follow com- mands	0 minutes	1.72 minutes (0.49 to 2.95)		48 (2 studies)	⊕⊕○○ low ^{2,3,4}
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval.					
GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.					

¹Follow-up durations were different among included studies.

²Performance and detection bias were likely to happen in the trials.

³Samples were small, which carries risk of inaccuracy.

⁴Heterogeneity in baseline characteristics existed.

DISCUSSION

Summary of main results

In this systematic review, we evaluated the efficacy and safety of different regimens of sedatives or hypnotics for anaesthesia of ECT. We included 18 trials (599 participants). The anaesthetic medications used in these trials were propofol, methohexital, thiopental, etomidate, midazolam and thiamylal. Included trials investigated nine possible combinations of anaesthetic medications. Data could be pooled only on studies comparing propofol with methohexital (four trials) and with thiopental (three trials). Cross-over studies were not pooled in the analysis.

No difference in the reduction in depression scores was reported among different anaesthetics. These studies were not designed to detect differences in depression scores.

Propofol seems to reduce EEG and motor seizure duration compared with methohexital and possibly with etomidate. No difference in EEG seizure duration was described when propofol was compared with thiopental. Motor seizure duration was longer after induction of anaesthesia with methohexital compared with propofol (see [Table 3](#)). Recovery times were shorter in participants treated with propofol compared with thiopental.

The paucity of trials reporting postanaesthesia adverse events did not allow an analysis of comparative safety between methohexital and propofol. No differences were found between propofol and thiopental or etomidate in terms of adverse events.

Overall completeness and applicability of evidence

All included trials were small and were conducted at single centres. No clear consensus was reached on defining the 'ideal' seizure quality that would be most effective in reducing depressive symptoms. The American Psychiatric Association recommends a motor seizure duration of greater than 20 seconds ([American Psychiatric Association 2000](#)). Differences in energies, waveforms and electrode placement influence the results. Included anaesthetics influence seizure duration to different degrees. Because of the unclear or controversial effects of seizure duration on reduction of depressive symptoms, it remains unclear whether the effect, for instance, of propofol in reducing seizure duration compared with methohexital is clinically relevant.

The number of ECT sessions in the studies is determined by participant response and improvement. Typical clinical endpoints at the conclusion of treatment are:

1. reduction in HDS scores greater than 50%;
2. HDS score less than a fixed number;
3. no further improvement; and
4. no improvement at all (nonresponder) ([American Psychiatric Association 2000](#);

[Lovieno 2012](#); [Maneeton 2012](#)).

This means that treatments are continued until one endpoint is met. Pooling of final scores simply reflects that participants achieved one of the endpoints and that treatment was successful. An ideal study investigating the effects of intravenous anaesthetics would need to show that the decline in depression scores is faster and/or that participants require fewer treatments to achieve a pre-set goal without altering any co-variants (e.g. energy or electrode placement), although it would be difficult to determine how data from participants who do not improve with ECT (non-responders) should be handled. Clinically the first step is to change the treatment modality, in this case ECT (titration), rather than a secondary variable, in this case anaesthetics. If an anaesthetic has a positive effect on depression scores, this would be evident in the decline in depression scores (not the final score) or in the total number of ECT sessions needed. Some included trials were cross-over studies, which did not allow comparison of this endpoint because participants were exposed to both medications. Evidence for other pairs of comparisons was obtained from small trials, and follow-up ended at different time points.

Quality of the evidence

In this systematic review, most included randomized controlled studies were small and of low quality. Only two trials showed high methodological quality, reporting Hamilton Depression Rating Scale scores, seizure duration, fluctuations in blood pressure and a variety of postanaesthetic cognitive tests ([Bauer 2009](#); [Geretsegger 2007](#)).

The presentation and the statistical methodology in most trials could be debated. Depression scale scores (e.g. from the HDS, an ordinal scale) are presented as means with SDs instead of medians with interquartile ranges (IQRs). Further, the study authors used statistical tests for continuous data (e.g. Student-t, analysis of variance (ANOVA), linear regression) to analyse depression scores (ordinal data). This becomes a matter of particular concern when evidence seems to show that "not all items of the HDS are equally sensitive to detect responding patients in clinical trials" ([Santen 2008](#)). Further, the 'independence' of experiments does influence the type of statistical test necessary to analyse the data. Does the ECT done two days ago influence the result of the ECT done today in the same participant? The answer to this question (independence and repeated measurement) should guide statistical methods used to analyse study results.

Another limitation was that different times were used to follow up on or to reassess depression scores after ECT sessions. Some trials reported depression scores right after ECT, whereas others waited eight weeks. It would be preferable to have clinical guidelines on assessing depression scores after ECT ([Geretsegger 2007](#); [Steidtmann 2013](#)).

Potential biases in the review process

Only two studies showed a low degree of bias (Bauer 2009; Geretsegger 2007). All remaining studies showed a high degree of bias. In this systematic review, the overall quality of evidence for different regimens of intravenous sedatives or hypnotics for the primary outcome (reduction in HDS scores) is low, and for postanaesthetic adverse events including cognitive events, it is very low.

Agreements and disagreements with other studies or reviews

Currently, intravenous sedatives or hypnotics are used for induction of anaesthesia for ECT. This review aimed to investigate the comparative efficacy and safety of intravenous anaesthetics. This was the first review that used pooled data to investigate anti-depression efficacy of anaesthetic agents used for ECT.

No difference in the reduction in depression scores was observed when propofol was compared with methohexital.

Participants receiving methohexital or etomidate showed significantly longer seizure duration compared with those given propofol. These results were similar to findings described in previous reports (Gabor 2007; Gazdag 2004; Eranti 2009; Tan 2009; Walder 2001). It seems that higher doses of propofol reduce seizure duration to a greater extent when compared with increasing doses of methohexital or etomidate (Avramov 1995). No differences in seizure duration were noted when propofol was compared with thiopental. Single eligible trials with significant methodological heterogeneity (Bauer 2009; Kumar 2012) and trials that included participants with multiple psychiatric diseases reported longer seizure duration with thiopental (Boey 1990; Villalonga 1993). Larger trials are needed to clarify this question.

In our review, cognitive recovery was measured as time to obey commands. No difference was seen between propofol, methohexital and etomidate, but thiopental seem to prolong recovery times. This finding was in accordance with those of systematic reviews of other psychiatric diseases (Hooten 2008; Walder 2001). Propofol has a well-established favourable recovery profile, making it the preferred hypnotic for short procedures with minimal discomfort, such as endoscopies (ASGE 2008).

Anaesthesia-related adverse events were rarely reported in eligible trials, and the incidence was low. Several reasons might account for this. Follow-up duration may not have been adequate to detect adverse events. This finding also might have been the result of enrolment of participants with relatively low risk (American Society of Anesthesiologists (ASA) I and II). Based on current evidence, nausea and vomiting were more frequent for thiopental and etomidate than for propofol. Headache and delirium occurred more frequently in participants receiving midazolam compared with thiopental. Myoclonus was reported only in the etomidate group. The profile of adverse events was in accordance with the

anaesthesia literature (Hines 1992). In conclusion, reporting of adverse events was neglected or heterogeneous in included trials. One adverse outcome was entirely neglected in depressive participants: adrenal suppression with etomidate. Lowered cortisol levels and disrupted circadian rhythm of its release have played a role in the pathogenesis of depression (Holland 2013). Measurements of cortisol and adrenocorticotrophic hormone after ECT did not show a significant difference between propofol and etomidate in participants with affective disorder and schizophrenia (Wang 2011). Future studies should help to clarify this issue in depressive patients. For other pairs of agents, one common problem was that all evidence came from several single low- to very low-quality trials and from orphan studies.

AUTHORS' CONCLUSIONS

Implications for practice

The included studies were of low quality and were liable to bias. The studies were not designed to detect differences in depression scores. Anaesthetic agents should be chosen on the basis of adverse effect profile, emergence and how these medications affect seizure duration. If it is difficult to elicit an adequate seizure, methohexital or etomidate may be superior to propofol or thiopental. If emergence from anaesthesia is slow, propofol may be preferable to thiopental. A factor of clinical concern that was not addressed by any study was adrenal suppression from etomidate. Another concern was that different doses of anaesthetic medications were used in included studies (see Table 2). This could have affected seizure duration, time to emergence and incidence of adverse effects.

