HTA Austria
Austrian Institute for
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Electroconvulsive therapy in treatment-resistant depression and treatment-resistant schizophrenia

Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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Content

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List of abbreviations

ADs.....Antidepressants
AEs .....Adverse events
APs .....Antipsychotics
BDI.....Beck Depression Inventory
BF .....Bifrontal
BMSGPK .....Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (Federal Ministry of Social Affairs, Health, Care and Consumer Protection)
BP .....Brief pulse
BPRS .....Brief Psychiatric Rating Scale
BSSI.....Beck Scale for Suicide Ideation
BT.....Bitemporal
CCMD-3 .....Chinese Classification of Mental Disorders
CGI-I .....Clinical Global Impression-Improvement
CGI-S .....Clinical Global Impression-Severity
C-RSSRS.....Columbia – Suicide Severity Rating Scale
CTT.....Color Trails Test
DSM-V .....Diagnostic and Statistical Manual of Mental Disorders-V
DSP .....Digit Span Test
ECT.....Electroconvulsive therapy
EUnetHTA ...European Network for Health Technology Assessment
FDA.....Food and Drug Administration
FGAs .....First-generation antipsychotics
GAF.....Global Assessment of Functioning
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
GSE-My ..... Global Self Evaluation of Memory
HAM-D .....Hamilton Rating Scale for Depression
HDRS .....Hamilton Depression Rating Scale
HVLT-R.....Hopkins verbal Learning Test-Revised
ICD-11 .....International Classification of Diseases
IM.....Intramuscular
INAHTA.....International Network of Agencies for Health Technology Assessment
MA.....Meta-analysis
MADRS .....Montgomery Asberg Depression Rating Scale
MAOIs.....Monoamine oxidase inhibitors
MD .....Mean difference
MDD.....Major depressive disorder
MDE .....Major depressive episode
mECT .....Maintenance ECT
MoCA.....Montreal Cognitive Assessment
NaSSA.....Noradrenergic and specific serotonergic antidepressants
NSRI .....Norepinephrine serotonin reuptake inhibitors
PANSS .....Positive and Negative Syndrome Scale
PHQ-9 .....Patient Health Questionnaire
QIDS-SR.....Quick Inventory of Depressive Symptomatology-Self-Report Scale

Q-LES-Q.....Quality of Life Enjoyment and Satisfaction Questionnaire
RAVLT.....Rey Auditory Verbal Learning Test
RCT.....Randomized controlled trial
RoB.....Risk of bias
ROBIS.....Risk of Bias Assessment Tool for Systematic Reviews
ROT.....Rey-Osterrieth Complex Figure Test
RR.....Relative risk
rTMS.....Repetitive transcranial magnetic stimulation
RUL.....Right unilateral
SAEs.....Serious adverse events
SANS.....Scale for the Assessment of Negative Symptoms
SAPS.....Scale for the Assessment of Positive Symptoms
SARA-SR.....Social Adjustment Scale-Self Report
ScoRS.....Schizophrenia Cognition Rating Scale
SCWT.....Stroop Color Word Test-Victoria version
SD.....Standard deviation
SDS.....Sheehan Disability Scale
SGAs.....Second-generation antipsychotics
SMCQ.....Squire Memory Com-plaint Questionnaire
SMD.....Standardised mean difference
SoF.....Summary of findings
SPARI.....Serotonin partial agonist reuptake inhibitor
SR.....Systematic review
SSRI.....Selective serotonin reuptake inhibitors
ST.....Seizure threshold
TCAs.....Tricyclic antidepressants
TESS.....Treatment Emergent Symptom Scale
TGAs.....Third-generation antipsychotics
TMT.....Trail Making Test
TRD.....Treatment-resistant depression
TRRIP.....Treatment Response and Resistance in Psychosis
TRS.....Treatment-resistant schizophrenia
UBP.....Ultrabrief pulse
WMD.....Weighted mean difference
WMS.....Wechsler Memory Scale

Executive Summary

Introduction

Health Problem

Treatment-resistant depression (TRD) and treatment-resistant schizophrenia (TRS) are the target populations in this assessment. TRD typically refers to major depressive disorder (MDD) showing resistance to treatment despite the use of at least two different antidepressant medications, regardless of whether they belong to the same or different classes, given in appropriate doses and durations with adequate adherence. Management options for TRD comprise dose adjustments, augmentation, combination, and switching medications, including intranasal esketamine. Add-on psychotherapy, electroconvulsive therapy (ECT), or repetitive transcranial magnetic stimulation (rTMS) are options at any treatment stage.

TRD: resistance to ≥ 2 antidepressants (ADs)

pharmacological and/or non-pharmacological treatment options

TRS criteria, require a schizophrenia diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, with at least moderate symptom severity, alongside functional impairment, and prior treatment involving at least two trials of antipsychotics lasting more than six weeks at a therapeutic dose. TRS management options include dose adjustments of antipsychotics, polypharmacy, clozapine, ECT and rTMS.

TRS: resistance to ≥ 2 antipsychotics (APs); pharmacological and/or non-pharmacological treatment options

Description of Technology

ECT involves applying a small electrical current to the scalp under general anaesthesia and muscle relaxants, inducing a controlled seizure. It is indicated for use in conditions like catatonia, severe depression in MDD or bipolar disorder in patients older than 13 years, especially those resistant to treatment or needing quick intervention. ECT treatments typically range from 6 to 12 sessions, two to three times a week. Common side effects include headaches, muscle soreness, and nausea, and negative impacts on the cognitive function.

ECT: induction of a seizure to the brain under general anaesthesia

Methods

This report aimed to investigate whether ECT is more effective than and at least as safe as standard treatment comprising pharmacological and/or non-pharmacological treatment options in the management of TRD and TRS.

aim: to assess ECT compared to standard care in patients with TRD or TRS

A systematic literature search in Medline and Cochrane Library, and a hand-search in PubMed was conducted in December 2023 to identify relevant systematic reviews (SRs) for TRD and TRS. The quality of the SRs was evaluated using the Risk of Bias Assessment Tool for Systematic Reviews (ROBIS). Three SRs for TRD and one for TRS met our pre-defined inclusion and quality criteria. Additionally, a systematic search in four databases for recent RCTs was conducted. After deduplication, 1,627 citations were identified. No additional citations were found by hand-search. The Cochrane risk of bias 2.0 tool was used to assess the quality of RCTs. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence. The quality and certainty assessments were performed by two independent researchers.

2-step systematic literature search:
1. SRs
2. RCTs to update the SRs

1,627 hits

quality appraisal, certainty assessment

Domain effectiveness

The following endpoints were considered critical for decision-making: mortality (suicide-related events), response and remission rate.

critical endpoints: suicide-related events, response, and remission

Domain safety

The following endpoints were considered critical for decision-making: serious adverse events (SAEs).

critical endpoints: serious adverse events

Results

Treatment-resistant depression

Available evidence

Three systematic reviews and four RCTs were included to investigate the effectiveness and safety of ECT for TRD. The review incorporates a total of 29 RCTs (n= 2,101), covering ECT versus ketamine (n=697), ECT versus rTMS (n=306), and ECT versus antidepressants (n=1,098). In terms of study design, two RCTs evaluated the non-inferiority of ketamine compared to ECT, while the rest of the RCTs had a superiority design. The mean age of patients across all studies ranged from 30 to 45 years. Follow-up duration ranged from one week to 12 months.

TRD: 3 SRs (27 RCTs) + 2 RCTs 2,101 patients

Clinical effectiveness

The *rTMS* comparison studies found that ECT was slightly more effective in reducing suicide scores, measured as the mean difference (MD) of the subscore on the Hamilton Depression Rating Scale (HAM-D/HDRS, n=113, HAM-D: MD -0.63, HDRS: MD -1.5) or on the Beck's Depression Inventory (n=73, MD -0.6). ECT was also more effective in alleviating depression symptoms (n=225, MD -5.85, 95% CI, -9.37 to -2.34) and improving response (n=126, risk ratio (RR) 1.72, 95% CI, 0.95 to 3.11) and remission rates (n=118, RR 1.44, 95% CI, 0.64 to 3.23), although these results were statistically non-significant. *Ketamine* comparison studies showed statistically non-significant minor advantages in depression symptoms with ECT (n=253, standardised mean difference (SMD) -0.3, 95% CI, -0.78 to 0.18) and statistically non-significant improvements with ECT on response (n=568, RR 1.02, 95% CI, 0.88 to 1.19) and remission rate (n=551, RR 0.97, 95% CI, 0.79 to 1.2). Suicide scores measured with the Beck Scale for Suicide Ideation decreased more in the ECT group. However, results were statistically significant only at 24 hours (MD -0.01, p=0.045) and at the second week after intervention (MD -0.31, p=0.033), but not at the 1-month follow-up (MD -1.53, p=0.7). Suicide scores measured with the Columbia-Suicide Severity Rating Scale showed no difference at the end of treatment. One patient died in the ECT group, and no one died in the ketamine group (n=181). Suicidal attempt was 3% more in the ECT group than in the ketamine group at 12 months (n=181) and 1% less at six months (n=178). Suicidal ideation was 1% more at the end of treatment with ECT (n=403) and 3% more at six months with ketamine (n=178). When ECT was *added to antidepressants*, significant improvements in response rates were found with ECT (n=871, RR 1.82, 95% CI, 1.55 to 2.14). ECT *monotherapy*, compared with antidepressants, also showed significant improvement in response rates (n=150, RR 2.24; 95% CI, 1.51 to 3.33).

ECT vs rTMS: ECT improves suicide and depression scores, response and remission rates

ECT vs ketamine: ECT improves depression symptoms, response and remission rates; inconsistent results for suicide scores, suicidal attempts, and suicidal ideation

ECT + ADs vs ADs and ECT vs ADs: ECT improves response rates

Safety

No SAEs occurred in the *rTMS* comparison studies (n=113). In *ketamine* comparison studies (n=589), SAEs did not show statistically significant differences (after treatment, 1% more ketamine patients, at 12 months, 11% more ECT patients experienced SAEs). The *antidepressant combination* therapy studies found no significant difference with ECT added to antidepressants for somatisation (n=710, RR 0.79, 95% CI, 0.61 to 1.01) and memory deterioration (n=292, RR 0.27, 95% CI, 0.03 to 2.4). Similarly, in studies comparing ECT monotherapy and *antidepressants*, no significant difference was detected for somatisation (n=191, RR 1.22, 95% CI, 0.69 to 2.17), and for memory deterioration with ECT (n=111, RR 0.88, 95% CI, 0.41 to 1.88).

ECT vs rTMS: no SAEs

ECT vs ketamine: no statistically significant (s.s.) difference

ECT+ADs vs ADs and ECT vs ADs: no s.s. difference in somatisation and memory deterioration

Treatment-resistant schizophrenia

Available evidence

One systematic review and three RCTs were included to investigate the efficacy and safety of ECT in treating TRS. The review incorporates a total of 18 RCTs involving 1,368 patients, comparing ECT as augmentation to antipsychotics against clozapine plus antipsychotics (ziprasidone, n=162), and antipsychotics alone (flupentixol, n=30), ECT as augmentation to standard care to standard care alone (n=1,137), as well as ECT versus sham-ECT (n=54). Standard care in the review refers to the treatment that the patients received during the trial alongside the trial intervention. The mean age of patients across all studies was between 18 and 48 years. The follow-up duration ranged from 4 to 12 weeks.

TRS: 1 SR (15 RCTs) + 3 RCTs 1,368 patients

Clinical effectiveness

Adding ECT to standard care improved schizophrenia symptoms significantly compared to *standard care alone*. The symptoms were measured with the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impression-Severity (CGI-S) at eight to twelve weeks after treatment (BPRS: n=345, MD -11.18, 95% CI, -12.61 to -9.76. PANSS: n=492, MD -24.06, 95% CI, -25.21 to -22.91. CGI-S: n=23, MD 0.12, 95% CI, -0.9 to 0.66). The response rate was significantly higher with ECT in the same comparison at four weeks (n= 819, RR 2.06, 95% CI, 1.75 to 2.42). When comparing ECT to *sham-ECT* (n=23), response rates in the two groups were similar at four weeks. In ECT plus antipsychotics versus *clozapine plus antipsychotics* studies, the response rate was higher with ECT. The result is, however, statistically non-significant (n=162, RR 1.23, 95% CI, 0.95 to 1.58). In the same comparison, the schizophrenia symptoms improved more with ECT at four weeks (BPRS: n=161, MD -5.2, 95% CI, -7.93 to -2.47). When compared with *antipsychotics*, ECT improved schizophrenia symptoms more (BPRS: n=30, MD -0.93, 95% CI, -6.95 to 5.09). However, the result is statistically non-significant. Overall mortality, suicidal attempts, and suicide ideation were not reported in the studies.

ECT + standard of care (SoC) vs SoC: ECT improves schizophrenia symptoms and response rates

ECT vs sham-ECT: no differences

ECT + antipsychotics (APs) vs clozapine + APs: ECT improves schizophrenia symptoms and response rates

ECT vs APs: ECT improves schizophrenia symptoms

Safety

One ECT plus standard care versus *standard care* study reported memory deterioration as part of the cognitive functioning outcomes, showing significantly more patients suffering memory loss with ECT (n=72, RR 27, 95% CI, 1.67 to 437.68). Serious adverse events were not reported in any of the other comparisons.

ECT + SoC vs SoC: memory deterioration significantly more with ECT

Upcoming evidence

2 large-scale trials

Two large-scale trials are ongoing. One trial, involving over 400 patients with MDD aims to investigate the efficacy of non-invasive neuromodulation techniques (including rTMS and ECT), and drug therapy on depression symptoms, response, and remission. The other trial, involving 1,500 patients with acute suicidal depression aims to investigate if ketamine is non-inferior to ECT in terms of suicidal ideation.

Discussion

uncertainties regarding long-term effectiveness and safety in general

small, open-label studies with high RoB

uncertain generalisability for older patients and adolescents

ECT is recognised as effective and safe by guidelines, yet uncertainties about its mechanism, long-term effectiveness and safety in general persist. The evidence primarily consists of older studies, mainly from the 2000s and early 2010s, except for more recent ketamine studies. The included studies often had small sample sizes, were open-label, and had a high risk of bias. Findings highlight an underreporting of safety outcomes, especially key safety concerns like potential brain damage and memory loss, obscuring risk-benefit assessments. There is a notable absence of studies comparing combination or augmentation with psychotherapy. The evidence does not cover broader populations, indicating a gap in generalisability, especially for older patients and adolescents. Variability in ECT protocols and including concomitant medications during trials reflect clinical practice but challenge standardisation and comparison of outcomes. Short follow-up periods and the absence of established minimum clinically important differences limit the ability to assess long-term effects and clinical significance. The review calls for further research on ECT's safety and long-term efficacy, including its use in sensitive groups and impact on cognitive functions and mortality.

limitations of our SR

Limitations of our assessment include data access issues, and we did not analyse demographic subgroups, electrode configurations, or pulse variations, all of which are significant to ECT's effectiveness and adverse effects. Furthermore, we did not explore ECT as a maintenance treatment and omitted studies on bipolar depression, except where they formed a small segment of the sample.

Conclusion

TRD: ECT + ADs is more effective and as safe as ADs, insufficient evidence for ECT vs rTMS, ketamine, and ADs

Moderate certainty evidence indicates that in TRD patients, adding ECT to antidepressants is more effective in improving clinical response without raising the risk of somatisation, in comparison to using antidepressants alone. Likewise, there is no elevated risk for memory deterioration associated with this combination. However, the certainty of the evidence regarding memory deterioration is low. Additionally, the currently available evidence is insufficient to prove the added benefit of ECT compared to rTMS, ketamine and antidepressants alone due to very low to low certainty of evidence. New study results may influence the effect estimate considerably.

TRS: ECT + SoC is more effective than SoC; safety uncertain, insufficient evidence for all other comparisons

Moderate certainty evidence indicates that in TRS patients, adding ECT to standard care is more effective in improving clinical response compared to standard care alone. The currently available evidence is insufficient to demonstrate that this combination is as safe as standard care. Furthermore, evidence comparing the effectiveness and safety of adding ECT to antipsychotics versus the combination of clozapine with antipsychotics is lacking. Similarly, there is inadequate evidence to assess ECT's comparative effectiveness and safety against sham-ECT or antipsychotics alone.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Therapieresistente Depression (TRD) und therapieresistente Schizophrenie (TRS) beschreiben psychische Erkrankungen, welche nicht adäquat auf eine Therapie ansprechen. Um tatsächlich von einer therapieresistenten Form der Depression oder Schizophrenie zu sprechen, müssen bestimmte Kriterien erfüllt werden. TRD bezieht sich in der Regel auf eine schwere Depression, die trotz der Einnahme von mindestens zwei verschiedenen Antidepressiva in einer angemessenen Dosis und Dauer resistent gegenüber der Behandlung ist. Behandlungsansätze umfassen die Anpassung der Medikamentendosierung, Augmentation (Add-on zu einer anderen Therapieform/eines anderen Wirkstoffes), Kombination und das Wechseln von Medikamenten, sowie intranasales Esketamin. Zur nicht medikamentösen Therapie zählen Add-on Psychotherapie, Elektrokonvulsionstherapie (EKT) und repetitive transkranielle Magnetstimulation (rTMS), welche in jeder Behandlungsphase möglich sind.

TRD: Resistenz gegenüber ≥2 Antidepressiva (AD)

medikamentöse und nicht medikamentöse Therapieoptionen

Für eine TRS definierte die Treatment Response and Resistance in Psychosis (TRRIP) Working Group 2017 Kriterien. Demnach ist eine Schizophrenie-Diagnose mit mindestens mittelschwerer Symptomatik, zusammen mit funktionaler Beeinträchtigung und vorheriger Behandlung mit mindestens zwei Antipsychotika , jeweils für einen Zeitraum von sechs Wochen, erforderlich, um von einer therapieresistenten Schizophrenie zu sprechen. Therapiemaßnahmen beinhalten die Anpassung der Antipsychotika, Polypharmazie, Clozapin, EKT und rTMS.

TRS: Resistenz gegenüber ≥2 Antipsychotika (AP)

medikamentöse und nicht medikamentöse Therapieoptionen

Die Lebenszeitprävalenz der schweren Depression beträgt 1,2 % in Österreich, wobei sich bei 20-30 % der Betroffenen eine therapieresistente Form entwickeln kann. Die Lebenszeitprävalenz der Schizophrenie beträgt weltweit zwischen 0,3 und 1 %, mit einer Inzidenz von 10,2-22,0 pro 100.000 Personen pro Jahr. Für Österreich bedeutet dies mehr als 1.000 Neuerkrankungen pro Jahr. Abhängig von der gewählten Definition kann die Rate der Therapieresistenz zwischen 20 % und 70 % variieren.