Implications for research

Larger well-designed randomized controlled trials are needed to clarify the optimal intravenous sedatives or hypnotics for ECT. More clinically relevant outcomes (e.g. remission of depressive symptoms, postanaesthetic adverse events, cognitive adverse events after ECT) during a longer follow-up period (longer than the immediate period after ECT) should be reported in future studies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abdollahi 2012

Methods	Trial design: two-week follow-up, single-centre, double-blind, randomized parallel trial Duration: 2009 to 2010
Participants	Inclusion criteria: 60 adult patients with major depressive disorder diagnosed according to <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision</i> criteria, referred for ECT in 2009 and 2010 Exclusion criteria: not specified
Interventions	Treatment: intravenous sodium thiopental 3 mg/kg + succinylcholine 0.5 mg/kg (N = 30) Control: etomidate 0.2 mg/kg + succinylcholine 0.5 mg/kg (N = 30) All participants received six sessions of ECT Electrode placement: bilateral Energy: not specified
Outcomes	Outcomes used in this review: 1. Beck Depression Inventory (BDI). 2. Motor seizure duration (each session). 3. Adverse events related to anaesthesia. Outcomes not used in this review: None
Abbreviations	
Notes	Aldrete and Kroulik's postanesthetic recovery score was mentioned but was not calculated Country: Iran Setting: Research Center for Psychiatry and Behavioral Sciences, Department of Psychiatry, Hafez Hospital, Shiraz, Iran Funding: The study authors mentioned no sources of external support

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method was provided, except that "There was a 1:1 ratio for randomization"
Allocation concealment (selection bias)	Unclear risk	No information on method was provided, except that "There was a 1:1 ratio for randomization"

Abdollahi 2012 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in outcome reporting, and no dropout was reported
Selective reporting (reporting bias)	Low risk	Although EEG seizure duration was not reported, outcomes related to efficacy and safety of anaesthesia for ECT were reported
Other bias	Unclear risk	None known
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotation: "The patients and the rater were blind to the groups"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotation: "The patients and the rater were blind to the groups"

Auriacombe 1995

Methods	Study design: single-centre, double-blind, randomized open-label trial Trial duration: two weeks (1989)
Participants	Number of randomly assigned: 18 Participant age: 33 to 75 years Gender: both Inclusion criteria: in-patients consecutively referred for ECT. They met <i>DSM-III-R</i> criteria for major depressive disorder with melancholia on the basis of clinical interviews Exclusion criteria: not specified
Interventions	Intervention: methohexital 1 mg/kg iv + suxamethonium 1 mg/kg iv; average of 6.25 sessions of ECT given (N = 9) Control: midazolam 0.1 mg/kg iv + suxamethonium 1 mg/kg iv; average of 7.12 sessions of ECT given (N = 9) Mean number of ECT sessions: 6.25 for methohexital group and 7.12 for midazolam group Electrode placement: unilateral Energy: sine wave unidirectional constant voltage (200 v)
Outcomes	Outcomes used in this review: 1. Motor seizure duration. 2. Change in Montgomery Asberg Depression Rating Scale (MADRS). 3. Response rate to ECT (at least 55% reduction in MADRS score). 4. Time to recovery (anaesthesia duration). Outcomes not used in this review: Memory test during and 48 hours after last ECT session
Abbreviations	

Notes	<p>Criteria of exclusion not provided</p> <p>Country: France</p> <p>Setting: ECT Research Group, Laboratory of Psychiatry, University of Bordeaux II, Centre Carreire, France</p> <p>Funding: The study author stated that this study was supported in part by a grant from Roche</p>
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<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors provided no information no method, except that they mentioned it Quotation: "After an informed consent procedure, subjects were randomly assigned to receive either methohexital (group 1) or midazolam (group 2) anaesthesia for ECT".
Allocation concealment (selection bias)	Unclear risk	The study authors provided no information on method, except that they mentioned it Quotation: "The anaesthesiologist was the only clinician aware of patient group assignment", yet we did know whether participants or clinicians were aware of allocation before and until the assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eighteen participants were initially included; two were excluded because of withdrawal of consent (methohexital group) and acute delirium (midazolam group), which appeared after the first ECT. The rest of the participants finished the trials (N = 8 for methohexital; N = 8 for propofol)
Selective reporting (reporting bias)	Low risk	The authors reported motor seizure duration, and time to recovery was defined as "anaesthesia duration". Data with or without statistical difference were both reported
Other bias	Unclear risk	None known
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quotation: "The anaesthesiologist was the only clinician aware of patient group assignment"; therefore, participants could also know the assigned medications

Auriacombe 1995 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotation: “The anaesthesiologist was the only clinician aware of patient group assignment. The rater was blind to patient group assignment and memory testing”
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Avramov 1995

Methods	Study design: single-centre, double-blind, randomized cross-over trial Trial duration: four weeks
Participants	Number of participants randomly assigned: 10 Participant age: 21 to 81 years Gender: both Inclusion criteria: patients diagnosed with chronic depression and consenting to ECT Exclusion criteria: not specified
Interventions	Intervention: methohexital 0.75, 1.0 or 1.5 mg/kg + succinylcholine 1.0 to 1.4 mg/kg iv (30 sessions) Intervention: etomidate 0.15, 0.2, 0.3 mg/kg + succinylcholine 1.0 to 1.4 mg/kg (30 sessions) Control: propofol 0.75, 1.0, 1.5 mg/kg + succinylcholine 1.0 to 1.4 mg/kg (30 sessions) Each participant received nine sessions of ECT (three for each arm) Electrode placement: bilateral Energy: not specified
Outcomes	Outcomes used in this review: 1. Motor seizure duration. 2. EEG seizure duration. 3. Recovery time. Outcomes not used in this review: 1. Participant self assessment of anxiety, confusion, fatigue, clumsiness and drowsiness. 2. Time to “fitness for discharge”.
Abbreviations	
Notes	Criteria of exclusion not provided Country: USA Setting: Anesthesiology and Pain Management and Psychiatry, University of Texas South-western Medical Center, Dallas, Texas Funding: The trial author stated that the doctors who conducted this study were supported in part by Abbott Laboratories

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
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Random sequence generation (selection bias)	Unclear risk	The study authors provided no information on method, except that they mentioned it Quotation: "Each patient received.....in a randomized order using a double-blind cross-over study design"
Allocation concealment (selection bias)	Unclear risk	The study authors provided no information on method, except that they mentioned it
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis Quotation: "The 10 patients, five male and five female....,received a total of 90 ECT study, all ECT sessions were included in this analysis"
Selective reporting (reporting bias)	High risk	Depression scores were not reported in the protocol. Trial authors stated that participant self assessment of anxiety, confusion, fatigue, clumsiness and drowsiness was used for postanaesthetic cognitive evaluation (data not shown; no statistical differences found), yet no objective postanaesthetic cognitive evaluation was carried out
Other bias	Unclear risk	None known
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors provided no information on method, except that they mentioned it Quotation: "each patient received.....in a randomized order using a double-blind cross-over study design"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors provided no information on method, except that they mentioned it Quotation: "each patient received.....in a randomized order using a double-blind cross-over study design"

Bauer 2009

Methods	Study design: single-centre, double-blind, randomized trial Trial duration: three to 36 ECT sessions (2004 to 2007)
Participants	Number randomly assigned: 62 Participant age: 24 to 86 years Gender: both Inclusion criteria: patients with diagnosis of major depression according to <i>International Classification of Disease, 10th edition</i> , were asked to participate in the study Exclusion criteria: patients unable to give informed consent because of severe psychotic symptoms and patients involuntarily hospitalized or involuntarily treated were excluded
Interventions	Treatment: thiopental 3 mg/kg + succinylcholine 0.4 mg/kg (N = 31) Control: propofol 1.5 mg/kg + succinylcholine 0.4 mg/kg (N = 31) Number of ECT sessions: three to 36 (range) Electrode placement: unilateral and bilateral Energy: not specified
Outcomes	Outcomes used in this review: 1. Motor seizure duration. 2. EEG seizure duration. 3. Rate of depression remission. 4. Hamilton Depression Rating Scale. 5. Beck Depression Inventory. Outcomes not used in this review: 1. Energy charges 2. Scores on minimal mental state evaluation five days after last ECT session
Abbreviations	
Notes	Country: Denmark Setting: Center of Psychiatry, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark The study authors mentioned no sources of external support

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotation: "Patients were randomized by drawing envelopes from larger envelopes kept in a locked office." Drawing envelopes was generally considered adequate for randomization
Allocation concealment (selection bias)	Low risk	Quotation: The authors conducted concealment by "drawing envelopes from larger envelopes kept in a locked office"

Incomplete outcome data (attrition bias) All outcomes	Low risk	During a period of three and one-half years, 62 participants were included in the study. 31 participants were randomly assigned to the thiopental group and 31 to the propofol group. At the end of the ECT sessions, 26 participants in the thiopental group had completed the trial and 26 participants in the propofol group had completed the trial
Selective reporting (reporting bias)	Low risk	Anesthesia-related adverse events were not reported in this trial, yet the study authors reported MMSE scores only after ECT procedures, so this category was deemed to be of low risk
Other bias	Unclear risk	None known
Blinding of participants and personnel (performance bias) All outcomes	High risk	Persons administering ECT were blinded, but the anaesthesiologists were not Quotation: "The psychiatrist responsible for ECT treatment did an observation of motor activity and checked the EEG seizure duration measured by the ECT device. Blood pressure, pulse, and PaO ₂ were measured before and after treatment."; "The anaesthetists decided whether the dose was appropriate or whether it should be increased or decreased during the series of treatment."; "The rating with HDRS was discussed openly in the session. Afterward, the score sheets were collected but without identification of the rater"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Persons performing ratings (HDRS) were blinded to the anaesthetic agent Quotation: "The psychiatrist responsible for ECT treatment did an observation of motor activity and checked the EEG seizure duration measured by the ECT device. Blood pressure, pulse, and PaO ₂ were measured before and after treatment"; "The anaesthetists decided whether the dose was appropriate or whether it should be increased or decreased during the series of

		treatment.”; “The rating with HDRS was discussed openly in the session. Afterward, the score sheets were collected but without identification of the rater”
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Butterfield 2004