Prävalenz: 1,2 % schwere Depression in Österreich, davon potenziell 20-30 % TRD; 0,3-1 % Schizophrenie weltweit, davon potenziell 20-70 % TRS

Beschreibung der Technologie

Elektrokonvulsionstherapie (EKT) löst unter Narkose und Muskelrelaxantien einen kontrollierten zerebralen Anfall durch eine kurze elektrische Stimulation aus. Indikationen für die EKT stellen unter anderem Katatonie, schwere Depressionen oder bipolare Störungen bei Patient*innen über 13 Jahren dar. Insbesondere wird EKT bei therapieresistenten Formen eingesetzt, oder wenn eine schnelle Intervention (z. B. bei Suizidalität) erforderlich ist. EKT-Behandlungen umfassen in der Regel sechs bis zwölf Einheiten, zwei bis drei Mal pro Woche, die genaue Anzahl kann jedoch variieren. Häufige Nebenwirkungen sind Kopfschmerzen, Muskelschmerzen und Übelkeit, wobei eine mögliche Beeinträchtigung der kognitiven Funktion ein bedeutender Risikofaktor ist.

kontrollierter zerebraler Anfall

Patient*innen über 13 Jahre

6-12 Einheiten, 2-3 Mal pro Woche

Nebenwirkungen möglich

Methoden

Dieser Bericht bewertet die Sicherheit und Wirksamkeit der EKT bei Erwachsenen mit TRD oder TRS.

Ziel: Sicherheit und Wirksamkeit der EKT bei TRD oder TRS

Es wurde zunächst eine systematische Literatursuche in zwei medizinischen Datenbanken (Medline, Cochrane Library) sowie eine Handsuche in PubMed durchgeführt, um relevante systematische Übersichtsarbeiten (SRs) für TRD und TRS zu identifizieren. Die Vertrauenswürdigkeit der SRs wurde mit dem Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) bewertet. Insgesamt wurden für beide Indikationen SRs mit ausreichender Qualität identifiziert. Danach wurde eine systematische Update-Suche nach rezenten randomisierten kontrollierten Studien (RCTs) in vier Datenbanken (Medline, Cochrane Library, Embase und die INAHTA Database) durchgeführt. Diese Suche ergab 1.627 Treffer nach Deduplizierung.

2-stufige Ansatz bei der Literatursuche:
1. SRs
2. RCTs für Update der SRs

Bewertung der Vertrauenswürdigkeit der SRs: ROBIS-Tool

Die Studienauswahl, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurde von zwei Autorinnen unabhängig voneinander durchgeführt. Eine dritte Autorin wurde bei Unstimmigkeiten zur Entscheidungsfindung involviert. Die Bewertung der eingeschlossenen RCTs erfolgte mit dem Cochrane Risk of Bias Tool v.2 (RoB2). Die Vertrauenswürdigkeit in die Evidenz wurde nach dem GRADE-Bewertungsschema (Grading of Recommendations, Assessment, Development and Evaluations) eingestuft.

Bewertung der Vertrauenswürdigkeit der RCTs mit RoB2, der Evidenz mit GRADE

Klinische Wirksamkeit

Zur Bewertung der klinischen Wirksamkeit wurden folgende Endpunkte als *entscheidungsrelevant* definiert: Mortalität (suizidbezogene Ereignisse), Ansprechen auf die Therapie und Remissionsrate.

entscheidungsrelevante Wirksamkeitsendpunkte

Sicherheit

Zur Bewertung der Sicherheit wurden folgende Endpunkte als *entscheidungsrelevant* definiert: schwerwiegende unerwünschte Ereignisse (SAEs).

entscheidungsrelevante Sicherheitsendpunkte

Ergebnisse

Therapieresistente Depression

Verfügbare Evidenz

Drei SRs und zweiRCTs erfüllten die vordefinierten Einschlusskriterien zur Untersuchung der Wirksamkeit und Sicherheit der EKT bei TRD. Insgesamt umfasst diese Übersichtsarbeit 29 RCTs mit 2.101 Patient*innen. Darunter waren zwei RCTs als Nichtunterlegenheitsstudien konzipiert (beide verglichen EKT mit Ketamin), während die restlichen RCTs ein Überlegenheitsdesign hatten. In den Studien wurde EKT mit Ketamin (n=697), rTMS (n=306) und Antidepressiva (n=1.098) verglichen. Im Mittel waren die Patient*innen zwischen 30 und 45 Jahre alt. Die Nachbeobachtungszeiten in den RCTs betrugen zwischen einer Woche und zwölf Monaten.

TRD: 3 SRs (27 RCTs) und 2 RCTs
2.101 Patient*innen

Klinische Wirksamkeit

EKT vs. rTMS: Suizid- und Depressionsscores, Ansprech- und Remissionsraten zugunsten EKT, aber nicht statistisch signifikant (n.s.)

Die Ergebnisse deuten darauf hin, dass die Anwendung von EKT möglicherweise zu einer etwas stärkeren Reduktion der Suizidalität im Vergleich mit rTMS führen kann. Die Suizidalität wurde anhand der Mittelwertdifferenz (MD) auf der Hamilton-Depressions-Skala (HAM-D/HDRS, n=113) sowie dem Beck-Depressions-Inventar (BDI, n=73) gemessen, (HAM-D: MD -0,63, HDRS: MD -1,5 und BDI: MD -0,6). Ebenso deutet sich eine mögliche Verbesserung der Depressionssymptome bei Anwendung von EKT an (n=225; MD -5,85; 95 % KI, -9,37 bis -2,34), sowie in einer Verbesserung der Ansprechrate (n=126, Risikoreduktion (RR) 1,72; 95 % KI, 0,95 bis 3,11) sowie der Remissionsraten (n=118; RR 1,44; 95 % KI, 0,64 bis 3,23), obwohl diese Ergebnisse statistisch nicht signifikant waren.

EKT vs. Ketamin: Depressionsscores, Ansprech- und Remissionsraten zugunsten EKT, aber n.s.

Suizidscores, Suizidversuche und Suizidgedanken zeigen inkonsistente Ergebnisse

Vergleichsstudien mit Ketamin zeigten statistisch nicht signifikante, nichtsdestotrotz etwas bessere Ergebnisse bei Depressionssymptomen (n=253, standardisierte Mittelwertdifferenz (SMD) -0,3; 95 % KI, -0,78 bis 0,18) zugunsten der EKT sowie statistisch nicht signifikante Verbesserungen der Ansprech- (n=568; RR 1,02; 95 % KI, 0,88 bis 1,19) und Remissionsraten (n=551; RR 0,97; 95 % KI, 0,79 bis 1,2) mit EKT. Die Suizidwerte, gemessen mit der Beck-Skala für Suizidgedanken, verringerten sich in der EKT-Gruppe stärker. Jedoch waren die Ergebnisse nur 24 Stunden (MD -0,01, p=0,045) und in der zweiten Woche nach der Intervention (MD -0,31, p=0,033) statistisch signifikant. Suizidwerte, gemessen mit der Columbia-Suizid-Schwere-Skala, zeigten am Ende der Behandlung keinen Unterschied zwischen den Gruppen. Ein Patient verstarb in der EKT-Gruppe, während in der Ketamin-Gruppe kein Todesfall verzeichnet wurde (n=181). Die Suizidversuchsrate war in der EKT-Gruppe nach zwölf Monaten um 3 % höher als in der Ketamin-Gruppe (n=181) und nach sechs Monaten um 1 % niedriger (n=178). Suizidgedanken waren am Ende der Behandlung mit EKT um 1 % höher (n=403) und nach sechs Monaten mit Ketamin um 3 % höher (n=178).

EKT + AD vs. AD sowie EKT vs. AD: zusätzliche EKT verbessert Ansprechraten

Die Augmentation von EKT zu Antidepressiva resultierte in signifikant höheren Ansprechraten (n= 871; RR 1,82; 95 % KI, 1,55 bis 2,14) im Vergleich zur alleinigen Therapie mit Antidepressiva. Ebenso wurden höhere Ansprechraten mit EKT als Monotherapie im Vergleich zu Antidepressiva festgestellt (n= 150; RR 2,24; 95 % KI, 1,51 bis 3,33).

Sicherheit

EKT vs. rTMS: keine SAEs

EKT vs. Ketamin: kein s.s. Unterschied

EKT+AD vs. AD und EKT vs. AD: kein s.s. Unterschied bei Somatisierung und Gedächtnisstörung

In den rTMS-Vergleichsstudien (n=113) traten keine schwerwiegenden unerwünschten Ereignisse (SAEs) auf. In den Ketamin-Vergleichsstudien (n=589) gab es keine statistisch signifikanten Unterschiede bei SAEs (1 % mehr Ketamin-Patient*innen erlebten SAEs nach der Behandlung, nach zwölf Monaten waren es 11 % mehr EKT-Patient*innen). Die EKT-Augmentation zu Antidepressiva zeigte keinen signifikanten Unterschied für Somatisierung (n=710; RR 0,79; 95 % KI, 0,61 bis 1,01) und Gedächtnisstörungen (n=292; RR 0,27; 95 % KI, 0,03 bis 2,4). Ebenso wurde in Vergleichsstudien von EKT-Monotherapie und Antidepressiva kein signifikanter Unterschied für Somatisierung (n=191; RR 1,22; 95 % KI, 0,69 bis 2,17) und für Gedächtnisstörungen (n=111; RR 0,88; 95 % KI, 0,41 bis 1,88) festgestellt.

Therapieresistente Schizophrenie

Verfügbare Evidenz

TRS:
1 SR (15 RCTs) und 3 RCTs

1.368 Patient*innen

Ein SR und drei RCTs wurden inkludiert, um die Wirksamkeit und Sicherheit der EKT bei der Behandlung von TRS zu untersuchen. Diese Übersichtsarbeit umfasst insgesamt 18 RCTs mit 1.368 Schizophrenie-Patient*innen mit einem Alter von 18 bis 48 Jahren. In den Studien wurde EKT als Augmentation zu Antipsychotika mit Clozapin und Antipsychotika (n=162), oder Antipsychotika allein (n=30) verglichen, EKT als Augmentation zur Standardtherapie mit alleiniger Standardtherapie (die Therapie, welche Patient*innen während der Studie neben der Interventionstherapie bekommen haben) (n=1.137), oder EKT mit Schein-EKT (n=53). Die Nachbeobachtungszeiten betrugen zwischen vier und zwölf Wochen.

Klinische Wirksamkeit

EKT + Standardtherapie (ST) vs. ST: EKT verbessert Schizophreniesymptome und Ansprechrate (s.s.)

EKT vs. Schein-EKT: keine Unterschiede

EKT + AP vs. Clozapin + AP: EKT verbessert Schizophreniesymptome und Ansprechrate

EKT vs. AP: EKT verbessert Schizophreniesymptome

EKT-Augmentation zur Standardtherapie zeigte signifikante Verbesserungen der Schizophreniesymptome im Vergleich zur alleinigen Standardtherapie. Die Symptome wurden mit der Kurzform der Psychiatrischen Beurteilungsskala (BPRS), der Skala für Positive und Negative Syndrome (PANSS) und der Klinischen Gesamteindruck-Schweregrad-Skala (CGI-S) acht bis zwölf Wochen nach der Behandlung gemessen (BPRS: n=345; MD -11,18; 95 % KI, -12,61 bis -9,76. PANSS: n= 492; MD -24,06; 95 % KI, -25,21 bis -22,91. CGI-S: n=23; MD 0,12; 95 % KI, -0,9 bis 0,66). Im selben Vergleich war die Ansprechrate mit EKT nach vier Wochen signifikant höher (n=819; RR 2,06; 95 % KI, 1,75 bis 2,42). Beim Vergleich von EKT mit Schein-EKT (n=23) waren die Ansprechraten in beiden Gruppen nach vier Wochen ähnlich. In Studien, die EKT plus Antipsychotika versus Clozapin plus Antipsychotika verglichen, war die Ansprechrate mit EKT höher. Das Ergebnis ist jedoch statistisch nicht signifikant (n=162; RR 1,23; 95 % KI, 0,95 bis 1,58). Im selben Vergleich verbesserten sich die Schizophreniesymptome mit EKT nach 4 Wochen stärker (BPRS: n=161; MD -5,2; 95 % KI, -7,93 bis -2,47). Im Vergleich zu Antipsychotika verbesserte EKT die Schizophreniesymptome stärker (BPRS: n=30; MD -0,93; 95 % KI, -6,95 bis 5,09). Allerdings ist das Ergebnis statistisch nicht signifikant. Gesamtmortalität, Suizidversuche und Suizidgedanken wurden in den Studien nicht berichtet.

Sicherheit

EKT + ST vs. ST: signifikant mehr Gedächtnisstörungen mit EKT

Eine Studie, die EKT plus Standardtherapie gegenüber der Standardtherapie verglich, berichtete über Gedächtnisstörungen als Teil der kognitiven Funktions-Ergebnisse und zeigte signifikant mehr Patient*innen, die unter Gedächtnisstörungen durch EKT litten (n=72, RR 27, 95 % KI, 1.67 bis 437.68). SAEs wurden in keiner der anderen Vergleiche berichtet.

Laufende Studien

2 laufende Studien

Es konnten zwei laufende Studien, welche 400 und 1.500 Patient*innen mit schweren Depressionen und Depressionen mit akuter Suizidalität inkludieren identifiziert werden. Eine Studie (n=1.500) untersucht die Wirksamkeit der EKT gegenüber Ketamin im Zuge einer Nichtunterlegenheitsstudie. In der anderen Studie, einer Überlegenheitsstudie (n=400), wird EKT mit rTMS und medikamentöser Therapie verglichen, um die Wirksamkeit in Bezug auf Suizidgedanken, Symptomen, Ansprechen auf die Therapie und Remission zu untersuchen.

Diskussion

Unklarheiten zu Langzeitwirkungen und Sicherheit

EKT wird in den klinischen Leitlinien als sicher und wirksam beschrieben. Dennoch bestehen Unklarheiten bezüglich des genauen Wirkmechanismus, potenzieller Langzeitwirkungen und der Sicherheit der Behandlung. Die vorliegende Evidenz basiert größtenteils auf älteren Studien, die im Zeitraum 2000 bis Anfang der 2010er Jahre durchgeführt wurden, abgesehen von den neueren Studien zu Ketamin. Die einbezogenen Studien hatten oft kleine Stichprobengrößen, waren unverblindet und wiesen ein hohes Risiko für Verzerrungen auf. Hinsichtlich des Sicherheitsprofils der EKT gibt es Evidenzlücken. Insbesondere die potenzielle Schädigung des Gehirns und mögliche Gedächtnisstörungen werden nicht ausreichend berichtet, was eine Risiko-Nutzen-Bewertung erschwert. Ebenso fehlen Studien, die die Kombination oder Augmentation von EKT mit Psychotherapie untersuchen. Die vorliegende Evidenz deckt nur eine begrenzte Altersgruppe der Patient*innen ab, was die Verallgemeinerung der Ergebnisse erschwert, insbesondere für ältere Patient*innen und Jugendliche. Die Unterschiede in den EKT-Protokollen und die Einbeziehung bestehender Medikation spiegeln die Praxis wider, stellen aber eine zusätzliche Herausforderung für die Standardisierung und den Vergleich von Ergebnissen dar. Konkrete Schlussfolgerungen werden durch die kurze Follow-Up Zeiten und das Fehlen etablierter minimal klinisch relevanter Unterschiede erschwert. Weitere Untersuchungen zur Sicherheit der EKT, besonders in Hinblick auf Langzeitwirkungen und den Einsatz in sensiblen Gruppen ist notwendig.

kleine Stichprobengrößen, hohes RoB

Evidenz schließt eine begrenzte Altersgruppe ein, was eine Verallgemeinerung der Ergebnisse erschwert

Untersuchungen zu Langzeitwirkungen notwendig

Limitationen

Die Limitationen dieser Übersichtsarbeit umfassen den mangelnden Zugang zu Daten aus Primärstudien (der verwendeten SR). Die Limitationen der Evidenz sind das Fehlen einer Analyse demographischer Untergruppen, Informationen zu Elektrodenplatzierungen und Impulsbreite. Diese Aspekte haben einen entscheidenden Einfluss auf die Wirksamkeit und Sicherheit der EKT. Zudem wurde die EKT als Erhaltungstherapie nicht untersucht. Ebenso wurden Studien mit Patient*innen mit bipolarer Störung ausgeschlossen, es sei denn, es handelte sich um eine kleine Gruppe.

Schlussfolgerung

TRD: mögliche verbesserte Ansprechrate bei gleicher Sicherheit mit EKT + AD, unzureichende Evidenz zum Vergleich mit anderen Therapien

Die Evidenz deutet darauf hin, dass TRD-Patient*innen, die zusätzlich zu Antidepressiva EKT erhalten, eine verbesserte Ansprechrate zeigen, ohne das Risiko für Somatisierung im Vergleich zur alleinigen Verwendung von Antidepressiva zu erhöhen. Ebenso ist mit dieser Kombinationsbehandlung kein erhöhtes Risiko für Gedächtnisstörungen verbunden. Allerdings ist die Vertrauenswürdigkeit der Evidenz für die Ansprechrate und Somatisierung moderat und für Gedächtnisstörungen niedrig. Zudem reicht die verfügbare Evidenz nicht aus, um einen Zusatznutzen von EKT im Vergleich zu rTMS, Ketamin und EKT-Monotherapie gegenüber Antidepressiva abzuleiten. Ergebnisse aus den laufenden Studien könnten den Effekt erheblich beeinflussen.

TRS: mögliche verbesserte Ansprechrate mit EKT + ST, unzureichende Evidenz zur Sicherheit und zum Vergleich mit anderen Therapien

Die Evidenz weist auf eine verbesserte Ansprechrate für TRS-Patient*innen hin, die EKT plus Standardtherapie erhielten, im Vergleich zur alleinigen Standardtherapie. Die Evidenz ist unzureichend, um eine Aussage zu therapiebedingten Nebenwirkungen treffen zu können. Ebenso ist die Evidenz für den Vergleich von EKT mit Schein-EKT, EKT mit anderen Antipsychotika, sowie von EKT plus Antipsychotika zu Clozapin plus Antipsychotika nicht ausreichend.

1 Background

1.1 Overview of the disease, health condition and target population[1]

Treatment-resistant depression (TRD)

schwere Depression ohne Ansprechen auf Therapie mit Antidepressiva (AD)

kein Konsens über Anzahl und Art der erfolglosen Antidepressiva-Behandlungen

Treatment-resistant depression (TRD) typically refers to major depressive disorder (MDD) that does not respond to treatment with at least two different antidepressant agents (of the *same or a different class*) prescribed in adequate dosages for adequate duration and adequate adherence [1-5]. The German S3 Guideline "Unipolar Depression" [6] defines TRD as no response to at least two different antidepressants from *different classes*, adequately dosed, meaning that non-response to an initial therapy and at least one additional treatment strategy is required. The above definitions do not address add-on strategies (e.g. psychotherapeutic interventions, especially when combined with pharmacological treatment) nor differentiate between partial and no response [4, 6]. Additionally, due to the lack of consensus in describing acute antidepressant responses, the actual diagnosis of TRD might vary.