Methods	Study design: single-centre, double-blind, randomized cross-over trial Trial duration: four to six ECT sessions
Participants	Number randomly assigned: 19 Participant age: 18 to 75 years Gender: both Inclusion criteria: 19 right-handed patients scheduled to receive right unilateral ECT as the clinically indicated treatment of depression, with an American Society of Anesthesiologists physical status of I or II, between 18 and 75 years of age and able to provide written informed consent Exclusion criteria: patients with serious or uncorrected visual impairment, ongoing substance abuse, known or family history of reactions to study drugs or inadequate proficiency in English
Interventions	Treatment: thiopental 3.0 ± 0.6 mg/kg + succinylcholine 0.6 ± 0.1 mg/kg (N = 15) Control: propofol 1.9 ± 0.4 mg/kg + succinylcholine 0.6 ± 0.1 mg/kg (N = 15) Electrode placement: unilateral Energy: frequency of 70 Hz, pulse width of 0.5 milliseconds and current of 0.9 A
Outcomes	
Abbreviations	
Notes	Country: Canada Setting: Departments of Pharmacology & Therapeutics, Anesthesia, Psychology, and Psychiatry, Centre for Anesthesia and Analgesia, The University of British Columbia, Vancouver, Canada The study authors mentioned no sources of external support

Risk of bias***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors Quotation: “A crossover design was used where thiopental and propofol were administered on an alternating basis throughout a course of ECT”

Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors Quotation: "A crossover design was used where thiopental and propofol were administered on an alternating basis throughout a course of ECT" No information on method was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotation: "Nineteen subjects were initially recruited into the study. 2 patients were excluded as a result of early discontinuation of their ECT treatment course, unrelated to the study. Two other patients completed the study but were excluded from data analysis; 1 patient who was given lidocaine (a potent anticonvulsant) with the propofol treatments, resulting in a significantly shortened seizure duration, and the other patient who experienced emergence delirium in 2 of 4 treatments, one for each of the treatment"; "for the rest of the participants, all but 2 patients received an equal number of ECT sessions of both"; "2 patients completed 5 study treatments"; therefore, if two more sessions of ECT were allocated to the thiopental or propofol group, no statistically significant difference was noted between the two groups
Selective reporting (reporting bias)	Low risk	Change in depression score and adverse events were not reported, yet cognitive tests were performed after ECT
Other bias	Unclear risk	None known
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors provided no information on the method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors provided no information on the method

Methods	Study design: single-centre, double-blind, randomized cross-over trial Trial duration: six ECT sessions
Participants	Number randomly assigned: 14 Participant age: older than 18 years Gender: both Inclusion criteria: 14 American Society of Anesthesiologists I patients diagnosed with major depression were included Exclusion criteria: patients younger than 18 years, pregnant and with permanent pace-makers, diabetes mellitus, atrial fibrillation or flutter and electrolyte imbalance and patients taking antiarrhythmics and A-blockers. Inability to provide informed consent was also an exclusion criterion
Interventions	Treatment: etomidate at 0.2 mg/kg intravenous + succinylcholine 1 mg/kg iv) (N = 14, 42 ECT sessions) or propofol at 1 mg/kg intravenous + succinylcholine (1 mg/kg iv) (N = 14, 42 ECT sessions) Electrode placement: bilateral Energy: not specified
Outcomes	Outcomes used in this review: 1. Motor seizure duration. 2. EEG seizure duration. 3. Recovery time. Outcomes not used in this review: Corrected Q-T interval
Abbreviations	
Notes	Country: Turkey Setting: Department of Anesthesiology and Reanimation, School of Medicine, Inonu University, Malatya, Turkey The study authors mentioned no sources of external support

Risk of bias***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers were used for randomization Quotation: "Patients enrolled in the study were randomly allocated by computer-generated random numbers to receive either propofol or etomidate for their initial ECT session"
Allocation concealment (selection bias)	Unclear risk	No information on method was provided

Erdil 2009 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All 14 participants were included in the analysis, and no dropout of participants was reported
Selective reporting (reporting bias)	High risk	Depression scores and adverse events were not reported
Other bias	Unclear risk	None
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors provided no information on method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors provided no information on method, except that "Electrocardiogram recordings were assessed by a blinded cardiologist"

Fear 1994

Methods	Study design: single-centre, double-blind, randomized parallel trial Mean trial duration: seven ECT sessions
Participants	Number randomly assigned: 20 Participant age: 37 to 77 years Gender: both Inclusion criteria: patients diagnosed with major depression disorder according to <i>DSM-III-R</i> criteria Exclusion criteria: Patients who had received a course of ECT within the previous 12-month period; those with organic brain disease; those taking anticonvulsants; those with neurological, cardiovascular or respiratory disease; those detained under the Mental Health Act; and those deemed unable to give valid consent were excluded
Interventions	Treatment: methohexitone 1.13 mg/kg (SD 0.27 mg/kg) + suxamethonium 35 to 50 mg (N = 10) Control: propofol 2.12 mg/kg (SD 0.37 mg/kg) + suxamethonium 35 to 50 mg (N = 10) Electrode placement: bilateral Energy: 275 to 310 millicoulombs
Outcomes	Outcomes used in this review: 1. Motor seizure duration. 2. Scores on Hamilton Depression Rating Scale (HDRS). 3. Scores on Beck Depression Inventory (BDI). Outcomes not used in this review: None

Abbreviations	
Notes	Country: Turkey Setting: Academic Subdepartment of Psychological Medicine, North Wales Hospital, Denbigh, UK The study authors stated no sources of external support

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	No information on method was provided Quotation: "A prospective randomized, double-blind design was used to compare the relationship between clinical outcomes, seizure duration, and anaesthetic induction agent in patients..."	
Allocation concealment (selection bias)	Unclear risk	No information on method was provided. Quotation: "A prospective randomized, double-blind design was used to compare the relationship between clinical outcomes, seizure duration, and anaesthetic induction agent in patients..."	
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the analysis, and all participants (including two participants without symptom remission) were included in the data analysis	
Selective reporting (reporting bias)	High risk	Adverse events and time to recovery were not reported	
Other bias	Unclear risk	None	
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on method was provided by the study authors	
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on method was provided by the study authors	

Fredman 1994

Methods	Study design: single-centre, double-blind, randomized cross-over trial Trial duration: four or six ECT sessions
Participants	Inclusion criteria: 13 patients consenting, chronically depressed were included Exclusion criteria: Study authors provided no information on exclusion criteria
Interventions	Treatment: methohexital at 0.75 mg/kg iv + succinylcholine (1.4 mg/kg iv) (N = 13, 36 ECT sessions) Control: propofol at 0.75 mg/kg iv + succinylcholine (1.4 mg/kg iv) (N = 13, 36 ECT sessions) Electrode placement: unilateral Energy: 25.2 (1.9) J for methohexital group and 26.4 (3.1) J for propofol group
Outcomes	Outcomes used in the review: 1. Motor seizure duration. 2. EEG seizure duration. 3. Recovery time. Outcomes not used in this review: Participants' self assessment of postanaesthetic anxiety, confusion, fatigue, clumsiness, drowsiness and awareness of neuromuscular block and ECT
Abbreviations	
Notes	Country: USA Setting: Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center The study authors stated no sources of external support

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors
Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the analysis and no dropout was reported
Selective reporting (reporting bias)	High risk	Depression score and adverse events were not reported
Other bias	Unclear risk	None
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on methods was provided by the study authors

Fredman 1994 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on methods was provided by the study authors
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Geretsegger 2007

Methods	Study design: single-centre, double-blind, randomized parallel trial Trial duration: not specified
Participants	inclusion criteria: in-patients 18 years of age and older meeting <i>Diagnostic and Statistical Manual of Mental Disorders, Third Edition</i> , criteria for recurrent major depression or bipolar disorder Exclusion criteria: ongoing substance addiction
Interventions	Treatment: methohexital 1.43 ± 0.35 mg/kg iv + succinylcholine 58.0 ± 12.1 mg iv (N = 25) Control: propofol 1.72 ± 0.80 mg/kg iv + succinylcholine 61.4 ± 14.0 mg iv (N = 25) Electrode placement: unilateral Energy: bidirectional, square wave, brief pulse with pulse width of 0.5 milliseconds
Outcomes	Outcomes used in this review: 1. EEG seizure duration. 2. Hamilton Depression Rating Scale. Outcomes not used in this review: 1. Systolic BP. 2. Diastolic BP. 3. Cognitive test.
Abbreviations	
Notes	Follow-up period started from initiation of treatment to two months after last session of treatment Country: Austria Setting: University Clinic for Psychiatry I, Paracelsus Medical University, Salzburg, Austria The study authors stated no sources of external support nor conflicts of interest

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotation: "We opted for a 1:1 randomization ratio for propofol versus methohexital anesthesia"
Allocation concealment (selection bias)	Low risk	Quotation: "Randomization was carried out confidentially by the anaesthetist, so that the psychiatrists

Geretsegger 2007 (Continued)

		who evaluated the data were blinded”
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the data analysis and no dropout was reported
Selective reporting (reporting bias)	Low risk	Adverse events were not reported, yet cognitive tests were performed after ECT
Other bias	Unclear risk	None
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotation: “The patients and the psychiatric staff were blinded in regard to propofol/methohexital arrangement”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The psychiatrists who evaluated the data were blinded to the arrangement of participants

Grati 2005

Methods	Study design: single-centre, double-blind, randomized parallel trial Mean trial duration: 2.1 ECT sessions Single-centre, prospective, randomized controlled trial
Participants	
Interventions	Treatment: etomidate 0.15 mg/kg + succinylcholine 0.75 mg/kg (N = 13) Control: propofol 1.5 mg/kg + succinylcholine 0.75 mg/kg (N = 12) Electrode placement: not specified Energy: The intensity of the stimulation current was variable between 50 and 80 joules
Outcomes	Outcomes used in this review: 1. Seizure duration (unclear whether motor or EEG). 2. Pain of injection. 3. Nausea and vomiting. Outcomes not used in this review: Fluctuations in blood pressure
Abbreviations	
Notes	Duration of follow-up not specified Country: France Setting: Grati, service d’anesthésieréanimation, Centre hospitalo-universitaire, F. Bourguiba, France The study authors stated no sources of external support nor conflicts of interest

Risk of bias

Risk of bias

Grati 2005 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors Quotation: "Après accord du comité d'éthique et le consentement éclairé des patients ou de leurs tuteurs légaux, une étude prospective incluant des malades ASA I, II et III, ayant des troubles dépressifs majeurs et devant avoir des séances d'ECT programmée a été réalisée"
Allocation concealment (selection bias)	Unclear risk	No information on method was provided Quotation: "Après accord du comité d'éthique et le consentement éclairé des patients ou de leurs tuteurs légaux, une étude prospective incluant des malades ASA I, II et III, ayant des troubles dépressifs majeurs et devant avoir des séances d'ECT programmée a été réalisée"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the data analysis and no dropout was reported
Selective reporting (reporting bias)	High risk	Depression scores, time to recovery and adverse events were not reported in the trial
Other bias	Unclear risk	None
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on method was provided by the study authors
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on method was provided by the study authors

Kirkby 1995

Methods	Study design: single-centre, double-blind, randomized parallel trial Median trial duration: six ECT sessions
Participants	Inclusion criteria: 37 patients met <i>DSM-III-R</i> diagnostic criteria for a major depressive episode Exclusion criteria: those who require compulsory ECT under the Mental Health Act, left-handed, referred for bilateral ECT

Kirkby 1995 (Continued)

Interventions	Treatment: methohexital 1.01 (0.24) mg/kg iv + suxamethonium 0.5 mg/kg iv (N = 18) Control: propofol 1.37 (0.42) mg/kg iv + suxamethonium 0.5 mg/kg iv (N = 19) Electrode placement: unilateral Energy: This machine has a stimulus intensity (amplitude) dial with settings from one to nine; an intensity setting of seven delivers 700 mA into a 300-ohm load
Outcomes	Outcomes used in this review: 1. Motor seizure duration. 2. Scores of Hamilton Rating Scale before, during and one month after treatment Outcomes not used in this review: None
Abbreviations	
Notes	Follow-up period extended from initiation of ECT to two months after last session of treatment Country: Tasmania, Australia Setting: University of Tasmania, Royal Hobart Hospital, GPO Box 1061L, Hobart, Tasmania, Australia The study authors stated no sources of external support nor conflicts of interest

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors	
Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data were unavailable for three participants in the propofol group and for two participants in the methohexitone group. The results reported are then for the 16 participants in each group for whom complete data were available; no statistically significant difference was noted between the two groups, and the dropout rate did not exceed 20%	
Selective reporting (reporting bias)	High risk	Time to recovery and adverse events were not reported	
Other bias	Unclear risk	None	
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on method was provided by the study authors	

Kirkby 1995 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on method was provided by the study authors
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Kumar 2012

Methods	Study design: single-centre, double-blind, randomized parallel trial Mean trial duration: eight ECT sessions
Participants	Inclusion criteria: 28 adult patients, 18 years of age or older, with a major depressive episode as part of a diagnosis of major depressive disorder or bipolar disorder (<i>International Classification of Diseases, 10th edition</i> , Code 296), were included in the study Exclusion criteria: Patients were excluded from the study if they fulfilled criteria for <i>DSM-IV</i> (<i>Diagnostic and Statistical Manual of Mental Disorders</i>) substance abuse disorder in the past 12 months, had received ECT within the previous six months or were in ASA III/ IV
Interventions	Treatment: thiopentone 3 mg/kg iv + succinylcholine 0.4 mg/kg iv (N = 14) Control: propofol 1.5 mg/kg intravenous iv + succinylcholine 0.4 mg/kg IV (N = 14) Electrode placement: bilateral Energy: 120 mC, 70 Hz/0.1 s
Outcomes	Outcomes used in this review: 1. Seizure duration. 2. Incidence of adverse effects during induction. 3. Incidence of adverse events after anaesthesia. 4. Recovery time. Outcomes not used in this review: Fluctuations in heart rate and blood pressure before and after ECT
Abbreviations	
Notes	Country: India Setting: Department of Anaesthesiology, Guwahati, Assam, India The study authors stated no sources of external support nor conflicts of interest

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors Quotation: "A double-blind, randomized trial was performed following clearance from Institutional Ethical Committee and an informed written consent from all subjects,,,,,a total of 28 patients were randomly divided into 2 groups, based on the choice

Kumar 2012 (Continued)

		of anaesthetic agent (thiopentone or propofol)”
Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors Quotation: “A double-blind, randomized trial was performed following clearance from Institutional Ethical Committee and an informed written consent from all subjects,,,,,a total of 28 patients were randomly divided into 2 groups, based on the choice of anaesthetic agent (thiopentone or propofol)”
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis and no dropout was reported
Selective reporting (reporting bias)	High risk	Cognitive adverse events were not reported in this trial
Other bias	Unclear risk	None
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quotation: “The psychiatrist was blinded to anaesthetic agent, and an independent observer, blinded to the type of drug being used, recorded the data” Participants could also know the assigned medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotation: “The psychiatrist was blinded to anaesthetic agent, and an independent observer, blinded to the type of drug being used, recorded the data”

Malsch 1994

Methods	Study design: single-centre, double-blind, randomized parallel trial Mean trial duration: 7.5 ECT sessions
Participants	Inclusion criteria: 69 patients diagnosed with major depression (<i>DSM-III-R</i>) with a minimum pretreatment Hamilton Rating Scale for Depression (HRSD) score of 18 accepted Participant age: 18 to 85 years ASA I to III Previous ECT had to be completed a minimum of three months before the study began Exclusion criteria: patients who received tricyclic antidepressants or lithium with 24 hours or MAO inhibitors with seven days before start of the study

Interventions	Treatment: methohexital at 0.75 to 1.5 mg/kg iv + succinylcholine 0.5 to 1.5 mg/kg iv (N = 35) Control: propofol at 1.0 to 2.5 mg/kg iv + succinylcholine 0.5 to 1.5 mg/kg iv (N = 34) Electrode placement: bilateral or unilateral Energy: 51.2 to 576 milliampere-seconds
Outcomes	Outcomes used in this review: 1. Motor seizure duration. 2. EEG motor duration. 3. Hamilton Rating Scale score before and after treatment. Outcomes not used in this review: None
Abbreviations	
Notes	Country: USA Setting: Department of Anaesthesiology, Medical College Hospitals and Friends Hospital, Philadelphia, Pennsylvania The study authors stated no sources of external support nor conflicts of interest

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors	
Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors	
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 participants had to be excluded from the final analysis for various reasons: six of the excluded participants had received propofol, so a statistically significant difference was found between two groups, and the dropout rate did exceed 20%	
Selective reporting (reporting bias)	High risk	Time to recovery and adverse events were not reported	
Other bias	Unclear risk	None	
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	None Known	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotation: "Psychiatrists who administered the ECT were blinded to the hyp-	

Malsch 1994 (Continued)

		notic drug. the assess both physical and EEG seizure duration and administered the Hamilton Rating Scale for Depression (HRSD) test..."
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Matters 1995