Zielgruppe: Patient*innen mit wiederkehrender, schwerer Depression, und Nichtansprechen auf 2 Behandlungsstrategien, oder

EKT-Kandidat*innen

In this report, the TRD population is defined as individuals with recurrent severe depressive disorder with or without psychotic features, manifesting any subtype of depression as per the International Classification of Diseases-11th Revision (ICD-11) or the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) or the Chinese Classification of Mental Disorders, Third Edition (CCMD-3) or their related earlier versions meeting the following criteria[2]:

- In the ongoing depressive episode, the patient has exhibited insufficient response to an initial therapeutic approach and one or more supplementary treatment strategies. This includes a lack of response to two antidepressant switches within the same class administered at appropriate durations and doses. Furthermore, the absence of response to a comprehensive psychological treatment course is classified as treatment failure or
- The patient is referred by a psychiatrist for electroconvulsive therapy (ECT).

[1] This section addresses the following assessment elements:
A0002 – What is the disease or health condition in the scope of this assessment?
A0003 – What are the known risk factors for the disease or health condition?
A0004 – What is the natural course of the disease or health condition?
A0005 – What is the burden of disease for patients with the disease or health condition?
A0006 – What are the consequences of the disease or health condition for the society?
A0007 – What is the target population in this assessment?
A0023 – How many people belong to the target population?

[2] Multiple taxonomies are available for diagnosing depressive disorders, including the American Psychiatric Association's DSM-V. A reasonable alternative to DSM-V is the World Health Organization's ICD-10 and 11 [7] or the CCMD-3 [8].

Risikofaktoren: u. a. Schwere der Symptome, Anzahl früherer Episoden, und Dauer der aktuellen Episode

TRD presents a complex challenge, particularly in its nature and progression. Initially, TRD appears as a standard depressive episode, and it becomes resistant to treatment over time, potentially leading to chronicity. The origin of a treatment-resistant episode remains unclear compared to initially responsive ones [3]. Factors associated with a higher occurrence of TRD include the severity of depressive symptoms, psychotic symptoms, suicidality, comorbid generalised anxiety disorder, the number of previous depressive episodes, and the duration of the current depressive episode [9].

Selbstmordversuche,

hohes Mortalitätsrisiko,

hohe Komorbidität,

Nebenwirkungen von Medikamenten

The most severe symptom of a major depressive episode (MDE) is suicide (including homicide). Moreover, individuals under 60 years with MDD face a higher mortality risk, independent of their lifestyle, attributed partly to factors such as multimorbidity and frailty [10]. Additionally, MDD is also associated with significant medical comorbidity, and it complicates recovery from other medical illnesses, such as myocardial infarction [11]. Other comorbid conditions that are more prevalent among TRD patients include joint, limb, or back pain, hypertension, dyslipidaemia, malaise or fatigue, anxiety, and personality disorder. Suicidal ideation is estimated to have a rate of 15±8% in TRD patients, 6% in treatment-responsive depression, and 1% in the general population [12]. Medication-related adverse events like decreased sexual desire, orgasmic dysfunction, blurred vision, dissociative reactions, ataxia, mixed states (dysphoric mania or agitated depression), tremor, and nausea also burden MDD patients. TRD is linked to a significant impact on productivity loss, with an estimated loss of 24,192 years of life due to disability and 5,692 years of life lost to premature death [13].

Prävalenzdaten: 1,2 % schwere Depression, davon etwa 20-30 % therapieresistent

Prevalence estimates of TRD differ across sources. The lifetime prevalence of MDD is estimated at 1,2% in Austria [14], with approximately 20-30% potentially being treatment-resistant [9]. Another study [13] assessing the cost of illness and the disease burden of TRD in Austria estimated TRD prevalence at 43,732 patients, translating to 583 per 100,000 population.

Treatment-resistant schizophrenia (TRS)

Nichtansprechen auf Therapie mit Antipsychotika (AP)

Patients with schizophrenia who do not respond adequately to two or more trials of standard antipsychotic medications are associated with treatment-resistant schizophrenia (TRS) [15]. However, research on TRS and the guidelines for its treatment rely on different definitions of the condition, which is why, in 2017, the Treatment Response and Resistance in Psychosis (TRRIP) Working Group published consensus-based criteria for diagnosing TRS [16]. Minimal TRRIP criteria for TRS contain a DSM-V diagnosis of schizophrenia, at least moderate symptom severity, indicated by a standardised scale, functional impairment, and prior treatment of at least two trials of antipsychotics for more than six weeks at a therapeutic dose. Optimal TRRIP criteria are met when minimal TRRIP criteria are fulfilled; symptom severity is prospectively assessed using a standardised scale, incorporating at least one long-acting injectable antipsychotic in one of the two trials and confirming antipsychotic adherence through the measurement of at least two antipsychotic plasma levels [17].

TRIPP Arbeitsgruppe: Kriterien für Diagnose

Schizophrenie und schizoaffektive Störung unterscheiden sich

In the ICD-10, schizophrenia and schizoaffective disorder were classified together [18]. However, the ICD-11 distinguishes them. In the ICD-11, schizoaffective disorder is characterised as an episodic condition where diagnostic criteria for both schizophrenia and a mood disorder (manic, mixed, or moderate to severe depressive episode) are met concurrently or within a few days during the same illness episode. Psychomotor disturbances, including cata-

tonia, may also be present. Persistence of these symptoms for at least one month is required for a diagnosis [19].

Prävalenz von Schizophrenie weltweit ähnlich: 2022 ungefähr 1 %

The prevalence of schizophrenic disorders is similar in various countries around the world, independent of sociocultural backgrounds. In 2008, the prevalence of schizophrenia ranged between 0.3 and 0.6% [20, 21]. In 2022, the prevalence is about 1% in women and men worldwide [22] with an incidence of 10.2–22.0 per 100,000 person-years [21]. For Austria, this means more than 1,000 new cases per year.

heterogener Krankheitsverlauf

The course of illness is characterised by its heterogeneity. Nevertheless, functional recovery tends to be less frequent during the early stages of the illness. In addition, the course is influenced by numerous factors, including early intervention, a multidisciplinary care approach, level of stressors, and adherence to medication regimen [23].

hohe Suizidrate oftmals ein Suizidversuch vor Therapiebeginn

zusätzliche mögliche Todesursachen aufgrund von Komorbiditäten

Schizophrenia is associated with a high suicide rate. Many patients have already attempted suicide at least once before starting therapy, and for some, the suicide attempt is the trigger for seeking help. Suicide attempts in patients with psychotic disorders are often serious, and those who survive the attempt may bear lasting consequences. Suicide risk is closely associated with depression, prior suicide attempts, substance abuse, agitation, as well as motor restlessness and poor therapy adherence [24]. In addition, not only suicides are associated with schizophrenia but also premature mortality due to cardiovascular disease, infections, respiratory tract diseases and cancer [25].

1.2 Current clinical practice[3]

Treatment-resistant depression (TRD)

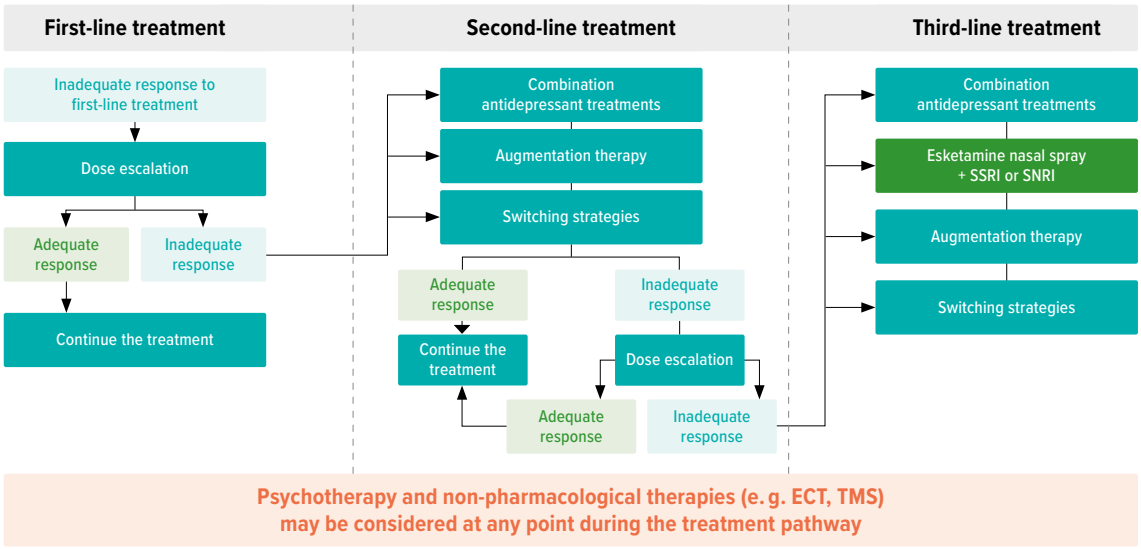
kein allgemein anerkannter Behandlungsalgorithmus

in Österreich: Dosiseskalation, Augmentationstherapie, Kombination antidepressiver Therapien, Switching, Esketamin-Nasenspray

Add-on Psychotherapie, EKT und rTMS können zu jederzeit eingesetzt werden

Clinical practice guidelines often lack detailed guidance for patients with at least two unsuccessful treatment attempts. The absence of an internationally accepted definition of TRD also hampers the development of a universally accepted treatment algorithm. However, an algorithm (see Figure 1-1) has recently been presented by Austrian experts that incorporates the considerations for dose escalation, augmentation (adding a second agent that is not an antidepressant but may enhance its effect, mainly lithium is used), combination (adding another antidepressant from a different class) and switching medication. Intranasal use of esketamine presents itself as a further possible treatment step. It is important to note that add-on psychotherapy, ECT, or repetitive transcranial magnetic stimulation (rTMS) can be considered at any treatment step. The patient should not be assigned to one of these treatments based on the severity or duration of treatment if there is evidence from the history or current status for a favourable response to this form of therapy [3]. In addition, reference should also be made to the German S3-Guideline "Unipolar Depression", which emphasises the importance of supportive strategies among other sports and psychosocial therapies [6].

[3] This section addresses the following assessment elements:
A0024 – How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025 – How is the disease or health condition currently managed according to published guidelines and in practice?



Abbreviations: ECT – electroconvulsive therapy; MDD – major depressive disorder; SNRI – serotonin and norepinephrine reuptake inhibitor; SSRI – selective serotonin reuptake inhibitor; TMS – transcranial magnetic stimulation.

Figure 1-1: Treatment algorithm for major depressive disorder (according to [3])

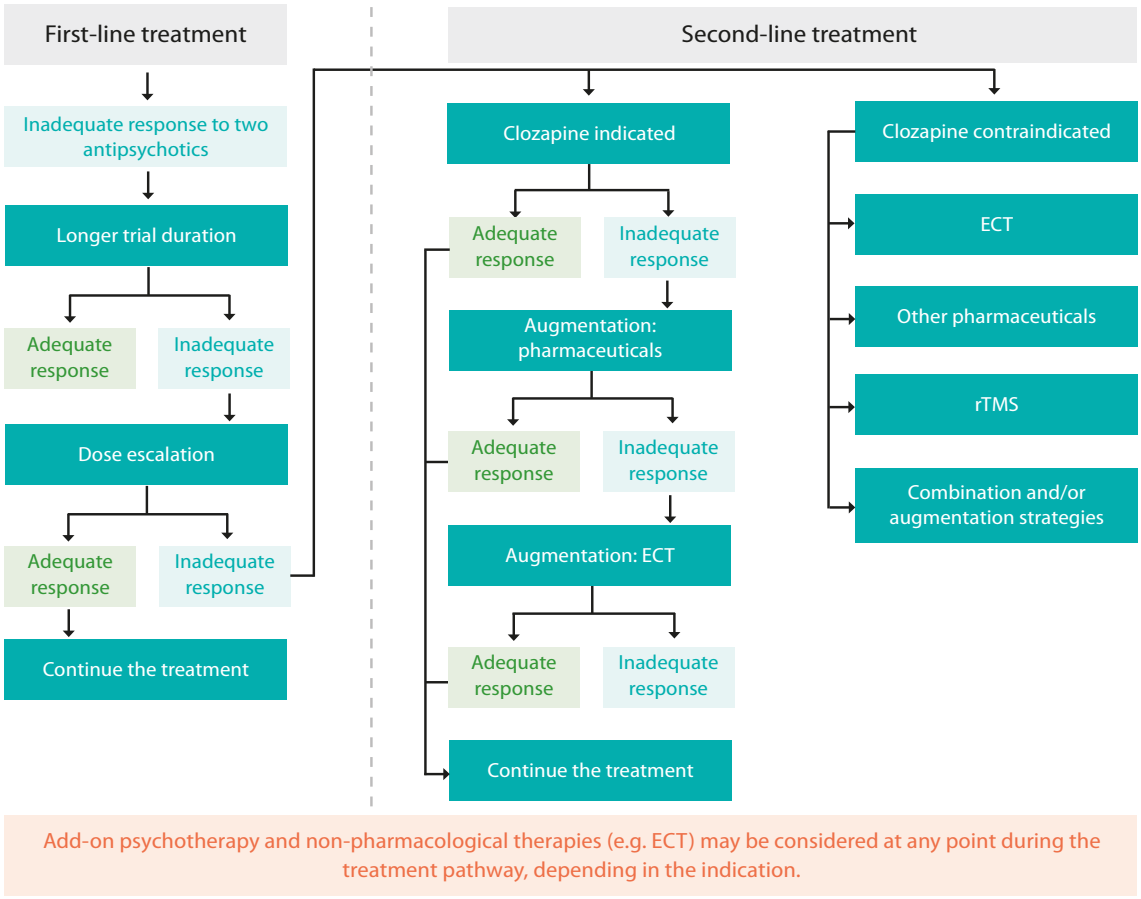
Treatment-resistant schizophrenia (TRS)

Anpassung der AP, Polypharmazie, Clozapin

Optimierung von Clozapin, Kombination/ Augmentation mit anderen Medikamenten, EKT oder rTMS

Clinical practice guidelines suggest re-assessing the treatment plan if there is no response after 12 weeks of treatment with two antipsychotics. Recommendations include extending antipsychotic trial durations, administering higher doses of non-clozapine antipsychotics, employing polypharmacy, and exploring alternative pharmacologic options like clozapine [26]. However, clozapine is not suitable for every patient. If clozapine is contraindicated, alternative strategies such as ECT, rTMS and other pharmaceuticals (e.g. lamotrigine, topiramate, minocycline) should be considered alongside combination and/or augmentation strategies [22, 28, 29]. The German S3-Guideline[4] and the American Psychological Association Practice Guideline advocate for optimising and continuing clozapine use before considering augmentation with another medication or ECT if other strategies do not yield adequate responses [27, 28]. Following an ineffective eight-week ECT augmentation trial, additional medications like lamotrigine, topiramate, minocycline, or rTMS augmentation are recommended [23]. In cases with a suicide risk, a two-week treatment duration may be deemed sufficient before assessing further clinical actions [26]. The guidelines did not provide a treatment algorithm. Hence, an algorithm was created based on the information derived from the included guidelines (Figure 1-2).

[4] Valid until March 2023, currently under revision.



Abbreviations: ECT – electroconvulsive therapy, rTMS – repetitive transcranial magnetic stimulation

Figure 1-2: Treatment algorithm for TRS

1.3 Features of the intervention[5]

Features of the assessed intervention

EKT: ältestes somatisches Behandlungsverfahren

Electroconvulsive therapy (ECT) is the oldest somatic therapy still in use in a wide variety of psychiatric disorders. The main indications for ECT are severe unipolar and bipolar depression, depression with psychotic features, and TRD. However, ECT is also indicated in severe manic and mixed affective episodes, as well as in paranoid and catatonic schizophrenia [3]. ECT devices have CE marking for treating catatonia, severe MDE associated with MDD or bipolar disorder in patients aged 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition [29]. ECT is claimed to be an effective non-pharmacological treatment of TRD with a good safety profile [3, 30, 31]. Additionally, ECT can also be employed as a continuation or maintenance strategy to reduce relapse [32].

Hauptindikationen: schwere unipolare und bipolare Depression, psychotische Depression und TRD, paranoide und katatonische Schizophrenie

Strom wird durch das Gehirn geleitet

Wirkmechanismus noch unklar

During ECT, an electric current is passed briefly through the brain via electrodes applied to the scalp to induce generalised seizure activity. The exact mechanism of action is still under investigation, but the main hypotheses include seizure-induced changes in neurotransmitters, neuroplasticity, and functional connectivity. ECT is a complex intervention, and its effectiveness and safety are affected by several parameters, including the placement of electrodes, dosage and waveform of the electrical stimulus and the frequency with which ECT is administered [32, 33]:

Elektrodenplatzierung

- Electrode position: bilateral (bitemporal or bifrontal) or right unilateral (RUL).

Intensität

- Electrical intensity is determined by the minimum amount required to induce a generalised seizure, referred to as the seizure threshold (ST). In bilateral treatments, 1.5 to 2.0 times the ST, while in RUL, 5-6 to 8 times the ST is used. A meta-analysis involving eight trials with a total of 617 participants revealed comparable effectiveness among the two forms of bilateral treatments and RUL. However, they may impact specific cognitive domains differently (bitemporal is associated with a higher incidence of short-term cognitive adverse effects).

Impulsbreite: Ultrakurz- und Kurzpulstechnik

- Pulse width: typically, a brief pulse (BP) width is employed, but in the last decade, there has been growing clinical use and research attention on ultra-brief pulse width (UBP), which is below 0.5 millisecond. UBP is potentially linked to reduced short-term cognitive impairment. Nonetheless, UBP may be associated with a slower pace of improvement and may necessitate a greater number of treatments compared to BP.

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[5] This section addresses the following assessment elements:
B0001 – What is the technology and the comparator(s)?
A0001 – For which health conditions, and for what purposes is the technology used?
A0020 – For which indications has the technology received marketing authorisation or CE marking?
B0002 – What is the claimed benefit of the technology in relation to the comparators?
B0003 – What is the phase of development and implementation of the technology and the comparator(s)?
B0004 – Who administers the technology and the comparators and in what context and level of care are they provided?
A0021 – What is the reimbursement status of the technology?