Methods	Study design: single-centre, double-blind, randomized parallel trial Mean trial duration: three ECT sessions
Participants	Inclusion criteria: 39 patients met <i>DSM-III-R</i> criteria for major depressive disorder Exclusion criteria: those who required compulsory ECT under the Mental Health Act, were left-handed or were referred for bilateral ECT
Interventions	Treatment: methohexital 1.37 ± 0.42 mg/kg iv + suxamethonium 0.5 mg/kg iv (N = 20) Control: propofol at 1.01 ± 0.24 mg/kg iv + suxamethonium 0.5 mg/kg iv (N = 19) Electrode placement: unilateral Electrode placement: bilateral or unilateral Energy: 51.2 to 576 milliampere-seconds
Outcomes	Outcomes used in this review: 1. Duration of seizure. 2. Hamilton Rating Scale scores. Outcomes not used in this review: 1. Digit symbol substitution test (DSST) score after ECT. 2. Finger tap score after ECT.
Abbreviations	
Notes	Country: Australia Setting: Department of Anesthetic Service, Royal Hobart Hospital, Tasmania, Australia The study authors stated no sources of external support nor conflicts of interest

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors
Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the analysis and no dropout was reported
Selective reporting (reporting bias)	Low risk	Change in depression scores and adverse events were not reported, yet cognitive tests

Matters 1995 (Continued)

		were performed after ECT
Other bias	Unclear risk	None
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quotation: "The drug group was known only to the administering anaesthetist and the induction agents was administered behind a screen to maintain blindness of other staff"; the anaesthesiologists could know the assigned medications
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotation: "The drug group was known only to the administering anaesthetist and the induction agents was administered behind a screen to maintain blindness of other staff"

Rosa 2008a

Methods	Study design: single-centre, double-blind, randomized parallel trial Mean trial duration: eight ECT sessions
Participants	Inclusion criteria: 30 patients 18 to 60 years of age, with major depression according to <i>DSM-IV</i> and a minimum score of 22 as measured by the Hamilton Rating Scale for Depression (HRSD) Exclusion criteria: not specified
Interventions	Treatment 1: etomidate at 0.15 to 0.30 mg/kg iv + succinylcholine 0.5 to 1.25 mg/kg iv (N = 10) Treatment 2: thiopental at 2.0 to 3.0 mg/kg iv + succinylcholine 0.5 to 1.25 mg/kg iv (N = 10) Control: propofol at 1.0 to 1.5 mg/kg iv + succinylcholine 0.5 to 1.25 mg/kg iv (N = 10) Electrode placement: unilateral Energy: a charge of six times seizure threshold
Outcomes	Outcomes used in this review: 1. Electric charge received. 2. Time to recovery. Outcomes not used in this review: Charge received
Abbreviations	
Notes	Country: Brazil Setting: Institute of Psychiatry, Clinical Hospital, Medical School, Universidade de São Paulo (USP), São Paulo (SP), Brazil The study authors stated no sources of external support nor conflicts of interest Duration of follow-up: not specified

Rosa 2008a (Continued)

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors	
Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors	
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the analysis and no dropout was reported	
Selective reporting (reporting bias)	High risk	Change in depression scores and adverse events were not reported	
Other bias	Unclear risk	None	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotation: "patients and raters were blinded to which anaesthetic drug was given"	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotation: "patients and raters were blinded to which anaesthetic drug was given"	

Rosa 2008b

Methods	Study design: single-centre, double-blind, randomized parallel trial Mean trial duration: eight ECT sessions (the same as in Rosa 2008a)
Participants	Inclusion criteria: 30 patients 18 to 60 years of age, with major depression according to <i>DSM-IV</i> and a minimum score of 22 as measured by the Hamilton Rating Scale for Depression (HRSD) Exclusion criteria: not specified
Interventions	Treatment one: etomidate at 0.15 to 0.30 mg/kg iv + succinylcholine 0.5 to 1.25 mg/kg iv (N = 10) Treatment two: thiopental at 2.0 to 3.0 mg/kg iv + succinylcholine 0.5 to 1.25 mg/kg iv (N = 10) Control: propofol at 1.0 to 1.5 mg/kg iv + succinylcholine 0.5 to 1.25 mg/kg iv (N = 10) Electrode placement: unilateral Energy: a charge of six times seizure threshold

Rosa 2008b (Continued)

Outcomes	Outcomes used in this review: None Outcomes not used in this review: Change in blood pressure and heart rate
Abbreviations	
Notes	Country: Brazil Setting: Institute of Psychiatry, Clinical Hospital, Medical School, Universidade de São Paulo (USP), São Paulo (SP), Brazil The study authors stated no sources of external support nor conflicts of interest

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors
Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the analysis and no dropout was reported
Selective reporting (reporting bias)	High risk	Change in depression scores and adverse events were not reported
Other bias	Unclear risk	None
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotation: "Patients and raters were blinded to which anaesthetic drug was given"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotation: "Patients and raters were blinded to which anaesthetic drug was given"

Sakamoto 1999

Methods	Study design: single-centre, double-blind, randomized parallel trial Mean trial duration: 11 ECT sessions
Participants	Inclusion criteria: 15 chronically depressed patients were included Exclusion criteria: not specified

Interventions	Treatment: thiamylal 4 mg/kg iv + succinylcholine 1.0 mg/kg iv (20 ECT sessions) Control: propofol 1.0 mg/kg iv + succinylcholine 1.0 mg/kg iv (49 ECT sessions); propofol 1.5 mg/kg iv + succinylcholine 1.5 mg/kg iv (49 ECT sessions); propofol 2.0 mg/kg iv + succinylcholine 1.0 mg/kg iv (51 ECT sessions) Electrode placement: bilateral Energy: 110 volt setting for seven seconds
Outcomes	Outcomes used in this review: 1. Seizure duration. 2. Change in blood pressure. 3. Mini-mental score. Outcomes not used in this review: None
Abbreviations	
Notes	Country: Japan Setting: Department of Anesthesiology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan The study authors stated no sources of external support nor conflicts of interest

Risk of bias***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method was provided by the study authors
Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the analysis and no dropout was reported
Selective reporting (reporting bias)	High risk	Change in depression score and adverse events were not reported
Other bias	Unclear risk	None
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on method was provided by the study authors
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on method was provided by the study authors

Methods	Study design: single-centre, double-blind, randomized parallel trial Mean trial duration: not specified
Participants	Inclusion criteria: 90 patients of ASA I to II of either sex, 18 to 60 years of age, scheduled for ECT Exclusion criteria: those with a history of a full stomach, major illness like TB, bronchial asthma, drug allergy, neuromuscular disorders, acute respiratory disorder, hypertension, epilepsy, cardiovascular disease
Interventions	Treatment: thiopentone 5 mg/kg + succinylcholine 0.5 mg/kg (N = 30) Control 1: propofol 2 mg/kg + succinylcholine 0.5 mg/kg (N = 30) Control 2: midazolam 0.2 mg/kg + succinylcholine 0.5 mg/kg (N = 30) Electrode placement: not specified Energy: 90 to 120 volts for two milliseconds
Outcomes	Outcomes used in this review: 1. Seizure duration. 2. Incidence of adverse effects during induction. 3. Incidence of adverse events after anaesthesia. 4. Recovery time. Outcomes not used in this review: Fluctuations in heart rate and blood pressure before and after ECT
Abbreviations	
Notes	Number of ECT sessions: not specified Country: India Setting: Department of Anesthesiology and Critical Care, Pt J.N.M. Medical College and Dr BRAM Hospital, Raipur (CG), India The study authors stated no sources of external support nor conflicts of interest

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	Computer-generated table was used	
Allocation concealment (selection bias)	Unclear risk	No information on method was provided by the study authors as to how to conceal the allocation	
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the analysis and no dropout was reported	
Selective reporting (reporting bias)	Low risk	Only depression score was not reported	
Other bias	Unclear risk	None	

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on method was provided by the study authors
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on method was provided by the study authors

· Abbreviations

ASA = American Society of Anesthesiologists.

BDI = Beck Depression Inventory.

BP = blood pressure.

DSM = *Diagnostic and Statistical Manual of Mental Disorders*.

DSST = Digit Symbol Substitution Test.

ECT = electroconvulsive therapy.

EEG = electroencephalograph.

HDRS = Hamilton Depression Rating Scale.

iv = intravenous.

MADRS = Montgomery Asberg Depression Rating Scale.

MMSE = Mini Mental State Examination.

SD = standard deviation.