- The number of ECT treatments required to achieve response and/or remission ranges between six and 15. ECT is usually delivered two to three treatments per week until response and/or remission is achieved (except for pernicious catatonia). More than three treatments per week are not recommended, as they are associated with a higher frequency of cognitive side effects.

zwischen 6 und 15 EKT Behandlungen, 2-3-Mal pro Woche empfohlen

ECT has been available since the 1930s. Over the years, the technique has undergone various adjustments, incorporating the utilisation of general anaesthesia and muscle relaxants (also known as modified ECT) [6, 33].

unter Kurznarkose und Muskelrelaxation

While there are no absolute contraindications to ECT, the following conditions may be associated with an increased safety risk: space-occupying cerebral lesion, increased intracranial pressure, recent myocardial infarction, recent cerebral haemorrhage, unstable vascular aneurysm or malformation, pheochromocytoma, and class four or five anaesthesia risk [32]. The most common adverse events of ECT include but are not limited to headaches, muscle soreness, nausea etc. Additionally, ECT negatively impacts cognitive function limiting its overall acceptability [34].

häufigste Nebenwirkungen: Kopfschmerzen, Muskelschmerzen und Übelkeit, negative Auswirkung auf die kognitive Funktion

The ECT procedure necessitates patients to complete a consent form and undergo a thorough pre-assessment examination. The decision to use ECT should be made jointly by the individual and the clinician(s) based on an informed discussion [32]. ECT can be conducted on either an inpatient or outpatient basis [35]. However, in Austria, it is offered exclusively as an inpatient therapy [3]. It necessitates the presence of three adequately equipped rooms: a preparation room, an administration room, and a recovery room. The procedure is conducted by a team comprising a psychiatrist, an anaesthesiologist, and a nurse, who continuously monitor the patient's condition throughout the entire process to implement appropriate interventions as needed [30, 36, 37].

EKT stationär oder ambulant möglich (in Österreich nur stationär)

Team zur Beobachtung während der Durchführung notwendig

ECT is included in the Austrian benefit catalogue (code AA210). The intervention is delivered under general anaesthesia with muscle relaxation by a specially trained team (specialists in psychiatry and anaesthesia, nurses from anaesthesia and psychiatry) [38].

Kosten werden für die EKT rückerstattet

Currently, ECT is offered at the psychiatric departments of the following Austrian university clinics and hospitals: Medical University of Vienna, Medical University of Graz, Medical University of Innsbruck, Kepler University Hospital Neuromed Campus Linz, University Hospital Salzburg, State Hospital Rankweil, Pyhrn-Eisenwurzen Clinic Steyr, State Hospital Villach, Private Clinic Villach, Salzkammergut Clinic Vöcklabruck, and Clinic Wels-Grieskirchen. Additionally, the State Clinic Neunkirchen is currently working on implementing ECT. The number of ECT treatments per year is estimated to be between 1,500 and 2,000 ECT in routine care at psychiatric departments in Austria for about 150 patients with severe affective or schizophrenic disorders [3]. However, this estimation is likely to be on the conservative side, based on expert input.

Einrichtungen in Österreich: u. a. medizinische Universität Wien, Graz, Innsbruck, sowie andere Einrichtungen in den Bundesländern

Features of the comparators

Standard care consisting of third-line pharmacotherapy in the context of TRD and second-line pharmacotherapy in the context of TRS and non-pharmacotherapy are considered as comparators in this assessment. From the wide range of non-pharmacological treatment strategies, only the non-experimental

Komparatoren: medikamentöse und nicht-medikamentöse Therapien aus Leitlinien

treatments established in clinical guidelines are considered.

The following comparator interventions can be used combined with one another or as an augmentation to enhance treatment effects.

Third-line pharmacotherapy in TRD

Antidepressiva

Antidepressants are a group of medications with a wide array of classes available for the treatment of depression. There are several different classes, including:

- Atypical antidepressants,
- Monoamine oxidase inhibitors (MAOIs),
- Noradrenergic and specific serotonergic antidepressants (NaSSA),
- Norepinephrine serotonin reuptake inhibitors (NSRIs),
- Serotonin partial agonist reuptake inhibitors (SPARIs),
- Selective serotonin reuptake inhibitors (SSRIs),
- Tricyclic antidepressants (TCAs), and
- Unicyclic antidepressants.

AD als Initialbehandlung

Verbesserungen mit medikamentöser Therapie oft nach 4-6 Wochen

mögl. Nebenwirkungen: Magenbeschwerden, Müdigkeit, sexuelle Dysfunktion

Antidepressant medication can be employed as the initial treatment for patients experiencing mild, moderate, or severe depressive episodes. The selection of antidepressant medications depends on both patient-specific and drug-specific factors. Typically, SSRIs are considered the first-line antidepressants due to their favourable side effect and safety profiles. Other preferred options include tricyclic antidepressants, mirtazapine, bupropion, and venlafaxine. Improvement with pharmacotherapy is often noticeable after four to six weeks of treatment. There are several kinds of medications (and brands) within each class, and each has different possible side effects. In general, common side effects of antidepressants include diarrhoea, headache, drowsiness, and sexual dysfunction. Possible complications associated with antidepressants include the risk of suicidal thoughts or behaviour, antidepressants discontinuation syndrome, serotonin syndrome and overdose [39].

Lithium: Augmentation (wenn AD nicht ansprechen)

Lithium is primarily employed in the treatment of bipolar disorder. Additionally, lithium can be used as augmentation to antidepressants in case of inadequate response in the treatment of unipolar depression. It is also utilised as monotherapy for managing acute episodes of unipolar depression and as a maintenance treatment to prevent the recurrence of unipolar depressive episodes [40].

Ketamin und Esketamin: bei TRD

Verabreichung: oral, intravenös, intramuskulär, intranasal

Nebenwirkungen: Dissoziation, psychotomimetische Effekte, erhöhter Blutdruck

Ketamin-Missbrauch

Ketamine is racemic mixture comprising two enantiomers, S-ketamine (esketamine) and R-ketamine. Ketamine or esketamine may be considered for the treatment of treatment-resistant, severe unipolar MDD lacking psychotic features when patients have not responded to or declined other recommended treatments. The precise mechanism of action for the rapid antidepressant effects of ketamine and esketamine remains unknown. Nevertheless, various studies suggest that ketamine exhibits an affinity for multiple receptors. The optimal route, frequency, and dose of administering ketamine in the context of TRD have not been conclusively established (intravenous administration, intramuscular (IM), intranasal, oral, subcutaneous, and sublingual formulations). Short-term adverse effects include dissociation, psychotomimetic effects, and cardiovascular changes such as elevated systolic and diastolic blood pressure and increased pulse; most of these side effects resolve quickly. However, ketamine has the potential to act as a transient intoxicant and is susceptible to abuse, addiction, and diversion as an illicit recreational drug. Keta-

mine abuse is also associated with neurotoxicity and bladder dysfunction. Regarding esketamine, it is usually given intranasally [41].

AP: 3 Generationen (FGA, SGA, TGA)

Nebenwirkungen mit: GA: u. a. Dyskinesien, plötzlicher Tod; SGA: u. a. Gewichtszunahme, niedriger Blutdruck; TGA: u. a. Gewichtszunahme, Dyskinesie, Krampfanfälle

Antipsychotics can be categorised into three generations. First-generation antipsychotics (FGAs) are known as typical or conventional antipsychotics, and second-generation antipsychotics (SGAs) are atypical antipsychotics. Third-generation antipsychotics (TGAs) are partial agonists of dopamine receptors and were introduced in the 2000s. Common side effects of FGAs encompass extrapyramidal symptoms, tardive dyskinesia, hyperprolactinemia, neuroleptic malignant syndrome, sudden death, and an elevated mortality risk. SGAs commonly induce weight gain, metabolic effects, hypotension, sedation, anticholinergic symptoms, hyperprolactinemia, extrapyramidal symptoms, cardiac effects, and sexual dysfunction. Still, they present lower risks of extrapyramidal symptoms and tardive dyskinesia than FGAs. Common adverse reactions of TGAs include weight gain, akathisia, dyskinesia, orthostatic hypotension, and seizures. FGAs and SGAs generally exhibit similar clinical effectiveness. The choice of antipsychotic depends on dosing, administration route, pharmacokinetics, side effect profile, and costs [42-44].

Second-line pharmacotherapy in TRS

Empfehlung für Clozapin bei TRS, allerdings häufig mit Nebenwirkungen verbunden

Antipsychotics: second-line antipsychotic treatment comprises a non-clozapine FGA or SGA (e.g., ziprasidone). Clozapine is an SGA, mostly recommended in TRS, but can also be indicated in earlier stages. It is associated with a lower risk of suicide or suicide attempts in comparison to other antipsychotics, as well as a better response to treatment. However, side effects which are related to clozapine are not uncommon, including sialorrhea, fever, dizziness, sedation, constipation, and nausea [27].

Augmentationstherapien

Non-antipsychotic medications are considered as a pharmaceutical augmentation of antipsychotics, which include therapy with lamotrigine, minocycline as well as topiramate [23, 45].

Non-pharmacotherapy in TRD and TRS

rTMS: nicht invasive Gehirnstimulation durch ein magnetisches Feld

Behandlungsprotokoll

weder Narkose noch Muskelrelaxantien notwendig

Repetitive transcranial magnetic stimulation (rTMS) involves the non-invasive stimulation of brain tissue by generating a magnetic field of either high or low intensity, with the aim of modulating cortical excitability. The neuromodulatory outcomes are contingent upon diverse stimulation parameters, including frequency, intensity, duration, cortical target, number of sessions, and individual factors such as age, disease status, medication history, and specific symptoms [46]. Various treatment protocols are available, but the protocol recommended by the Food and Drug Administration (FDA) is commonly followed. It specifies an intensity of 120% of the patient's motor threshold, with a total of 3,000 pulses per session, lasting 37.5 minutes [47]. Compared to ECT, there is no need to apply anaesthesia or muscle relaxants [6]. The primary adverse effects of rTMS include scalp pain during stimulation, and transient headache after stimulation, both diminishing over treatment, and resulting in low discontinuation rates. The most severe adverse event associated with rTMS is seizure induction, with fewer than 25 reported cases worldwide to date [32].

Psychotherapie

Psychotherapy is tailored to each patient. The use of psychotherapies as standalone treatment in TRD or TRS is not supported by evidence. Nonetheless, there is evidence that supports the effectiveness of psychotherapy when combined with pharmacotherapy [48, 49].

Table 1-1: Features of the intervention and comparators

	Intervention/ Technology	Pharmacotherapy comparators (monotherapy or combination, unless defined otherwise)		Non-pharmacotherapy comparators
		TRD	TRS	
Name	ECT Monotherapy, combination, or augmentation therapy	*Antidepressants* *Antipsychotics* *Lithium* (augmentation) Ketamine and esketamine	*Anti-psychotics*	*rTMS* *Psychotherapy* (add-on therapy)
Proprietary name (manufacturer) of medical device	Thymatron® (Somatics, LL) Spectrum ECT devices (production discontinued in 2019 and replaced by Sigma ECT devices) (MECTA) Ectonustim series (ECTRON)	Within each category and class, numerous pharmacological agents are available. Specific brand names will not be listed.		Neurostar® MS System (Neurostar) PowerMAG (Mag&More) Rapid2 Therapy System, Super Rapid2 (Magstim) Neuro-MS (Neurosoft) MagVita TMS Therapy System (Magventure)
Class of medical device	IIb	NA		IIa

Abbreviations: ECT – Electroconvulsive therapy, rTMS – repetitive Transcranial Magnetic Simulation, TRD – treatment-resistant depression, TRS – treatment-resistant schizophrenia

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is electroconvulsive therapy (ECT) as monotherapy, combination therapy or as augmentation to another non-pharmaceutical or pharmaceutical intervention in comparison to standard care in patients with treatment-resistant depression (TRD) and patients with treatment-resistant schizophrenia (TRS) more effective and safe concerning mortality (suicide-related events), as well as response and remission rates?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	**1. Treatment-resistant depression (TRD)** Patients with recurrent depressive disorder presenting any subtype of depression (e.g. chronic, with catatonic features, with melancholic features, with atypical features, and with seasonal pattern) as per ICD-11 and earlier versions, DSM-V, and earlier versions or CCMD and meeting the following criteria: a. within the current depressive episode, have not sufficiently responded to[6] an initial therapy as well as one or more additional treatment strategies or b. referred as being candidates for electroconvulsive therapy. ICD-10: F33. 2 Recurrent depressive disorder, current episode severe without psychotic symptoms, F33.3 Recurrent depressive disorder, current episode severe with psychotic symptoms, F06.1 Organic catatonic disorder. ICD 11: 6A71.3 Recurrent depressive disorder, current episode severe, without psychotic symptoms, 6A71.4 Recurrent depressive disorder, current episode severe, with psychotic symptoms. DSM V: 296.33 Major depressive disorder, severe. 296.34 Major depressive disorder, severe with psychotic features. 293.89 (F06.1) Major depression with catatonia. ICD-9 and DSM-III codes approximating these codes are also appropriate. Mesh-term: Depressive disorder, treatment-resistant, F03.600.300.388 **2. Treatment-resistant schizophrenia (TRS)** Patients with any subtype of schizophrenia and schizoaffective disorder as per ICD-11 or earlier versions, DSM-V, or earlier versions or CCMD, and having treatment resistance as per Modified Kane's criteria or Treatment Response and Resistance in Psychosis (TRRIP) Working Group criteria. ICD-10: F20 Schizophrenia, F25: Schizoaffective disorder, F06.1 Organic catatonic disorder. ICD-11: 6A20 Schizophrenia, 6A21 Schizoaffective disorder. DSM V: 295.90 (F06.1) Schizophrenia, 293.89 (F06.1) Schizoaffective disorder. ICD-9 and DSM-III codes approximating these codes are also appropriate. Mesh-term: Schizophrenia, treatment-resistant, F03.700.750.650 *Rationale*: informed by guidelines "S3-Leitlinie Nationale Versorgungsleitlinie Unipolare Depression" [6], NICE "Depression in adults: treatment and management" [50], "APA Clinical practice guideline for the treatment of depression across three age cohorts" [51], "S3-Leitlinie Schizophrenie" [28], the Consensus statement of the Austrian Society for Neuropsychopharmacology and Biological Psychiatry (ÖGPB) on treatment-resistant depression [3] and best available evidence-based clinical information on current clinical practice (from UpToDate).

[6] Non-response to within-class antidepressant switches (e.g. two SSRIs, or two SNRIs) for sufficient doses and treatment duration will be considered failing two trials of antidepressants. Similarly, failure to respond to an adequate course of psychological treatment will be considered treatment failure. Studies including patients with bipolar disorder will be eligible for inclusion if <20% of the included patients were diagnosed with bipolar depression.

Intervention	**Electroconvulsive therapy (ECT)** as *monotherapy* or in *combination* with standard care (non-pharmaceutical or pharmaceutical intervention or their combination) or as an *augmentation* to another non-pharmaceutical or pharmaceutical intervention. ECT is indicated as third-line and further-line treatment for TRD and second-line and further-line for TRS. MeSH-term: Electroconvulsive Therapy, F04.570.200.583, F04.669.224.300 Product names: ■ MECTA spECTrum (production discontinued in 2019), MECTA Simga ECT ■ ECTRON Ectonus and Ectonustim series ■ Somatics Thymatron® System *Exclusion*: maintenance and continuation ECT (one ECT per month for six months or longer) will be excluded, as it is indicated for ECT responders who have a history of relapse after completing an ECT series with the primary goal of preventing renewed relapse. We will also exclude studies assessing a single session of ECT because an effect can only be expected after four to five treatments [3].
Control	Standard care consisting of any of the following: ■ Pharmacotherapy ■ Non-pharmacological treatment (non-experimental treatments established in clinical practice guidelines) *Rationale*: informed by clinical guidelines "S3-Leitlinie Nationale Versorgungsleitlinie Unipolare Depression" [6], NICE "Depression in adults: treatment and management" [50], "APA Clinical Practice guideline for the Treatment of Depression Across Three Age Cohorts" [51], and best available evidence-based clinical information on current clinical practice (UpToDate). We will not include studies comparing various ECT modalities (unilateral versus bilateral or ECT treatments with different pulse widths).
Outcomes	

Effectiveness	■ Mortality (suicide-related events),
	■ Response to treatment,
	■ Remission/relapse,
	■ Functional outcomes:
	  ■ General functioning measured by a validated instrument,
	  ■ Cognitive functioning measured by a validated instrument,
	■ Quality of life,
	■ Satisfaction and acceptability of treatment (drop-out rate from the study).
	■ Symptom outcomes in TRD
	  ■ Depression score measured by a clinician-administered tool,
	  ■ Depression score measured by a self-administered questionnaire.
	■ Symptom outcomes in TRS
	  ■ Schizophrenia symptoms measured by a validated instrument.

Safety	Any adverse event Any serious adverse event
Study design	
Effectiveness	Systematic reviews (SRs) and meta-analysis Randomised controlled trials (RCTs)
Safety	SRs and meta-analysis RCTs

3 Methods

3.1 Research questions

EUnetHTA Core Model® Version 4.2

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment.

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

Suche nach SRs in 2 Datenbanken

Evaluierung nach PIKO und RoB

3 SRs für TRD, 1 SR für TRS inkludiert

A preliminary systematic search for SRs in Medline and the Cochrane Library databases and a hand-search in Pubmed were conducted on 07.12.2023 to identify the most recent SRs that meet the present assessment's scope. The identified SRs were evaluated based on their scope, inclusion and exclusion criteria, and quality using the Risk of Bias Assessment Tool for Systematic Reviews (ROBIS). Three SRs for TRD and one SR for TRS met our criteria for inclusion. Search strategy and the ROBIS assessment of the selected SRs are presented in the Appendix.

systematische Suche nach RCTs für beide Indikationen

For each indication and comparison, we updated the evidence of the highest quality SR. A systematic literature search was conducted specifically for RCTs published after the literature search date of the selected SRs. The time of the search for TRD was from November 2014 to December 2023, and for TRS, it was from January 2017 to December 2023. The search was limited to English and German languages.

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted between the 20.12.2023 and 22.12.2023 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- International Network of Agencies for Health Technology Assessment (INAHTA)

insgesamt 1.627 Publikationen identifiziert

By hand-search, no additional citations were found. After deduplication, 1,627 citations remained for title and abstract inspection. The specific search strategy can be found in the Appendix.

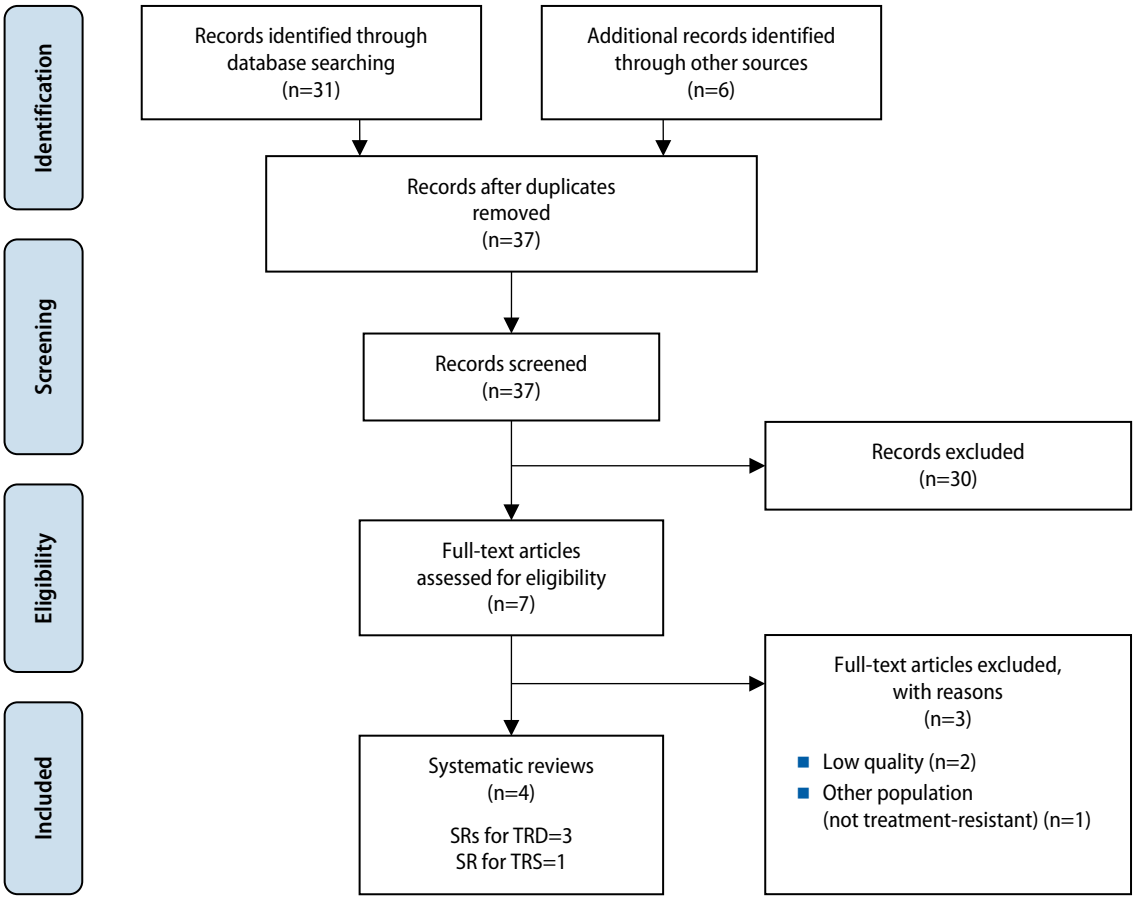
Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in clinical trials registries (ClinicalTrials.gov; WHO-ICTRP) was conducted on 04.01.2024 and 08.02.2024, resulting in 21 potentially relevant hits (14 with one or several of the comparators in our scope and seven with new and emerging treatments options, but not in our current scope).

3.2.2 Flow chart of study selection

Literaturauswahl

In the search for SRs, 31 hits were identified via database search and four additional publications were identified via hand-search. After deduplication, 37 hits were screened for eligibility. Two independent researchers screened the titles and abstracts and the full-text articles. A third researcher was involved in case of disagreements. The selection process for SRs is displayed in Figure 3-1.



Abbreviations: SR – systematic review, TRD – treatment-resistant depression, TRS – treatment-resistant schizophrenia

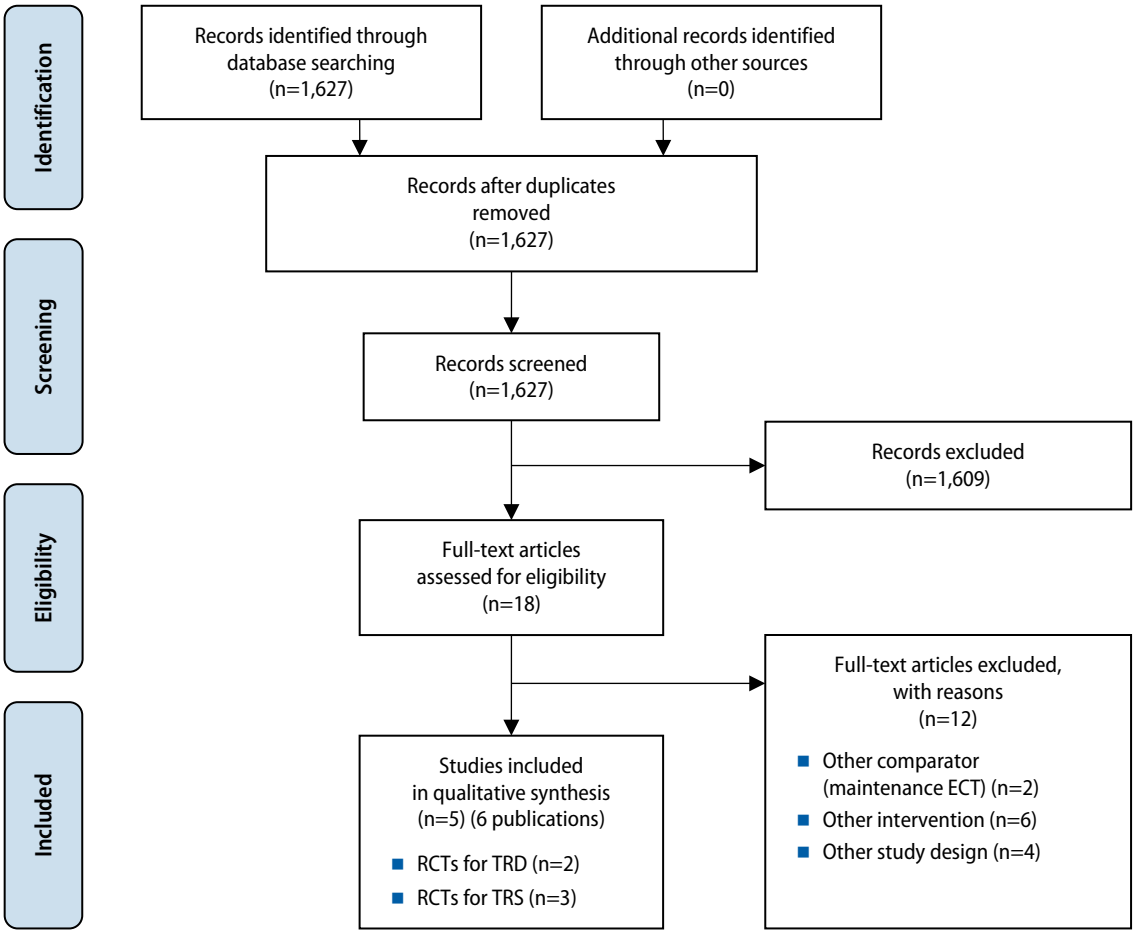
Figure 3-1: Systematic reviews – flow chart of study selection (PRISMA Flow Diagram)

4 SRs eingeschlossen

Four of the 37 SRs were evaluated as fitting the scope and of high quality and were included to be updated with primary studies.

5 RCTs eingeschlossen

In the search for RCTs 1,627 hits were identified. Two independent researchers undertook the title and abstract screening, and in case of disagreement, a third researcher was involved to solve the differences. Three independent reviewers undertook full-text review. The selection process is displayed in Figure 3-2.



Abbreviations: ECT – electroconvulsive therapy, RCT – randomised controlled trial, TRD – treatment-resistant depression, TRS – treatment-resistant schizophrenia

Figure 3-2: Primary studies – flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Datenextraktion

Bewertung des Verzerrungspotenzials: ROBIS tool und Cochrane RoB v.2

Data from the SRs and the primary studies identified in the update search were extracted into data extraction tables based on the research question. The primary studies included in the SRs were only extracted in case the information presented in the SR was deemed insufficient for the present assessment, and the primary study was available for us (see Appendix Table A-3 to Table A-4). An independent second reviewer validated the data for accuracy. Two researchers independently conducted risk of bias assessments (RoB). Differences were resolved by consensus. The methodological quality of the four identified up-to-date SRs was assessed using the ROBIS tool [52]. The RoB of the included primary studies was assessed using the Cochrane RoB v.2 tool [53]. The quality assessment of primary studies in the included SRs was adopted (see Table A-5 to Table A-7).

3.2.4 Synthesis

Synthese der Ergebnisse: Meta-Analyse – aus SR übernommen

zusätzliche Meta-Analysen, wenn möglich –MetaXL

Data on each selected outcome were synthesised based on the data extraction tables (see Appendix Table A-3 to Table A-4). If the update search yielded no additional studies, the meta-analysis from the included SR was presented without modification. Conversely, if new studies were found that reported on an outcome already synthesised in the meta-analysis and met the inclusion criteria, pairwise meta-analyses were then carried out using the MetaXL software, following the methodology defined by the respective meta-analysis. Dichotomous data were expressed as relative risk (RR) with 95% confidence intervals (CIs) or as the number of events and percentages. We estimated mean differences (MD) between the groups for continuous outcomes. In case in at least three studies, different measurement instruments were used, we calculated the effect size as the difference between the means of the two groups divided by the standard deviation (SD), a statistical method known as standardised mean difference (SMD) using Hedges'g or Cohen's method. We used Cohen's conventional definition of small, medium, and large effect size as 0.2, 0.5, and 0.8, respectively. If at least three trials used scales of considerable similarity, the pooled effect sizes were calculated using weighted mean difference (WMD).

Fixed- oder Random-Effekte Modell

We used the fixed or random effects model using the Mantel-Haenszel method (for dichotomous data) or the Inverse Variance method (for continuous data) to synthesise the results. The random effects model was used if increased heterogeneity ($I^2 > 30\%$) was observed. We identified heterogeneity by visually inspecting the forest plots and using the I^2 statistics [54]. The level of heterogeneity was considered as part of the assessment of the certainty of the evidence (inconsistency).

Studies which do not comply with the safety guidelines on rTMS use [55, 56] will be excluded from the meta-analysis.

Bewertung der Vertrauenswürdigkeit der Evidenz mit GRADE

Certainty of evidence was assessed across studies for each outcome according to GRADE (Grading of Recommendations Assessment, Development and Evaluation [57]). The questions were answered in plain text format with reference to GRADE evidence tables presented in the Appendix (see Table Table A-8 to Table Table A-15), and results were summarised in Table 5-1 to Table 5-8.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

The following outcomes were defined as *critical* to derive a recommendation for both indications:

entscheidungsrelevante Wirksamkeitsendpunkte: Mortalität (suizidbezogene Ereignisse),

- Mortality (suicide-related events):
  - Suicide,
  - Suicidal attempt,
  - Suicidal ideation,
  - Suicide score.

Ansprechen auf die Behandlung und Remission

- Response to treatment as defined by each study (including the time to onset of response).
- Remission or relapse rate as defined by each study.

Beurteilungsskala zur Suizidalität: C-SSRS und BSSI messen den Schweregrad der Suizidgedanken und des suizidalen Verhaltens

Suicide score: the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Beck Scale for Suicidal Ideation (BSSI) are both designed to quantify the severity of suicidal ideation and behaviour. They have been widely validated and used in clinical practice, research, and community settings. Although these two scales are commonly referenced and utilised by healthcare professionals for evaluating suicide risk, they both have limitations in their design. Currently, there is no universally accepted gold standard tool for this purpose. Clinical rating scales alone are insufficient for predicting individual suicide cases, and rigid cut-off scores should not solely determine actions such as hospital admission. Nevertheless, the data these scales offer can significantly enhance the assessment of suicide risk, especially in psychiatric emergency contexts. Their capacity to predict actual suicide attempts or completions is inconsistent and should ideally be integrated with a thorough clinical evaluation.

Response, remission, and relapse were defined differently for the two indications.

Treatment-resistant depression (TRD)

Ansprechen auf Behandlung bei TRD: Reduktion von mind. 50 % auf einer Messskala

Response is usually measured by the magnitude of the reduction on the scales used to measure depressive symptoms. To consider the patient response, a reduction of at least 50% is usually required [58]. Many of the included RCTs have used this threshold. Some studies utilised multiple scales; for instance, one study [59] used the Quick Inventory of Depressive Symptomatology-Self-Report Scale (QIDS-SR-16) or the Montgomery Asberg Depression Rating Scale (MADRS) scales, while another study [60] used the Beck's Depression Inventory (BDI) or the MADRS scales. Conversely, other studies used only one scale: the MADRS scale [61] or the Hamilton Rating Scale for Depression (HAM-D/HDRS) scale [62, 63]. In one study, a dual criterion was used, meaning that response was defined as a decrease of 50% or more in the HAM-D, plus a final Global Assessment of Functioning (GAF) rating of at least 60 [64]. Also, in a systematic review [65], a different threshold was used, which was a 25% reduction on the HAM-D scale.

Remission is usually defined as the alleviation of the depressive syndrome, typically quantified by achieving a depression rating scale score equal to or below a specific cut-off point that defines the normal range. Studies using the 17-item HAM-D or the MADRS often define remission as a score at least 7 [58]. Also, a score of less than five on the QIDS-SR means no depression [66]. Regarding the BDI scale, a score of 12 or less is usually considered remission [67]. Different RCTs used different scales and thresholds to define remission. One study [59] defined remission as a score of at least 5 on the QIDS-SR scale or a score of at least 10 on the MADRS scale, while another study [57] used the criterion of at least 10 on the MADRS scale. In three studies[62, 63, 68, 69], they defined remission using the 17-item HAM-D scale, where a score of at least 8 was set for the first two studies, and a score of at least 7 was set for the third study. In a different study[70], it was defined as either at least 8 on the 17-item HAMD scale or at least 15 on the BDI scale and finally, in a systematic review[65], it was defined as a 50% score reduction on the HAM-D scale.

Remission:
HAM-D, MADRS:
≤7, QIDS-SR <5

unterschiedliche Skalen und Grenzwerte in den Studien

Relapse is defined as the return of the index MDE following the onset of remission but before fulfilling the criteria for recovery [71]. Relapse was reported in two studies. In one study [59], it was defined as a score greater than 11 on the QIDS-SR-16 scale, and in the second study [57], it was defined as when a patient was considered to meet the criteria for depression.

Rückfall: Verschlechterung der Symptome nach einer Remission
QIDS-SR-16 >11

Treatment-resistant schizophrenia (TRS)

Response criteria for determining patient response vary significantly in the studies. Typically, the extent of symptom reduction on various scales is used to measure response. For instance, one study suggests that a 50% reduction in the Positive and Negative Syndrome Scale (PANSS) score indicates a response, but in populations resistant to treatment, even a 25% improvement may be considered significant [72]. Different clinical studies have utilised various thresholds ranging from 20% to 50% reduction in the Brief Psychiatric Rating Scale (BPRS) score to define response [72]. One study [73] identified three levels of improvement on the PANSS scale: 20% reduction for the minimal level of response, 30% for "minimally improved", and 40% for "much improved". Another study [74] considered a greater than 20% reduction on the PANSS scale as the benchmark for response. Yet another [75] defined response as a 40% or more reduction in the BPRS, a Clinical Global Impression – Severity (CGI-S) rating of mild or less, and a CGI-Improvement (CGI-I) rating of much improved or better. A systematic review [76] set a standard of 50% reduction on scales like the BPRS or PANSS to indicate clinically significant response, using primary cut-offs provided by original authors when specific data were not available.

Ansprechen auf Behandlung bei TRS: Reduktion von mind. 50 % oder 25 % beim PANSS

Reduktion von 20-50 % beim BPRS

unterschiedliche Grenzwerte in den Studien

Remission of schizophrenia refers to a state in which the individual has no symptoms or minimal symptoms which do not interfere with behaviour for at least six months [15]. No studies have measured the remission rate.

Remission – mind. 6 Monate wenige oder keine Symptome

Relapse is defined as a return or worsening of symptoms following a period of remission [77]. The relapse rate was only reported in one study [74], where it was defined as symptom exacerbation following a period of partial recovery.

Rückfall: Verschlechterung der Symptome

The following outcomes were defined as *important* for both indications:

- Functional outcomes (measured by validated instruments):
  - General functioning,
  - Cognitive functioning,
- Quality of life,
- Satisfaction and acceptability of treatment, and
- Symptom outcomes.

wichtige Wirksamkeitsendpunkte: Funktionsfähigkeit, kognitive Funktion, Lebensqualität, Patient*innenzufriedenheit, symptombezogene Endpunkte

Depression symptoms are measured either by a clinician-administered tool (any version of the HAM-D/HDRS, or the MADRS) or self-administered questionnaire (BDI).

Depressionssymptome: HAM-D/HDRS, MADRS, BDI

Schizophrenia symptoms are measured by PANSS, the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), or BPRS.

Schizophreniesymtome: PANSS, SAPS, SANS, BPRS

A detailed description of instruments for all outcomes is provided in Table A-22.

4.1.2 Outcomes safety

The following outcomes were defined as *critical* to derive a recommendation:

- Serious adverse events (SAEs).

entscheidungsrelevante Sicherheitsendpunkte: schwerwiegende unerwünschte Ereignisse (SAEs)

The following outcomes were defined as *important*:

- Adverse events (AEs).

One systematic review [65] defined SAEs as memory deterioration and somatisation. In this review, no definitive instruments were described for assessing the status of adverse reactions; only events were reported. Somatisation resulted from some psychological problems caused by TRD. In another systematic review [76], adverse events were categorised into general and specific adverse events, presenting not only the number of events but the average endpoint in general adverse event score and average change in adverse event score and death. Death was considered in the included SRs and RCTs as a safety outcome. In our report, we included mortality related to suicide as an effectiveness outcome because TRD patients have a sevenfold increase in suicide rate [3], and 5-15% of people with schizophrenia commit suicide (about 10% of people with newly diagnosed schizophrenia attempt suicide within a year) [28]. The most common adverse events reported in the included studies were headache, nausea, vomiting, blurred vision, fatigue, insomnia, musculoskeletal pain, joint pain, and so forth.

SAEs: Somatisierung, Gedächtnisstörungen

kein einheitliches System zur Erhebung der Komplikationen

4.2 Included studies

4.2.1 Included studies for effectiveness

Treatment-resistant depression

Three SRs were included in our review. However, one RCT from an SR was excluded because it did not meet our predefined population criteria, resulting in a total of 27 RCTs identified through SRs. With the addition of two more RCTs, the overall total reached 29 RCTs involving 2,101 patients. Among these, five RCTs compared ECT with ketamine (n=697), seven compared it with rTMS (n=306), and 17 compared it with various antidepressants (n=1,098).