TB = tuberculosis

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abdallah 2012	Ketamine was used as induction agent
Anthony 1989	Enrolled participants included patients with other psychological diseases
Arya 2008	Enrolled participants included patients with other psychological diseases
Begec 2007	Enrolled participants included patients with other psychological diseases
Eranti 2009	A naturalistic comparison study
Erdogan 2012	Ketamine was used as induction agent
Geretssegger 1998	Enrolled participants included patients with other psychological diseases
Ingram 2007	It was not reported as a randomized controlled trial
Martensson 1994	Enrolled participants included patients with other psychological diseases

(Continued)

Mizrak 2009	Anaesthetic agents were not used as induction agents
Mokriski 1992	Diseases of participants were not specified
Nguyen 1997	Diseases of participants were not specified
Saffer 1998	The trial was not reported as randomized controlled
Tan 2009	This trial was a single-blind controlled trial
Villalonga 1993	The trial was not reported as randomized controlled
Wang 2012	Ketamine was used as induction agent
Yalcin 2012	Ketamine was used as induction agent

Characteristics of studies awaiting assessment [ordered by study ID]

Canbek 2015

Methods	Trial design: two-week follow-up, single-centre, double-blind, randomized parallel trial Duration: 2010 to 2011
Participants	Number of patient assigned:56 age:20 to 60 Gender:male Inclusion criteria: patients diagnosed with unipolar depression,bipolar affective disorder, schizophrenia,Schizoaffective disorder,Atypical psychosis. Exclusion criteria :Patients who were previously diagnosed cardiovascular disorder
Interventions	1.Group 1 received propofol (0.75 to 1.0 mg/kg)(n=20) versus etomidate (0.15 to 0.25 mg/kg) (n=16) versus thiopental (1.5 to 2.5 mg/kg) (n=15) 2. Bitemporo-frontal ECT was used. 3.The dose of muscle relaxant (ie, succinylcholine) was 0.5 mg/kg
Outcomes	1.Brief Psychiatric Rating Scale (BPRS) was used in all patients, Scale for the Assessment of Positive Symptoms (SAPS) was used in patients with psychotic disorder, Young Mania Rating Scale (YMRS) was used in patients with mania, Hamilton Depression Rating Scale was used in patients with depression 2. Motor and EEG seizure duration 3.Change in cardiovascular system parameters (heart rate [HR], blood pressure, and blood oxygenation 4. Time to recovery
Notes	Country: Turkey. Setting: Seventh Psychiatry Clinics of Bakırköy Teaching,Hospital for Psychiatry, Neurology, and Neurosurgery,, Ankara

Canbek 2015 (Continued)

	The study authors mentioned no sources of external support
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Jarineshin 2016

Methods	Trial design: A prospective double blind randomized clinical trial with a cross over design Duration: year not specified.
Participants	Number of patient assigned:50 Age:18 to 50 Gender:male (60%) and female (40%) Inclusion criteria: patients diagnosed with schizophrenia, major depression disorder,bipolar disorder,obsessive-Compulsive disorder and other psychological diseases. Exclusion criteria :Not specified.
Interventions	2-3 mg/kg intravenous sodium thiopental (50 ECT cycles) versus 1-1.5 mg/kg intravenous Propofol (50 ECT cycles) the muscle relaxant succinylcholine at dose of 0.5 mg/kg
Outcomes	1. Flunctuation of blood pressure and heart rate 2.EEG seizure duration
Notes	Country:Iran Setting: Fereydoon Fekrat, Anesthesiology, Critical Care and Pain Management Research Center, Bandar Abbas The study authors mentioned no sources of external support

Mir 2017

Methods	Trial design: A single-centre, double-blind, randomized parallel trial Duration: not specified
Participants	Number of patient assigned:90 Age:16 to 60 Gender:male (60%) and female (40%) Inclusion criteria: patients diagnosed with schizophrenia, major depression disorder,bipolar disorder,obsessive-Compulsive disorder and other psychological diseases. Exclusion criteria :Patients with full stomach, neuromuscular disorders, hypertension and other cardiovascular disorders, epilepsy, hypopituitarism, drug allergy and major illnesses,like bronchial asthma and tuberculosis, were excluded from the study
Interventions	propofol 1% · 1.5 mg/Kg (n=30) versus etomidate · 0.2 mg/Kg (n=30) versus thiopentone 2.5% · 5 mg/Kg(n=30)
Outcomes	1. Induction time 2. Motor seizure duration 3. Hemodynamic parameters 4.time to recovery

Mir 2017 (Continued)

Notes	Country: India. Setting: Department of Anaesthesiology, Government Medical College, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir The study authors mentioned no sources of external support
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Purtuloglu 2013

Methods	Trial design: two-week follow-up, single-centre, double-blind, randomized parallel trial Duration: 2010 to 2012
Participants	number of patient assigned: 96 age: 27 to 43 gender: not specified. Inclusion criteria: types of psychological diseases not specified. Exclusion criteria: Patients who were unable to give an informed consent owing to severe psychotic symptoms and patients who were involuntarily hospitalized or treated were excluded
Interventions	intravenous sodium thiopental (2.5/3 mg/kg) (n=48) versus intravenous propofol (1.5 mg/kg) (n=48) Intravenous succinylcholine (0.5 mg/kg) was administered for neuromuscular relaxation bilateral temporal stimulation was used for ECT.
Outcomes	1. EEG seizure duration. 2. Time to recovery
Notes	Country: Turkey. Setting: the Departments of *Anesthesiology and Reanimation and Psychiatry, Gulhane Military Medical Academy, Ankara The study authors mentioned no sources of external support

Characteristics of ongoing studies [ordered by study ID]

Godfrey 2011

Trial name or title	The relationship between anaesthetic induction agent type or dose and clinical outcome in patients with depression undergoing electroconvulsive therapy (ECT)
Methods	
Participants	
Interventions	Randomly assigned 40 participants to each of the four anaesthetic induction agent groups (not specified)
Outcomes	Pre-ECT Hamilton Depression Rating Scale (HAM-D) score. Six sessions of ECT, observed motor seizure during, electroencephalogram (EEG) seizure duration in seconds. Post ECT HAM-D score done one to two days after ECT treatment

Godfrey 2011 (Continued)

Starting date	01/03/2003
Contact information	dhmail@doh.gsi.org.uk
Notes	Not finished until 03/11/2011

DATA AND ANALYSES

Comparison 1. Methohexital versus propofol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in Hamilton Depression Scale (HDS) score	4	185	Mean Difference (IV, Fixed, 95% CI)	1.10 [-0.56, 2.77]
1.1 Unilateral electrode placement	4	165	Mean Difference (IV, Fixed, 95% CI)	1.20 [-0.55, 2.95]
1.2 Bilateral electrode placement	1	20	Mean Difference (IV, Fixed, 95% CI)	0.20 [-5.22, 5.62]
2 Baseline Hamilton Depression Scale score	4	165	Mean Difference (IV, Fixed, 95% CI)	3.59 [1.62, 5.55]
3 Post-treatment Hamilton Depression Scale score	4	165	Mean Difference (IV, Fixed, 95% CI)	2.49 [0.08, 4.90]
4 EEG seizure duration (seconds)	2	108	Mean Difference (IV, Fixed, 95% CI)	7.42 [0.39, 14.44]
5 Motor seizure duration (seconds)	2	78	Mean Difference (IV, Fixed, 95% CI)	5.87 [1.97, 9.77]

Comparison 2. Thiopental versus propofol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 EEG seizure duration (seconds)	2	90	Mean Difference (IV, Random, 95% CI)	2.26 [-18.35, 22.87]
2 Time to recovery (minutes)	2	48	Mean Difference (IV, Fixed, 95% CI)	1.72 [0.49, 2.95]

Analysis 1.1. Comparison 1 Methohexital versus propofol, Outcome 1 Change in Hamilton Depression Scale (HDS) score.

Review: Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression

Comparison: 1 Methohexital versus propofol

Outcome: 1 Change in Hamilton Depression Scale (HDS) score

Analysis 1.2. Comparison 1 Methohexital versus propofol, Outcome 2 Baseline Hamilton Depression Scale score.

Review: Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression

Comparison: 1 Methohexital versus propofol

Outcome: 2 Baseline Hamilton Depression Scale score

Analysis 1.3. Comparison 1 Methohexital versus propofol, Outcome 3 Post-treatment Hamilton Depression Scale score.

Review: Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression

Comparison: 1 Methohexital versus propofol

Outcome: 3 Post-treatment Hamilton Depression Scale score

Analysis 1.4. Comparison 1 Methohexital versus propofol, Outcome 4 EEG seizure duration (seconds).

Review: Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression

Comparison: 1 Methohexital versus propofol

Outcome: 4 EEG seizure duration (seconds)

Analysis 1.5. Comparison 1 Methohexital versus propofol, Outcome 5 Motor seizure duration (seconds).

Review: Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression

Comparison: 1 Methohexital versus propofol

Outcome: 5 Motor seizure duration (seconds)

Analysis 2.1. Comparison 2 Thiopental versus propofol, Outcome 1 EEG seizure duration (seconds).

Review: Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression

Comparison: 2 Thiopental versus propofol

Outcome: 1 EEG seizure duration (seconds)

Analysis 2.2. Comparison 2 Thiopental versus propofol, Outcome 2 Time to recovery (minutes).