TRD: 3 SRs (27 RCTs) und 4 RCTs

Komparatoren: Ketamin, rTMS, und Antidepressiva (AD)

The mean ages of participants across the studies range from the early 30s to mid-40s. Three studies with rTMS [62, 64, 68] have older mean ages (64 and 68 years). The length of illness was not reported in the studies with rTMS and ketamine. In contrast, in the studies with antidepressant comparison [65], it varies significantly among the studies, with some participants having been ill for as short as 14 weeks and others for as long as 8.8 years. Patients were diagnosed with TRD in all the antidepressant comparison studies [65]. However, the definition of TRD was not detailed. In the ECT versus rTMS studies, the diagnosis was heterogeneous in terms of the criteria for treatment-resistance. Some studies considered ECT failure [64, 70, 78], others considered non-response to initial treatment strategies with at least one [68] or two antidepressants [63, 69], and one study did not report the total number of failed treatments but the failed antidepressants in the current episode [62]. The ketamine versus ECT studies mainly focused on patients with MDD who do not exhibit psychotic symptoms [59, 79] or MDD with agitation or suicidal ideation [80], recurrent MDD patients with a history of ECT [61], MDD patients also suffering from anxiety, a frequent and complicating comorbidity [60].

mittleres Alter zwischen 30 und 45 Jahre alt

wenn berichtet: Krankheitsdauer zwischen 14 Wochen und 8,8 Jahren

Diagnosen, Ausprägungen der Symptome und frühere Therapien heterogen

The interventions vary significantly regarding therapy type, frequency, and anaesthesia. The monotherapy approach was less frequent as it was used in two studies[63, 64] and in four additional studies included in a systematic review [65]. The combination therapy approach was more prevalent as it was used in 13 studies in a systematic review [65], along with eight other studies [59, 61, 62, 68-70, 78, 80].

unterschiedliche Therapieformen, Häufigkeiten und Anästhetika

The frequency of ECT sessions was two to three times per week in three studies [78-80], one to three times in one systematic review[65] and precisely three times in five studies [59-61, 69, 70], while in two studies it was precisely twice a week [62, 68]. Therefore, the frequency of ECT sessions mostly ranged from 2 to 3 times per week, which is a common schedule in clinical practice. The duration of treatment varied, with some studies specifying a set number of sessions, ranging from three to twelve [59-61, 65, 69, 78, 80], and others continuing until remission was achieved [62, 79] or not reported the total number of sessions delivered [63, 64, 68, 70]. Regarding the comparator treatments, the studies also applied the intervention in a heterogeneous manner: ketamine was administered twice or three times weekly, but the duration of treatment ranged from three to twelve sessions or until complete remission. The administered dose was homogeneous among the studies, all reporting a 0.5mg/kg dose. In terms of the rTMS comparisons, the frequency was five times a week in all studies [62-64, 68, 69, 78] (one study did not report this

großteils 2-3 EKT-Einheiten pro Woche

3 bis 12 Einheiten insgesamt

Ketamin: 2-3 Mal pro Woche,

rTMS: 5 Mal pro Woche

[70]). The total number of sessions being delivered varied from ten to 25. One study [63] did not comply with the safety standards established for rTMS.

Anästhesieprotokolle unterschiedlich

Anaesthesia protocols varied, including atropine, thiopental, succinylcholine, methohexitone, suxamethonium, etomidate, and methoheital. Not all studies specified the type of anaesthesia used [59, 65, 78].

Elektrodenplatzierung variiert

Electrode placement was another area of variation, with right unilateral [61], bilateral [60, 69, 78-80], and a mix of both [62] being reported. Some studies allowed for adjustment of electrode placement based on patient response [59, 63, 68]. The antidepressant comparison studies [65] and two rTMS comparison studies [64, 70] did not report the electrode placement.

Großteil der Studien: nicht verblindet
2 RCTs: doppelblind

Most of the studies were unblinded or open-label ([59, 61, 64, 68, 69, 80] except one study in a systematic review [65]). Five RCTs were assessor-blinded [60, 62, 63, 70, 78], and two were double-blind ([75], and another study was included in a systematic review [65]). Follow-up times range from 1 week to 12 months, with some studies not reporting this information.

Treatment-resistant schizophrenia

1 SR (15 RCTs, 1.285 Teilnehmer*innen)
Komparatoren: Schein-EKT, Clozapin + Standardtherapie (ST), ST, Flupentixol

One SR, comprising 15 RCTs analysing 1,285 participants (1,264 completers), was included. One RCT analysed ECT in comparison to sham-ECT plus standard care (chlorpromazine) [81], one RCT compared ECT plus standard care to clozapine plus standard care (ziprasidone) [82], 13 studies analysed ECT plus standard care versus standard care alone (various antipsychotics) [83-95], and one study compared ECT monotherapy to flupenthixol alone [85].

update Literaturrecherche: 3 RCTs (4 Publikationen)

In the update search three additional RCTs (four publications) [73-75, 96], involving 122 patients were identified. These additional studies compared ECT to sham-ECT [73, 96] or ECT in combination with clozapine to clozapine only study [74, 75].

18 RCTs, 1.368 Teilnehmer*innen

Consequently, this report includes 18 RCTs, involving 1,368 participants at randomisation, comparing ECT as augmentation to antipsychotics against clozapine plus antipsychotics (ziprasidone, n=162), and antipsychotics alone (flupentixol, n=30), ECT as augmentation to standard care to standard care alone (n=1137[7]), as well as ECT versus sham-ECT (n=54).

Alter: 18-48

The age of participants ranged from 18 to 48 years. Three studies did not report the age of the 14 participants who left early [81, 85, 87].

Diagnose: TRS nach CCMD, DSM-IV, ICD-10

The included participants were all diagnosed with TRS by international standards, including CCMD-2-R, CCMD-3, DSM-IV, and ICD-10. The average length of illness ranged from 6.3 to 18.6 years, while four studies (n=287) did not report the average length of the illness [73, 83, 86, 89, 90].

EKT oder modifizierte EKT

The intervention group received either ECT or modified ECT in the included studies.

1 Studie mit 3 Gruppen (EKT + ST vs. EKT vs. ST)

In the studies where standard care was an active intervention, ECT was given as augmentation. One of the studies [85] had three treatment arms (ECT plus standard care, ECT alone and standard care alone).

Elektrodenplatzierung: bilateral oder nicht berichtet

Seven studies (n=522) reported the use of bilateral electrode placement [73, 74, 81, 85, 86, 91, 95], while the placement was unclear in the remaining ten studies. A short course (6 to 12 sessions) of ECT was applied in twelve studies (n=870; [73, 81-84, 86, 87, 89-93]. Four studies (n=420) used a long course (14 to 20 ses-

[7] Fifteen patients were also counted in the comparison with antipsychotics alone.

sions) [85, 86, 94, 95], while one study (n=78) [88] did not report the course of ECT. All studies, except for one study [88] used ECT multiple times per week; most of these used ECT three times [73, 81, 83, 89, 91, 93] per week for two to four weeks [82, 84-87, 92, 94, 95]. The treatment duration of the included studies ranged from 2 weeks in two studies [74, 81] to 24 weeks (one study [85]). The treatment duration in the other studies was four weeks [73, 89, 91], eight weeks [82, 83, 86, 88, 93-95], or 12 weeks [84, 87, 90, 92].

Behandlungsdauer zwischen 2 und 24 Wochen

Sensitivity analyses were conducted for the ECT plus standard care versus standard care comparison. One sensitivity analysis was conducted for assumptions for lost binary data for one primary outcome (medium-term response to treatment), indicating consistent results between the incorporation of lost data with and without an intention-to-treat analysis (see Table 5-8). Another analysis was conducted with both the fixed-effect and the random-effects model for the "medium-term response to treatment" outcome. Results were consistent between fixed-effect and random effects models (see Table 5-8)

Sensitivitätsanalyse

4.2.2 Additional included studies for safety

No additional studies were included for safety.

keine zusätzlichen Studien für Sicherheit

4.3 Results

4.3.1 Treatment-resistant depression

ECT versus rTMS

Mortality[8]

Overall mortality, suicidal attempts and **suicidal ideation** were not reported in any of the included studies. **Suicide score** was reported in two RCTs. One RCT (n=40) [78]reported a statistically significant change in HAM-D suicide subscore in favour of ECT, showing a 0.63 points greater decrease measured from baseline in the ECT group than in the rTMS group. In the other RCT (n=73) [69], when pretreatment and posttreatment HDRS suicide subscores within each group were compared, both treatment groups showed a decrease in mean suicide score (2 score decrease in the ECT group versus 0.5 score decrease in the rTMS group). The same study measured BDI suicide subscores, too, which showed a mean decrease of 0.9 points in the ECT group and a mean decrease of 0.3 points in the rTMS group.

EKT vs. rTMS
Mortalität, Suizidversuche, Suizidgedanken nicht berichtet

Suizidscore: s.s. Unterschied zugunsten EKT

[8] **D0001** – What is the expected beneficial effect of ECT on mortality compared to rTMS?

Morbidity[9,10]

Six studies reported **depression scores** at baseline and follow-up [62, 64, 68-70, 78], but one of them exceeded the limit set by the rTMS safety guidelines [55, 56]. Therefore, this RCT was excluded from the meta-analysis (n=225). Follow-up, if reported, varied between seven weeks [78] and six months [64]. One study reported mean differences only, without standard deviation data. The weighted mean difference was –5.85 points (95% CI, –9.37 to –2.34) in favour of ECT (in the ECT group, the depression score decreased by a mean of 5.85 score more than in the rTMS group, where the higher score means a poorer outcome). The degree of heterogeneity among studies was high (I^2= 66%, p=0.02, see Figure 4-1). This point value is higher than the minimal clinically important difference (MCID), which is defined to be between 3 and 5.

Depressionsscore: s.s. Unterschied zugunsten EKT

klinisch relevanter Unterschied

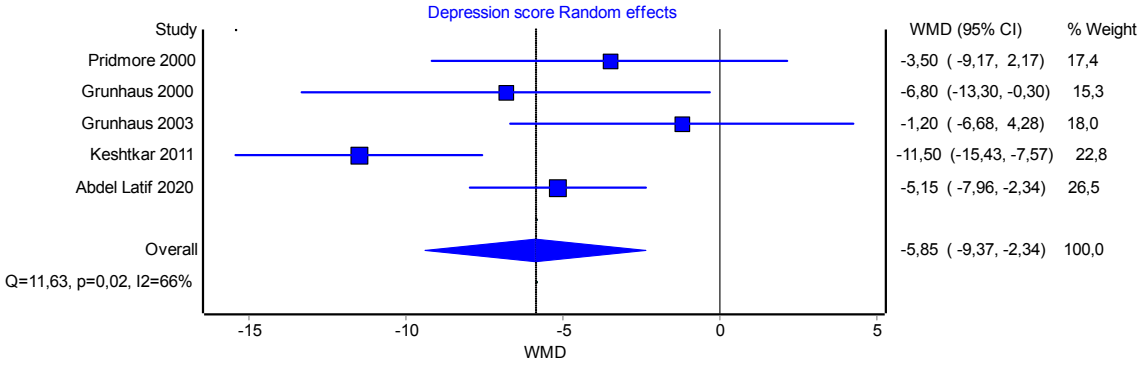


Figure 4-1: Depression score weighted mean difference: ECT vs rTMS

Remission rate was reported only by three of the six studies (n=118) [62, 68, 70] that complied with safety standards and, therefore, were included in the pooled RR calculation, which was 1.44 (95% CI, 0.64 to 3.23, p=0.375, see Figure 4-2) at the end of treatment, favouring ECT. However, these results are not significant. Studies had a high degree of heterogeneity (I^2=69.1%, p=0.039). The pooled RR did not reach a significance level, as the studies used different ECT protocols and were very heterogeneous.

Remission: keine s.. s. Unterschiede

Response rate was reported in three of the six studies (n=126) [62, 64, 68] that complied with the safety standards reported. The pooled RR for response at the end of treatment was 1.72 (95% CI, 0.95 to 3.11, p=0.072, see Figure 4-3), favouring ECT. Again, there was a high degree of heterogeneity among studies (I^2=60.6%, p=0.079). While the effect is not statistically significant, this pooled estimate would suggest a higher response with ECT than with rTMS. The benefit increase was 29% (95% CI, 0.07 to 0.5, p=.010) favouring ECT.

Ansprechen auf Behandlung: keine s.s. Unterschiede

[9] **D0005** – How does ECT affect symptoms (severity, frequency) of TRD compared to rTMS?

[10] **D0006** – How does ECT affect the progression (or recurrence) of TRD compared to rTMS?

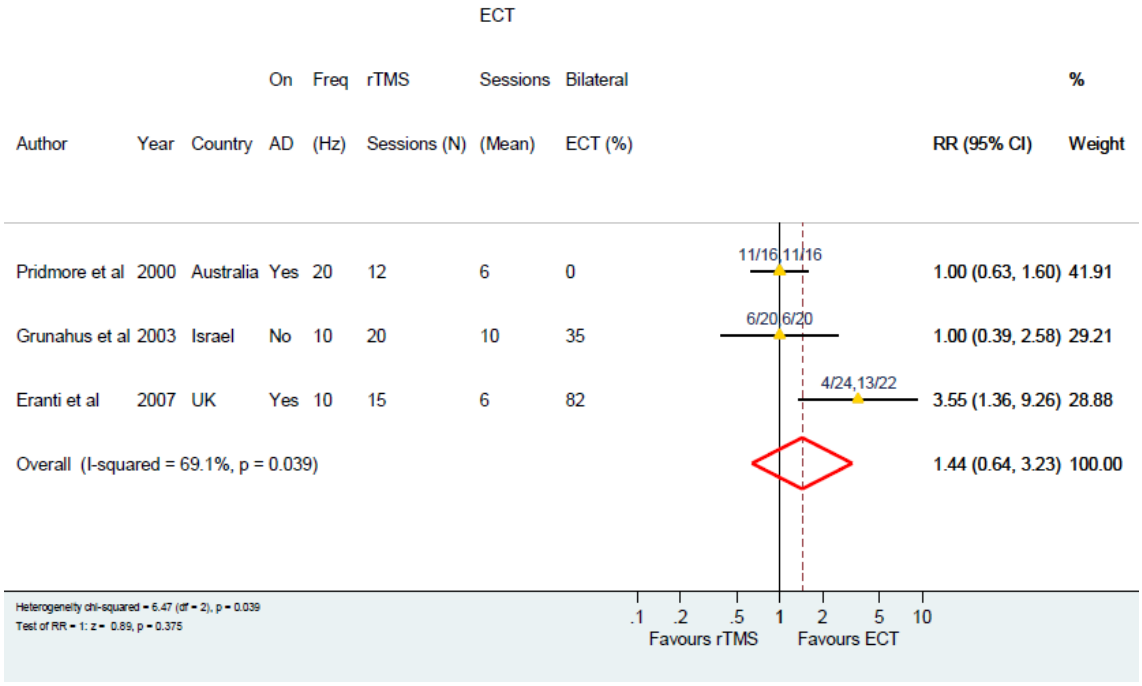


Figure 4-2: Remission rate: ECT vs rTMS (source [1])

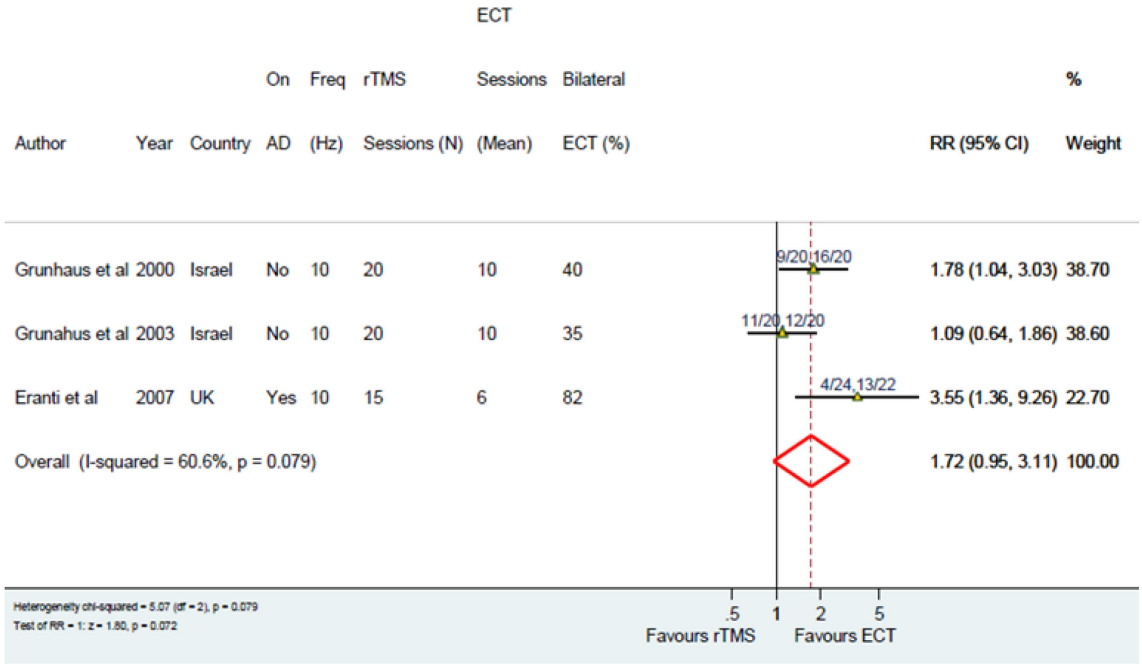


Figure 4-3: Response rate: ECT vs rTMS (source [1])

Function[11,12]

General functioning was reported in one study (n=40) [78] but without baseline data. At 6-month follow-up, the results were: 72.8±12 vs 77.8±17.1.

Funktionsfähigkeit: 1 RCT

Cognitive functioning was reported in one study (n=40) [78]. Several outcome measures were employed, none showing a statistically significant change favouring ECT. DSP showed a statistically significant improvement in the rTMS group compared to the ECT group (p=0.02), indicating an improvement in short-term memory and attention span. The rTMS group showed statistically significant improvement in the Stroop Color Word Test-Victoria version (SCWTV) (p=0.02 for dots, p=0.03 for words, and p=0.01 for colors) and Color Trails Test (CTT) (p=0.009 for trial 1 and p=0.001 for trial 2) scores, as scores decreased more than those in the ECT group, implying better performance in tasks where higher scores denote poorer outcomes. On the Rey-Osterrieth-Complex Figure Test (ROT), improvements were not statistically significant in the delay task (p=0.09), with no change observed in the copy task (p=1), suggesting minimal difference between the groups in visuospatial construction and memory.

kognitive Funktion: DSP, SCWTV und CTT: s.s. Unterschied zugunsten rTMS

ROT: kein s.s. Unterschied

Health-related quality of life[13,14]

None of the included studies addressed **quality of life** outcomes.

QoL: keine Studien

Patient satisfaction

None of the included studies addressed **patient satisfaction** per se, but four studies reported **dropouts** from the study, which might have been associated with satisfaction and acceptability of treatment. One study reported that no dropouts occurred [64]; one did not report from which treatment arms patients dropped out, but 13% of patients stopped their treatment [62]. In two studies, a higher percentage of patients stopped treatment in the ECT group than in the rTMS group (24% vs 14% and 33% vs 10%, respectively) [63, 69].

Patient*innenzufriedenheit: keine Studien

mehrere Studienabbrecher*innen in der EKT-Gruppe

Patient safety[15]

Two studies did not report adverse events [63, 78]. Two studies reported that no SAEs occurred (namely **seizure**) [64, 69], three studies reported on headache [64, 68, 69], one on device-related insomnia [68], and two studies used side-effect rating scores [62, 70], but did not report explicitly which side-effects occurred. No data was reported on other adverse events. The most common side-effect was headache in rTMS-treated patients, ranging from three to 25% across studies. No adverse events occurred in ECT-treated patients.

Sicherheit: keine SAEs

[11] **D0011** – What is the effect of ECT on patients' body functions?

[12] **D0016** – How does ECT affect activities of daily living?

[13] **D0012** – How does ECT affect generic health-related quality of life?

[14] **D0013** – What is the effect of ECT on disease-specific quality of life?

[15] **C0008** – How safe is ECT in comparison to rTMS?

ECT versus ketamine

Mortality[16]

Overall mortality was reported by one study (n=181) [61]. One patient committed suicide in the ECT group and none in the ketamine group over the 12-month follow-up period. **Suicidal attempt** was reported in two RCTs [59, 61]. One RCT (n=181) [61] reported 7% ECT patients versus 4% ketamine patients attempting suicide. The other RCT (n=365) [59] reported 1% in the ECT group and none in the ketamine group. **Suicidal ideation** was reported by one RCT (n=403) [59], in which 1% of the ECT versus 2% of ketamine group patients reported this outcome at the end of treatment and 1% versus 4% at 6-month follow-up, respectively. **Suicide score** was reported in two studies [59, 80], but different measurement instruments were used. One RCT (n=403) [59] reported Columbia-Suicide Severity Rating Scale (CSSRS) scores, which decreased from baseline 1.8 ± 0.1 versus 1.7 ± 0.1 to 0.2 ± 0.1 versus 0.1 ± 0.1 by the end of treatment but increased again gradually by the 6-month follow-up to 0.8 ± 0.1 versus 0.6 ± 0.1. The other RCT [80], analysing three treatment arms (ECT, IM ketamine and oral ketamine) (n=39), reported that scores reduced significantly in all groups, but differences between the groups were significant only at 24 hours after the first intervention (5.7 ± 4 versus 3 ± 3.3 versus 2.7 ± 1.4, p=0.045) and at second week during the intervention (3.9 ± 3.5 versus 1.5 ± 2 versus 1.7 ± 1.4, p=0.033) and not at 1-month after the end of the treatment phase.

EKT vs. Ketamin
Mortalität: 1 EKT-Patient

Suizidversuche:
7 % vs. 4 %

Suizidgedanken:
1 % vs. 4 %

Suizidscore:
s.s. Unterschied zugunsten EKT um 24 Stunden und 2 Wochen nach der Intervention

Morbidity[17,18]

Depression symptom scores were measured by using HAM-D or MADRS. Four studies reported this outcome (n=253) [60, 61, 79, 80]. The standardised mean difference (SMD) was –0.3 (95% CI, –0.78 to 0.18), indicating a small effect favouring the ECT group. The degree of heterogeneity was moderate at 50% (p=0.11; see Figure 4-4).

Depressionscore: kleine Effektgröße zugunsten EKT

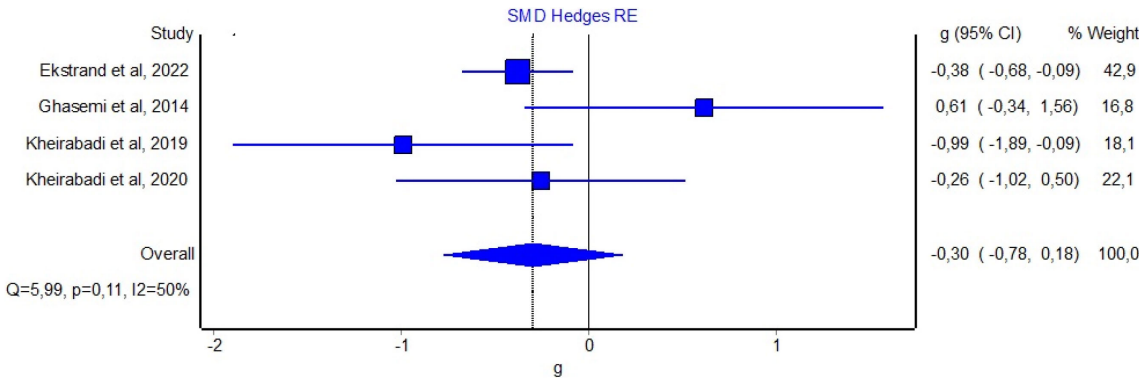


Figure 4-4: Depression score standardised mean difference: ECT vs ketamine

[16] **D0001** – What is the expected beneficial effect of ECT on mortality compared to ketamine?

[17] **D0005** – How does ECT affect symptoms (severity, frequency) of TRD compared to ketamine?

[18] **D0006** – How does ECT affect the progression (or recurrence) of TRD compared to ketamine?

Response rate was assessed in three studies (n=568) [59-61]. The pooled RR for response at the end of treatment was 1.02 (95% CI, 0.88 to 1.19, see Figure 4-5) favouring ECT. The degree of heterogeneity was high (I^2=74%, p=0.02).

Ansprechen auf Behandlung: kein s.s. Unterschied

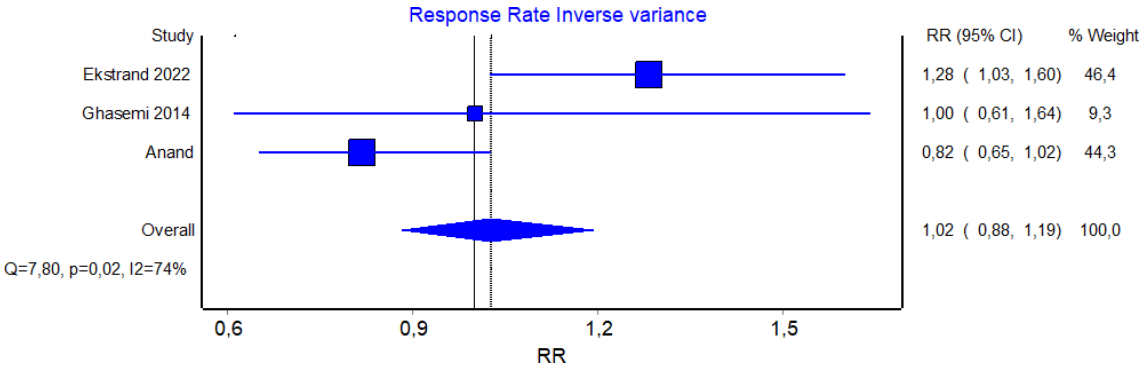


Figure 4-5: Response rate: ECT vs ketamine

Remission rate was assessed in two studies (n=551) [59, 61]. The pooled RR for remission at the end of treatment was 0.97 (95% CI, 0.79 to 1.2; see Figure 4-6), favouring ketamine. The degree of heterogeneity was high (I^2=93%, p<0.001).

Remission: kein s.s. Unterschied

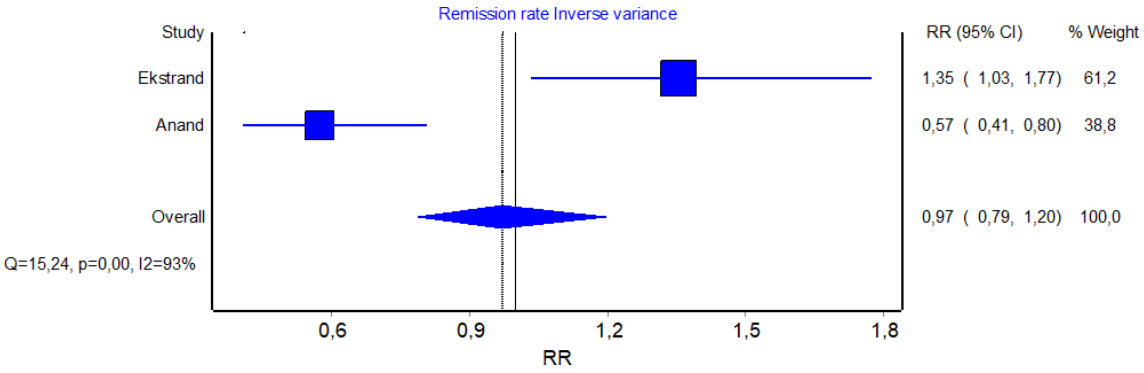


Figure 4-6: Remission rate: ECT vs ketamine

Function[19,20]

Outcomes measuring **general functioning** were not reported in any of the studies. **Cognitive functioning** was reported in two RCTs [59, 79]. One RCT with six months follow-up (n=403) [59] reported this outcome using three scales: a statistically significant change was reported in favour of the ketamine group in the Global Self Evaluation of Memory (GSE-My score; MD -1.1, 95% CI, -1.2 to -0.9), and in the Hopkins verbal Learning Test-Revised (HVLT-R) total score change (MD -5.3, 95% CI, -7.4 to -3.1) where higher scores mean better outcomes. The Squire Memory Complain Questionnaire (SMCQ score) was statistically significant, favouring the ketamine group (MD -0.9, 95% CI,

Funktionsfähigkeit: keine Studien

kognitive Funktion: 1 RCT s.s. Unterschied zugunsten EKT, 1 RCT kein s.s. Unterschied

[19] **D0011** – What is the effect of ECT on patients' body functions?

[20] **D0016** – How does ECT affect activities of daily living?

-13.0 to -5.1), where the higher scores mean better outcomes. The other RCT (n=32) [79] reported a statistically non-significant difference of 3.4 scores at one week and 2 scores at one-month follow-up in favour of ketamine.

Health-related quality of life[21][22]

Health-related quality of life was reported by one study (n=403) [59]. There was a statistically non-significant mean difference of 0.6 scores in favour of ECT after six months.

QoL: kein s.s. Unterschied

Patient satisfaction

None of the included studies reported this outcome.

Patient*innenzufriedenheit: keine Studien

Patient safety[23]

Two studies [59, 61] reported **serious adverse events**. In the study with 6-month follow-up [59] (n=365), after the initial treatment phase, 4/170 (2%) in the ECT group and 5/195 (3%) in the ketamine group experienced at least one serious adverse event, while at the 6-month follow-up, it was 3/70 (4%) and 8/108 (7%) of patients, respectively. Serious adverse events in the ECT group included infection, asystole, and homicidal ideation in the initial treatment phase, as well as suicidal ideation, in the follow-up period. In the ketamine group, chest pain, aborted suicide attempts and suicidal ideation were reported in the initial treatment phase; in the follow-up period, SAEs were the same as in the ECT group, as well as non-stress cardiomyopathy, and suicidal attempt. In the other study (n=181) [61], with a 12-month follow-up period, 23/90 (26%) ECT patients and 14/91 (15%) ketamine patients experienced at least one serious adverse event.

SAEs: 1 RCT 2 % vs. 3 %; 1 RCT 26 % vs. 15 %

ECT versus antidepressants

Mortality[24]

Overall mortality, suicidal attempts, suicidal ideation or **suicide scores** were not reported in any of the included studies.

Mortalität: keine Studien

Morbidity[25,26]

Depression scores and **remission rates** were not reported in any of the included studies.

Depressionsscore und Remission: keine Studien

Three studies [65] included data on **response rate** (n=150) and resulted in a pooled RR of 2.24 (95% CI, 1.51 to 3.33). ECT showed a statistically significant increase in the response rate compared to antidepressants. The heterogeneity among studies was low (I^2=0.0%, p=0.921).

Ansprechrate: s.s. Unterschied zugunsten EKT

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[21] **D0012** – What is the effect of ECT on generic health-related quality of life?

[22] **D0013** – What is the effect of ECT on disease-specific quality of life?

[23] **C0008** – How safe is ECT compared to ketamine?

[24] **D0001** – What is the expected beneficial effect of ECT on mortality compared to antidepressants?

[25] **D0005** – How does ECT affect symptoms (severity, frequency) of TRD compared to antidepressants?

[26] **D0006** – How does ECT affect progression (or recurrence) of TRD compared to antidepressants?

Function[27,28]

General functioning and **cognitive functioning** were not reported in any of the included studies.

Funktionsfähigkeit: keine Studien

Health-related quality of life[29,30]

Health-related quality of life was not reported in any of the included studies.

QoL: keine Studien

Patient satisfaction

Patient satisfaction was not reported in any of the included studies.

Patient*innenzufriedenheit: keine Studien

Patient safety[31]

Somatisation was reported in three studies [65] (n=191) with a pooled RR of 1.22 (95% CI, 0.69 to 2.17), which shows that no significant difference was detected between ECT compared with antidepressants alone. The heterogeneity among studies was low (I^2=10.0%, p=0.33).

Somatisierung: kein s.s. Unterschied

Memory deterioration was reported in two studies [65] (n=111) with a pooled RR of 0.88 (95% CI, 0.41 to 1.88), suggesting that ECT might not cause more memory deterioration compared with antidepressants alone. The heterogeneity among studies was low (I^2=0.0%, p=0.47).

Gedächtnisstörungen: kein s.s. Unterschied

ECT plus antidepressants versus antidepressants

Mortality[32]

Overall mortality, suicidal attempts and suicidal ideation were not reported in any of the included studies.

Mortalität: keine Studien

Morbidity[33,34]

Depression scores and **remission rates** were not reported in any of the included studies.

Depressionsscores und Remission: keine Studien

Thirteen studies [65] included data on **response rate** (n=871). Eight of them were completed in duration of treatment of four weeks (n=572), two lasted six weeks (n=136), and three (n=163) lasted for eight weeks after treatment. A subgroup analysis was adopted for the outcome according to different treatment durations. The RR after four weeks was 1.97 (95% CI, 1.56 to 2.47); after six weeks, 1.96 (95% CI, 1.14 to 3.37) and after eight weeks, 1.45 (95% CI, 1.17 to 1.81). The pooled RR of all the thirteen studies was 1.82 (95% CI,

Ansprechrate: s.s. Unterschied zugunsten EKT + AD

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[27] **D0011** – What is the effect of ECT on patients' body functions?

[28] **D0016** – How does ECT affect activities of daily living?

[29] **D0012** – What is the effect of ECT on generic health-related quality of life?

[30] **D0013** – What is the effect of ECT on disease-specific quality of life?

[31] **C0008** – How safe is ECT compared to antidepressants?

[32] **D0001** – What is the expected beneficial effect of adding ECT to antidepressants on mortality compared to antidepressants alone?

[33] **D0005** – How does adding ECT to antidepressants affect symptoms (severity, frequency) of TRD compared to antidepressants alone?

[34] **D0006** – How does adding ECT to antidepressants affect progression (or recurrence) of TRD compared to antidepressants alone?

1.55 to 2.14). ECT combined with antidepressants showed a statistically significant increase in the response rate relative to antidepressants alone. The heterogeneity among all studies was moderate (I^2=48%, p=0.027).

Two sensitivity analyses were conducted concerning this outcome. In the first one, four studies were excluded due to their low quality, yet the findings remained robust with a pooled RR of 1.72 (95% CI, 1.45 to 2.04, I^2=33%, p=0.152). In the second analysis, two studies were excluded due to heterogeneity, yielding consistent results (RR 1.81, 95% CI, 1.45 to 2.04, I^2=10.4%, p=0.345).

2 Sensitivitätsanalysen: Studien mit niedriger Qualität und hoher Heterogenität ausgeschlossen

Function[35,36]

General functioning and **cognitive functioning** were not reported in any of the included studies.

Funktionfähigkeit: keine Studien

Health-related quality of life[37,38]

Health-related quality of life was not reported in any of the included studies.

QoL: keine Studien

Patient satisfaction

Patient satisfaction was not reported in any of the included studies.

Patient*innenzufriedenheit: keine Studien

Patient safety[39]

Somatisation was reported in ten studies [65] (n=710). Six of them were completed in four weeks within treatment (n=435), two lasted six weeks (n=136), and two lasted for eight weeks after treatment (n=139). A subgroup analysis was adopted for the outcome according to different durations. The RR after four weeks was 0.64 (95% CI, 0.42, 0.98); after six weeks, 0.80 (95% CI, 0.62 to 1.04); and after eight weeks, 1.07 (95% CI, 0.66 to 1.73). The pooled RR across all ten studies was 0.79 (95% CI, 0.61 to 1.01).

Somatisierung: kein s.s. Unterschied

The meta-analysis showed that ECT plus antidepressants increased the incidence of somatisation compared with antidepressants in the fourth week after treatment. However, the incidences were not significant in the sixth and eighth weeks after treatment. Moreover, the pooled result was not statistically significant. The heterogeneity among studies was high (I^2=54.9%, p =0.018).

Meta-Analyse: s.s. Unterschied nur um 4 Wochen, mehr Somatisierungen mit EKT

Sensitivity analysis was conducted for the 4-week subgroup by removing two studies due to heterogeneity. The results showed that there was no statistically significant difference between ECT combined with antidepressants compared to antidepressants (RR 0.82, 95% CI, 0.6-1.21, I^2 = 29.9%, p=0.23).

Sensitivitätsanalyse: Ausschluss von 2 Studien wegen hoher Heterogenität

Memory deterioration was reported in four studies [65] (n=292) with a pooled RR of 0.27 (95% CI, 0.03-2.4), suggesting that ETC combined with antidepressants may be not associated with a higher rate of memory deterioration as the result was not statistically significant. The heterogeneity among stud-

Gedächtnisstörungen: kein s.s. Unterschied

[35] **D0011** – What is the effect of ECT on patients' body functions?

[36] **D0016** – How does ECT affect activities of daily living?

[37] **D0012** –What is the effect of adding ECT to antidepressants on generic health-related quality of life?

[38] **D0013** – What is the effect of adding ECT to antidepressants on disease-specific quality of life?

[39] **C0008** – How safe is adding ECT to antidepressants compared to antidepressants alone?

ies was high (I^2=67.9%, p=0.025). A sensitivity analysis was conducted by excluding one study due to high heterogeneity. The results showed that ECT combined with antidepressants increased the incidence of memory deterioration (RR 0.09, 95% CI, 0.02–0.49, I^2=0%, p<0.001).

4.3.2 Treatment-resistant schizophrenia

ECT versus sham-ECT

Mortality[40]

Overall mortality, suicidal attempts and **suicidal ideation** were not reported in any of the included studies.

Mortalität: keine Studien

Morbidity[41]

Schizophrenia symptoms were reported in one study [76] (n=25) using the BPRS score. There was no clear difference in the short-term follow-up BPRS[42] score for mental state between the ECT and the sham-ECT groups (MD 3.60, 95% CI, -3.69 to -10.89). Another study [73] (n=23) used other scales to measure schizophrenia symptoms including the PANSS scale and the CGI scale. For the PANSS scale, there was no statistically significant difference between the two arms (MD 2.89, 95% CI, -17.22 to -11.44, p=0.68). For the CGI scale, there was no statistically significant difference between the two arms (MD 0.12, 95% CI, -0.9 to -0.66, p=0.908).

Schizophreniesymptome: keine s.s. Unterschiede

Response rate was reported in one study [73] (n=23) which was measured by the mean reduction at PANSS positive subscale. Response rates were defined according to three levels: a 20% reduction (two patients in ECT arm versus two patients in the sham-ECT arm), 30% reduction (one patient in ECT arm versus two patients in the sham-ECT arm and, 40% reduction (one patient in ECT compared to zero in the sham-ECT arm). No p-values were reported.