Review: Different regimens of intravenous sedatives or hypnotics for electroconvulsive therapy (ECT) in adult patients with depression

Comparison: 2 Thiopental versus propofol

Outcome: 2 Time to recovery (minutes)

ADDITIONAL TABLES

Table 1. List of abbreviations used in this review

Abbreviation	Full name
ECT	Electroconvulsive therapy (synonym for modified electroconvulsive therapy in this review)
MADRS	Montgomery-Asberg Depression Scale
HDRS	Hamilton Depression Rating Scale
DSM-IV	<i>The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i>
WHO	World Health Organization
DALY	Disability-adjusted life-year

Table 2. Doses of anaesthetics in mg/kg

Study	Propofol	Methohexital	Thiopental	Etomidate	Midazolam	Thiamylal
Avramov 1995	0.75-1.5	0.75-1.5		0.15-0.3		
Fear 1994	2.1	1.1				
Fredman 1994	0.79	0.79				
Geretsegger 2007	1.7	1.4				
Kirkby 1995	1.4	1.0				
Malsch 1994	1.24	1.1				
Matters 1995	1.4	1.0				
Bauer 2009	1.5		3.0			
Butterfield 2004	1.9		3.0			
Kumar 2012	1.5		3.0			
Rosa 2008a; Rosa 2008b	1.0-1.5		2.0-3.0			
Shah 2010	2.0		5.0		0.2	
Abdollahi 2012			3.0	0.2		

Table 2. Doses of anaesthetics in mg/kg (Continued)

Auriacombe 1995		1.0			0.1	
Sakamoto 1999	1.0-2.0					4.0
Grati 2005	1.5			0.15		

Table 3. Comparisons of seizure duration

Pairs of comparisons	Agents with longer seizure duration
Methohexital versus propofol	Methohexital (EEG and motor)
Thiopental versus propofol	No difference
Etomidate versus propofol	Etomidate (motor)

APPENDICES

Appendix 1. Search strategy for MEDLINE (Ovid SP)

1. Depressive Disorder/ or Depression/ or Depressive Disorder, Major/ or Bipolar Disorder/ or Cognition Disorders/ or exp Electroconvulsive Therapy/ or ((electroconvulsive or electrovulsive) adj3 therapy).mp. or ECT.mp. or (disorder* adj3 (depressive or bipolar or cognition)).ti,ab. or depression.ti,ab.
2. Anesthesia, Intravenous/ or Anesthetics/ or "Hypnotics and Sedatives"/ or Anesthesia/ or Anesthetics, Intravenous/ or (an?esth* adj3 regimen*).mp. or (hypnotic* or sedative* or an?esthetic*).ti,ab.
3. 1 and 2
4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 2. Search strategy for CENTRAL, *The Cochrane Library*

- #1 MeSH descriptor Depressive Disorder, this term only
- #2 MeSH descriptor Depression, this term only
- #3 MeSH descriptor Depressive Disorder, Major, this term only
- #4 MeSH descriptor Bipolar Disorder explode all trees
- #5 MeSH descriptor Cognition Disorders, this term only
- #6 MeSH descriptor Electroconvulsive Therapy explode all trees
- #7 ((electroconvulsive or electrovulsive) near therapy):ti,ab or ECT:ti,ab or (disorder* near2 (depressive or bipolar or cognition)):ti,ab or depression:ti,ab
- #8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
- #9 MeSH descriptor Anesthesia, Intravenous, this term only

#10 MeSH descriptor Anesthetics, this term only
 #11 MeSH descriptor Hypnotics and Sedatives, this term only
 #12 MeSH descriptor Anesthesia, this term only
 #13 MeSH descriptor Anesthetics, Intravenous, this term only
 #14 (an?esth* near2 regimen*):ti,ab or (hypnotic* or sedative* or an?esthetic*):ti,ab
 #15 (#9 OR #10 OR #11 OR #12 OR #13 OR #14)
 #16 (#8 AND #15)

Appendix 3. Search strategy for EMBASE (Ovid SP)

1. depression/ or major depression/ or bipolar disorder/ or cognitive defect/ or exp electroconvulsive therapy/ or ((electroconvulsive or electrovulsive) adj3 therapy).mp. or ECT.mp. or (disorder* adj3 (depressive or bipolar or cognition)).ti,ab. or depression.ti,ab.
 2. intravenous anesthesia/ or anesthetic agent/ or hypnotic agent/ or sedative agent/ or Anesthesia/ or intravenous anesthetic agent/ or (an?esth* adj3 regimen*).mp. or (hypnotic* or sedative* or an?esthetic*):ti,ab.
 3. 1 and 2
 4. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)):ti,ab.) not (animals not (humans and animals)).sh.
 5. 3 and 4

Appendix 4. Study selection form

Included number	trial	First Year	author/	Journal/ Conference proceedings, etc	RCT	Relevant participants	Relevant interventions	Relevant outcomes
					Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear

Appendix 5. Quality assessment of included trials

Randomization	
State here method used to generate allocation and reasons for grading	Grade (circle)
Comment on allocation by review authors or included study quote concerning allocation	Low risk of bias
	High risk of bias
	Unclear risk of bias
Allocation concealment	

(Continued)

State here method used to conceal allocation and reasons for grading	Grade (circle)
Comment on allocation concealment by review authors or included study quote concerning allocation	Low risk of bias
	High risk of bias
	Unclear risk of bias
Blinding	Low risk/high risk/unclear
	Participant low risk/high risk/unclear
	Outcome assessor low risk/high risk/unclear
	Other (please specify) low risk/high risk
	Unclear
Intention-to-treat analysis	Low risk/high risk/unclear
Percentage of participants excluded from the analysis	
Percentage of participants withdrawn from the trial	
Others	

Appendix 6. Characteristics of included trials

Trial characteristics	Further details
Single-centre/Multi-centre	
Country/Countries	
Characteristics of included participants?	
Number of enrolled participants	

(Continued)

Number of participants randomly assigned in each intervention group	
Number of participants who received intended treatment	
Number of participants who were analysed	
Treatment group (types of medications and dosages)	
Control group (types of medications and dosages)	
Dose/Frequency of administration	
Duration of treatment (state weeks/months, etc, if cross-over trial give length of time in each arm)	
Median (range) length of follow-up reported in this paper (state weeks, months or years or if not stated)	
Time points when measurements were taken during the study	
Time points reported in the study	
Trial design (e.g. parallel/cross-over*)	
Others	

Appendix 7. Outcomes extraction form

First author/Publication year	Outcome parameters	Treatment group (no./N)	Control group (no./N)	Treatment group (Mean _i ±SD)	Control group (Mean _i ±SD)
	Primary outcomes				
	Rate of remission of depressive symptoms (after the same sessions of ECT)				
	Reduction in scores of depression rating scale (specified)				

(Continued)

	Anaesthesia-related mortality				
	Time to emergence				
	Time to recovery				
	Electroconvulsive seizure motor duration				
	Electroconvulsive therapy-induced seizure EEG duration				
	Secondary outcomes				
	Risk of postanaesthetic delirium/agitation				
	Risk of postanaesthetic memory loss				
	Postanaesthetic scores of cognitive rating scale (specified)				
	Risk of anaesthesia-related adverse events (specified)				
	Changes in blood pressure (before and after ECT)				
	Changes in heart rate (before and after ECT)				

Did this report include any references to published reports of potentially eligible trials not already identified for this review?

Did this report include any references to potentially eligible trials not already identified for this review?

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list of contact name and details

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list of contact name and details

(Continued)

from potentially
not already ident
view? If yes, give
name and details

Appendix 8. Methohexital versus propofol (Beck Depression Inventory)

Study	Outcomes	Methohexital (N = 11)	Propofol (N = 9)	MD (95% CI)
		Mean (SD)	Mean (SD)	
Fear 1994	Change in Beck Depression Inventory (BDI)	13.3 (7.62)	15.5 (6.92)	-2.20 (-8.58 to 4.18) (P value 0.50)

Appendix 9. Thiopental versus propofol

Study	Outcomes	Thiopental (N = 31)	Propofol (N = 31)	OR (95% CI)
		n (%)	n (%)	
Bauer 2009	Rate of participants with HDRS less than 10	14 (45.2)	17 (54.8)	0.68 (0.25 to 1.84) (P value 0.45)
Bauer 2009	Rate of participants with at least 50% reduction in HDRS	6 (19.4)	5 (16.1)	1.25 (0.34 to 4.63) (P value 0.74)
Study	Outcomes	Thiopental (N = 14)	Propofol (N = 14)	MD (95% CI)
		Mean (SD)	Mean (SD)	
Kumar 2012	Change in Beck Depression Inventory (BDI)	12.0 (9.1)	19.0 (7.1)	-7.00 (-13.05 to -0.95) (P value 0.02)
Butterfield 2004	EEG seizure duration (44 sessions each group) (seconds)	47.2 (11.0)	32.8 (15.1)	14.40 (8.88 to 19.92) (P < 0.001)

(Continued)

Shah 2010	Motor seizure duration (30 sessions each group) (seconds)	36.2 (4.8)	26.3 (2.8)	9.90 (7.90 to 11.90) (P < 0.001)
Butterfield 2004	Time to recovery (44 sessions each group) (minutes)	12.1 (4.2)	9.9 (2.8)	2.20 (0.71 to 3.69) (P value 0.004)

Appendix 10. Thiopental versus etomidate

Study	Outcomes	Thiopental	Etomidate	MD (95% CI)
		Mean/SD (N)	Mean/SD (N)	
Abdollahi 2012	Change in Beck Depression Inventory (BDI)	13.4/4.2 (30)	17.6/5.14 (30)	-4.20 (-6.58 to -1.82) (P < 0.001)
Rosa 2008a	Time to recovery (minutes)	9.4/2.3 (10)	10.7/3.6 (10)	-1.30 (-3.95 to 1.35) (P value 0.34)

Appendix 11. Methohexital versus midazolam

Study	Outcomes	Methohexital (n = 9)	Midazolam (n = 9)	MD (95% CI)
		Mean (SD)	Mean (SD)	
Auriacombe 1995	Change in depression scores (MADRS)	25.3 (4.2)	25.9 (4.2)	-0.6 (-4.4 to 3.2) (P value 0.76)
Auriacombe 1995	Motor seizure duration (seconds)	37.2 (9.0)	36.1 (6.4)	1.1 (-6.1 to 8.1) (P value 0.77)

Appendix 12. Methohexital versus propofol (an orphan cross-over trial)

Study	Outcomes	Methohexital (N = 13)	Propofol (N = 13)	P value
		Mean (SD)	Mean (SD)	
Fredman 1994	EEG seizure duration (seconds)	60.6 (3.03)	52.4 (2.86)	0.016
Fredman 1994	Time to recovery (minutes)	10.0 (0.94)	8.7 (0.4)	0.4

Appendix 13. Etomidate versus propofol

Study	Outcomes	Etomidate	Propofol (N = 14)	P value
		Mean (SD) (N)	Mean (SD) (N)	
Erdil 2009 (cross-over study)	EEG seizure duration (seconds)	44.5 (13.7) (14)	35.8 (11.6) (14)	< 0.05
Erdil 2009 (cross-over study)	Motor seizure duration (seconds)	34.6 (11.7) (14)	29.8 (9.1) (14)	< 0.05
Grati 2005	Motor seizure duration (seconds)	28.8 (3.3) (12)	23.8 (7.2) (13)	< 0.05
Erdil 2009 (cross-over study)	Time to recovery (minutes)	6.6 (2.3) (14)	5.8 (1.9) (14)	> 0.05
Rosa 2008a	Time to recovery (minutes)	10.7 (3.6) (10)	7.4 (1.9) (10)	0.01

Appendix 14. Methohexital versus etomidate

Study	Outcomes	Methohexital (30 sessions)	Etomidate (30 sessions)	MD (95% CI)
		Mean (SD)	Mean (SD)	
Avramov 1995	EEG seizure duration (seconds)	48-62	76-78	-19.1 (-30.7 to -7.5) (P value 0.001)
Avramov 1995	Motor seizure duration (seconds)	29-37	42-44	-8.1 (-13.5 to -2.7) (P value 0.004)
Avramov 1995	Time to recovery (minutes)	15 (7)	19 (10)	-4.0(-8.37 to 0.37) (P value 0.07)

Appendix 15. Methohexital versus propofol (motor seizure duration)

Study	Outcomes	Methohexital (N = 20)	Propofol (N = 19)	P value
		Median (interquartile range)	Median (interquartile range)	
Matters 1995	Motor seizure duration (seconds)	29 (17)	23 (10)	0.08

Appendix 16. Thiopental versus midazolam

Study	Outcomes	Thiopental (30 sessions)	Midazolam (30 sessions)	MD (95% CI)
		Mean/SD	Mean/SD	
Shah 2010	Motor seizure duration (seconds)	36.3 (4.8)	19.7 (3.6)	16.5 (14.3 to 18.7) (P < 0.001)

Appendix 17. Midazolam versus propofol (motor seizure duration)

Study	Outcomes	Midazolam (30 sessions)	Propofol (30 sessions)	MD (95% CI)
		Mean (SD)	Mean (SD)	
Shah 2010	Motor seizure duration (seconds)	19.7 (3.6)	26.4 (2.8)	-6.63(-8.3 to -5.0) (P < 0.001)

Appendix 18. Thiamylal versus propofol (time to recovery)

Study	Outcomes	Thiamylal (20 sessions)	Propofol (49 sessions)	MD (95% CI) (P value)
		Mean (SD)	Mean (SD)	
Sakamoto 1999	Time to recovery (minutes)	10.5 (4.2)	9.6 (3.3)	0.90 (-1.16 to 2.96) (P value 0.39)

Appendix 19. Etomidate versus propofol (postanaesthetic adverse events)

Study	Adverse events ^a	Etomidate (N = 13)	Propofol (N = 13)
		Events n (%)	Events n (%)
Grati 2005	Bradycardia	1 (7.7)	0 (0)
Grati 2005	Pain at injection site	0 (0)	1 (7.7)
Grati 2005	Nausea	3 (23)	0 (0)
Grati 2005	Vomiting	3 (23)	0 (0)

^aP > 0.05 for all pairs of comparisons.

Appendix 20. Thiopental versus etomidate (postanaesthetic adverse events)

Study	Adverse events ^a	Thiopentone (N = 30)	Etomidate (N = 30)
		n (%)	n (%)
Abdollahi 2012	Pain at injection sites	2 (6.6)	2 (6.6)
Abdollahi 2012	Allergy	2 (6.6)	2 (6.6)
Abdollahi 2012	Nausea and vomiting	3 (10)	5 (16.7)
Abdollahi 2012	Myoclonus	0 (0)	3 (10)

^aP > 0.05 for all pairs of comparisons.

Appendix 21. Thiopental versus propofol versus midazolam (postanaesthetic adverse events)

Study	Adverse events ^a	Thiopental (N = 30)	Midazolam (N = 30)	Propofol (N = 30)
		n (%)	n (%)	n (%)
Shah 2010	Delirium	4 (13.3)	6 (20)	0 (0)
Shah 2010	Headache	2 (6.6)	7 (23.3)	0 (0)
Shah 2010	Nausea	7 (23.3)	2 (6.6)	0 (0)
Shah 2010	Vomiting	2 (6.6)	0 (0)	0 (0)
Shah 2010	Pyrexia	1 (3.3)	0 (0)	0 (0)
Shah 2010	Tachycardia	8 (26.7)	7 (23.3)	7 (23.3)
Shah 2010	Allergy	0 (0)	0 (0)	0 (0)
Shah 2010	Thrombophlebitis	0 (0)	1 (3.3)	1 (3.3)
Shah 2010	Apnea	1 (3.3)	0 (0)	0 (0)

^aP > 0.05 for all pairs of comparisons.

WHAT'S NEW

Last assessed as up-to-date: 31 December 2012.

Date	Event	Description
20 March 2017	Amended	A new literature research was conducted in February 2017; four studies aware awaiting classification

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: Peng Lihua (PL).

Co-ordinating the review: Min Su (MS).

Undertaking manual searches: Wei Ke (WK).

Screening search results: PL.

Organizing retrieval of papers: WK.

Screening retrieved papers against inclusion criteria: PL and WK.

Appraising quality of papers: PL and MS.

Abstracting data from papers: WK and PL.

Writing to authors of papers to ask for additional information: PL, Patrick Ziemann-Gimmel (PZG).

Providing additional data about papers: WK.

Obtaining and screening data on unpublished studies: PL.

Managing data for the review: MS, PZG.

Entering data into Review Manager ([RevMan 5.1](#)): PL, WK, PZG.

Analysing RevMan statistical data: PL, MS, PZG.

Performing other statistical analyses not using RevMan: none.

Interpreting data: PL and PZG.

Making statistical inferences: WK.

Writing the review: PL, WK and PZG.

Securing funding for the review: MS.

Performing previous work that provided the foundation for the present study: MS.

Serving as guarantor for the review: PL.

Taking responsibility for reading and checking the review before submission: MS.

DECLARATIONS OF INTEREST

Peng Lihua: none known.

Min Su: none known.

Wei Ke: none known.

Patrick Ziemann-Gimmel (PZG) is a shareholder in Cadence and J&J. PZG received honoraria from Cadence and Baxter.

SOURCES OF SUPPORT

Internal sources

- The First Affiliated Hospital of Chongqing Medical University, China.

Data gathering

External sources

- New Source of support, Other.
- Cochrane Anaesthesia Review Group (CARG), Other.

Data analysis and article writing

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol ([Lihua 2012](#)).

1. All data were published, and no unpublished data were identified.
2. Subgroup analysis according to gender, energy and electrode placement could not be performed because of insufficient data; yet different methods of assessing motor seizure duration (cuff/isolation arm method or visual observation) were counted in subgroup analyses.
3. Appendices 4 to 7 were used as primary screening tools for eligible trials, but study results were not presented in the review. We revised the background information to make it more succinct and to focus on the topic of this review.
4. A new review author (Patrick Ziemann-Gimmel) joined the review team.

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthetics, Intravenous [*administration & dosage]; Depression [*therapy]; Electroconvulsive Therapy [*adverse effects]; Epilepsy, Tonic-Clonic [*complications]; Etomidate [administration & dosage]; Hypnotics and Sedatives [*administration & dosage]; Methohexital [administration & dosage]; Midazolam [administration & dosage]; Propofol [administration & dosage]; Randomized Controlled Trials as Topic; Thiomytal [administration & dosage]; Thiopental [administration & dosage]

MeSH check words

Adult; Humans