Ansprechrate: kein s.s. Unterschied

Remission rate was not reported in any of the included studies.

Remission: keine Studien

Function[43]

General functioning and **cognitive functioning** were not reported in any of the included studies.

Funktionsfähigkeit: keine Studien

Health-related quality of life[44]

Health related quality of life was not reported in any of the included studies.

QoL: keine Studien

Patient satisfaction

Patient satisfaction was not reported in any of the included studies.

Patient*innenzufriedenheit: keine Studien

[40] **D0001** – What is the expected beneficial effect of ECT on mortality?

[41] **D0005** – How does ECT affect symptoms and findings (severity, frequency) of TRS?

[42] Reported in Sinclair [76] as “mental state”.

[43] **D0011** – What is the effect of ECT on patients’ body functions?

[44] **D0012** – What is the effect of ECT on generic health-related quality of life?

Patient safety[45]

Adverse events were not reported in any of the included studies.

Patient*innensicherheit: keine Studien

ECT plus antipsychotics versus clozapine plus antipsychotics[46]

Mortality[47]

Overall mortality, suicidal attempts and **suicidal ideation** were not reported in the included study [82].

Mortalität: keine Studien

Morbidity[48]

One study (n=162) [82] reported no clear medium-term difference in the number of clinically significant **responders** between patients receiving ECT plus ziprasidone and patients receiving clozapine plus ziprasidone (RR 1.23, 95% CI, 0.95 to 1.58). The study also assessed **schizophrenia symptoms** using the BPRS total score. Short-term results showed a lower total score after ECT treatment than after clozapine treatment (MD -5.20, 95%CI, -7.93 to -2.47). Medium-term results were derived from skewed data. Consequently, a parameter test was not applicable. Included studies also assessed specific symptom scores, which are reported in the included SR [76].

Ansprechrate: kein s.s. Unterschied

Schizophreniesymptome: BPRS niedriger mit EKT

Function[49]

General functioning as well as **cognitive functioning** were not reported in the included study [82].

Funktionsfähigkeit: keine Studien

Health-related quality of life[50]

The included study [82] did not report **health-related quality of life**.

QoL: keine Studien

Patient satisfaction

The included study [82] did not report patient **satisfaction**.

Patient*innenzufriedenheit: keine Studien

Patient safety[51]

One study (n=162) [82] reported the endpoint score of **adverse events** assessed by the Treatment Emergent Symptom Scale (TESS). The short-term difference between the two groups (MD -0.40, 95% CI, -0.91 to 0.11) was not statistically significant. Medium-term TESS scores were lower in the ECT group than in the clozapine group (MD -1.10, 95% CI, -1.40 to -0.80) [76]. The study did not report serious adverse events.

Sicherheit: kein s.s. Unterschied

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[45] **C0008** – How safe is ECT in comparison to sham-ECT?

[46] ziprasidone

[47] **D0001** – What is the expected beneficial effect of adding ECT to antipsychotics on mortality?

[48] **D0005** – How does adding ECT on antipsychotics affect symptoms and findings (severity, frequency) of TRS?

[49] **D0011** – What is the effect of adding ECT on antipsychotics on patients' body functions?

[50] **D0012** – What is the effect of adding ECT to antipsychotics on generic health-related quality of life?

[51] **C0008** – How safe is adding ECT to antipsychotics in comparison to adding clozapine to antipsychotics?

ECT versus antipsychotics[52]

Mortality[53]

Overall mortality, **suicidal attempts** and **suicidal ideation** were not reported in the included study [85].

Mortalität: keine Studien

Morbidity[54]

One study (n=30) [85] reported **schizophrenia symptoms** using the total BPRS score. Medium-term results did not show statistically significant difference between the two groups (MD -0.93, 95%CI, -6.95 to 5.09). The study did not report **response** to treatment [76].

Schizophreniesymptome: kein s.s. Unterschied
Ansprechrate: nicht berichtet

Function[55,56]

One study (n=30) [85] assessed the medium-term total score for **general functioning** using GAF. However, no clear differences between the two groups were found (MD -0.66, 95%CI, -3.60 to 2.28). **Cognitive function** was measured by the MMSE[57]. No statistically significant differences between study groups were detected (MD -0.20, 95%CI, -3.70 to 3.30) [76].

Funktionsfähigkeit: kein s.s. Unterschied;
kognitive Funktion: kein s.s. Unterschied

Health-related quality of life[58]

The included study [85] did not report **health-related quality of life**.

QoL: keine Studien

Patient satisfaction

The included study [85] did not report **patient satisfaction**.

Patient*innenzufriedenheit: keine Studien

Patient safety[59]

The included study [85] did not report **adverse events**.

Sicherheit: keine Studien

ECT plus standard care versus standard care

Mortality[60]

Overall mortality, suicidal attempts and **suicidal ideation** were not reported in the included studies.

Mortalität: keine Studien

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[52] flupentixol

[53] **D0001** – What is the expected beneficial effect of adding ECT to antipsychotics on mortality?

[54] **D0005** – How does adding ECT to antipsychotics affect symptoms and findings (severity, frequency) of TRS?

[55] **D0011** – What is the effect of adding ECT to antipsychotics on patients' body functions?

[56] **D0016** – How does adding ECT to antipsychotics affect activities of daily living?

[57] Reported in Sinclair [76] as "mental state".

[58] **D0012** – What is the effect of adding ECT to antipsychotics on generic health-related quality of life?

[59] **C0008** – How safe is adding ECT to antipsychotic in comparison to antipsychotic alone?

[60] **D0001** – What is the expected beneficial effect of adding ECT to standard care on mortality?

Morbidity[61]

Ansprechrate: s.s. Unterschied nach 4 Wochen zugunsten EKT

Nine studies (n=819) reported statistically significant **response** to treatment within four weeks of follow-up (medium-term) [83, 84, 86, 87, 90, 92-95]. The ECT plus standard care group had more responders than the standard care group (RR 2.06, 95% CI, 1.75 to 2.42, see Figure 4-7). One study (n=72) [91] reported the short-term responder rate, showing more responders in the ECT plus standard of care group than in the standard care alone group (RR 1.91, 95% CI, 1.09 to 3.36) [76].

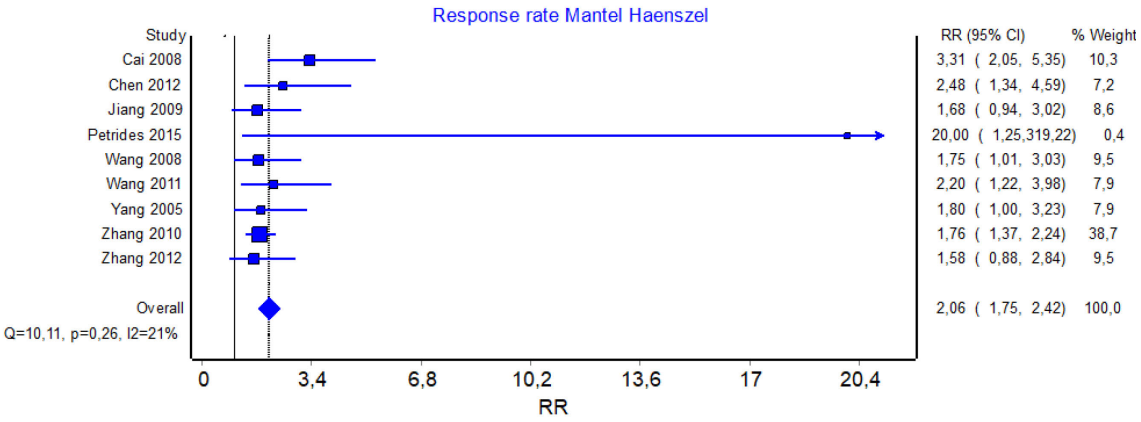

Figure 4-7: Response rate: ECT plus standard care vs standard care

Schizophreniesymptome: s.s. Unterschied zugunsten EKT

Sensitvitätsanalyse aufgrund hoher Heterogenität

Schizophrenia symptoms were measured by the total BPRS and the PANSS score. BPRS results were reported in two studies (n= 345) [83, 95]. The ECT group had lower short-term BPRS scores than the standard care group (MD -5.50, 95% CI, -6.99 to -4.00, I^2=66%), as well as medium-term BPRS scores (MD -11.18, 95% CI, -12.61 to -9.76) [76]. Six studies (n=434) [84, 87, 90, 92-94] reported short-term schizophrenia symptoms using the PANSS, resulting in lower PANSS scores in the ECT plus standard care group than the control group (MD -11.41, 95% CI, -13.49 to -9.34, I^2=94%) [76]. Due to the high heterogeneity, one study [93] was removed from the analysis and heterogeneity was reduced (MD -4.96, 95% CI, -7.48 to -2.44, I^2=0%) [76]. Seven studies (n=492) [74, 84, 87, 90, 92-94] assessed medium-term schizophrenia symptoms[62] using the PANSS. Participants receiving ECT had lower medium-term PANSS scores than participants who did not receive ECT (MD -24.06, 95% CI, -25.21 to -22.91, see Figure 4-8). For a detailed description of specific outcome scores, see the included SR [76].

[61] **D0005** –How does adding ECT to standard care affect symptoms and findings (severity, frequency) of TRS?

[62] Reported as "Mental state" in Sinclair [76]

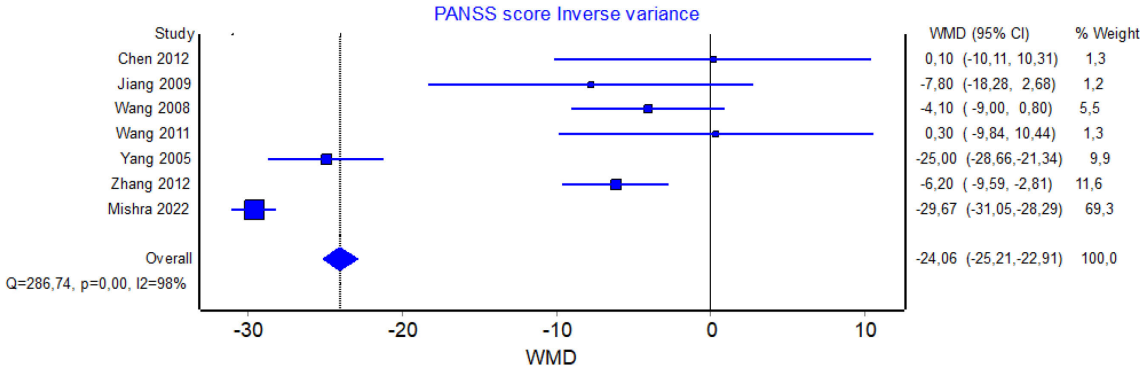

Figure 4-8: PANSS score: ECT vs standard care

Function[63,64]

Two studies (n=315) [87, 95] reported **cognitive functioning**. In one study (n=67) [87] cognitive functioning was measured by the WCST. However, data reported on perseveration and non-perseveration errors were skewed and were only reported as "other data" in the included SR [76]. One study (n=246) [95] reported cognitive functioning using the WMS. Short-term as well as medium-term results showed no clear differences in specific memory symptoms between the two groups; for a detailed description see the included SR [76].

kognitive Funktion: heterogene Ergebnisse

1 RCT kein s.s. Unterschied (WMS)

Two studies (n=69) [85, 86] reported cognitive functioning[65] by measuring total MMSE and medium-term follow-up scores. The intervention group had higher MMSE scores than the control group (MD 0.98, 95% CI, 0.30 to 1.65) [76].

2 RCTs: s.s. Unterschied (MMSE) zugunsten EKT

One study (n=60) [74] reported cognitive functioning using the MoCA. Both, the intervention, and the control group achieved statistically significant differences in the MoCA score between baseline and six weeks follow-up ($p<0.001$ vs $p<0.001$), the differences between the groups, however, did not show statistically significant differences.

1 RCT: kein s.s. Unterschied (MoCA)

Two studies (n=98) [85, 87] reported **general functioning** using total scores of GAF. One study (n=67) [87] yielded no clear difference in short-term GAF scores between the two groups (MD 4.32, 95% CI -0.20 to 8.84). Both studies found higher medium-term GAF scores in the ECT group (MD 10.66, 95% CI 6.98 to 14.34, $I^2=80\%$). While one study [85] used a long course of ECT (MD 20.47, 95% CI 11.21 to 29.73), the other study [87] used a short course (MD 8.82, 95% CI 4.81 to 12.83) [76].

Funktionsfähigkeit: kein s.s. Unterschied

Health-related quality of life[66]

The included studies did not report **health-related quality of life** [76].

QoL keine Studien

[63] **D0011** –What is the effect of adding ECT to standard care on patients' body functions?

[64] **D0016** –How does adding ECT to antipsychotics affect activities of daily living?

[65] Reported as "Mental state" in Sinclair [76]

[66] **D0012** –What is the effect of adding ECT to standard care on generic health-related quality of life?

Patient satisfaction

Patient*innenzufriedenheit: kein s.s. Unterschied

Three studies (n=354) reported the number of participants who left the study early at medium-term follow-up, showing no clear difference between the intervention and the control arm (RR 1.18, 95% CI 0.38 to 3.63) [76].

Patient safety[67]

SAEs: Gedächtnisstörung s.s. Unterschied

One study [91] (n=72) reported **memory deterioration** as part of the cognitive functioning outcomes. The pooled RR was 27 (95% CI, 1.67 to 437.68), suggesting a significant risk with ECT.

unerwünschte Ereignisse: kein Unterschied

One study (n=84) [94] reported no clear difference in the incidence of **adverse events** between the intervention and control group at medium-term follow-up (RR 1.33, 95% CI, 0.86 to 2.06) [76]. Three studies (n=499) [83, 87, 94] reported no clear difference in the short-term TESS total score between the two groups (MD -0.19, 95% CI, -0.96 to 0.57); however, the medium-term results [83, 87, 94, 95] showed lower TESS scores in the intervention group compared to the control group (MD -0.63, 95% CI, -1.01 to -0.25) [76]. One study (n=58) [74] reported that headaches occurred in 12 ECT patients. Two ECT patients had temporary cognitive deficits, whilst 18 standard of care patients had constipation. One study (n=72) [91] assessed short- and medium-term adverse events for specific symptoms; however, no clear differences between the two groups were detected. Adverse events were (amongst others) constipation, headache, lethargy, nausea, or vomiting, as well as salivation and weight gain. Results for specific symptoms are reported in the included SR [76].

[67] **C0008** –How safe is adding ECT to standard care in comparison to standard care alone?

5 Certainty of evidence

RoB

The risk of bias of primary studies was assessed with the Cochrane risk of bias tool 1 in four and with Cochrane 2.0 in one SR. The newly identified RCTs were assessed with the Cochrane 2.0 tool. Risk of bias assessment tables are presented in Table A-5 to Table A-7 in the Appendix.

32 von 46 RCTs: hohes RoB; Hauptgrund: keine Verblindung

Across the included RCTs, over 80% (32 out of 46) had a high risk of bias and just under 20% (14 out of 46) uncertain risk or some concerns (depending on which tool was used). The main reasons for the high risk of bias were mainly the non-blinding of participants and personnel, in some cases, concerns regarding the allocation concealment and high drop-out rates in the studies or concerns regarding the measurement of the outcome and the selection of reported results.

Vertrauenswürdigkeit der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [57] for each endpoint individually. Two independent reviewers rated each study. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [57].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

GRADE Tabelle nächste Seite und Anhang

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-8 to Table A-15.

Vertrauenswürdigkeit der Evidenz für ECT als Monotherapie …

Overall, the certainty of evidence for the effectiveness and safety of ECT compared to

- rTMS is low to very low,
- ketamine is very low to moderate,
- antidepressants is low,
- sham-ECT is very low, and
- antipsychotics alone is very low.

…oder als Augmentation

Overall, the certainty of evidence for the effectiveness and safety of adding ECT

- to antidepressants compared to antidepressants alone is very low to moderate.
- to antipsychotics compared to clozapine plus antipsychotics is low, and
- to standard of care compared to standard of care alone is very low to moderate.

Table 5-1: Summary of findings table of ECT versus rTMS in TRD

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty	Comments
	Risk with rTMS	Risk with ECT				
Mortality (suicide-related events): overall mortality, suicidal attempt, suicidal ideation	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Suicide score (HAM-D/HDRS, BDI)	Mean score ranged across rTMS groups from 0.37 to 1.4 (high=poor).	MD 1 RCT: 0.63 lower (HAM-D). 1 RCT: 1.5 lower (HDRS), 0.6 lower (BDI).	Not estimable	113 (2)	⨁◯◯◯ Very low	There is no established MCID for this outcome. The difference was statistically significant in one RCT (MD 0.63). The other RCT did not report p-values.
General functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Cognitive functioning (DSP, SCWTV, CTT, ROT)	Mean scores for the rTMS group were: DSP (high=good): 9.53 ± 0.77 SCWTV (high=poor) dots: 20.16 ± 6.62; words: 27 ± 7.65; colors: 38.37 ± 9.79 CTT (high=poor) trial 1: 74.32 ± 32.42; trial 2: 110 ± 41.50 ROT (high=good) copy: 36 ± 0.0; delay: 23.37 ± 3.76	MD DSP: 1.32 lower (1.25 to 1.39 lower) SCWTV dots: 2.20 higher (1.74 to 2.66 higher); words: 4.38 higher (4.27 to 4.49 higher); colors: 5.6 higher (5.17 to 6.03 higher) CTT trial 1: 11.14 higher (8.82 to 13.46 higher); trial 2: 22.71 higher (21.27 to 24.15 higher) ROT copy: 0.30 lower (0.60 higher to 1.20 lower); delay: 3.67 lower (2.86 to 4.48 lower)	Not estimable	40 (1)	⨁◯◯◯ Very low	Only 1 RCT reported this outcome. Results were statistically significant for SCWTV and CTT.
Quality of life	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Response rate	375 per 1,000	645 per 1,000 (356 to 1166)	RR 1.72 (0.95 to 3.11)	126 (3)	⨁◯◯◯ Very low	
Remission rate	350 per 1,000	504 per 1,000 (224 to 1,131)	RR 1.44 (0.64 to 3.23)	118 (3)	⨁◯◯◯ Very low	
Depression symptoms: mean difference in depression scores	Mean score ranged across rTMS groups from 5.9 to 16.26 points (high=poor).	MD 5.85 lower (from 2.34 to 9.37 lower)	Not estimable	225 (5)	⨁⨁◯◯ Low	MCID is between 3 and 5, therefore this change is above the clinically meaningful change. Statistically significant result.
Safety: serious adverse events (seizures)	Not pooled			113 (2)	⨁⨁◯◯ Low	No event occurred in the 2 RCTs which reported on SAEs.

***Abbreviations**: CI – confidence interval, CTT – Color Trails Test, DSP – Digit Span Test, ECT – electroconvulsive therapy, MCID – minimal clinically important difference, MD – mean difference, RCT – randomised controlled trial, ROT – Rey- Osterrieth Complex Figure Test, RR – risk ratio, rTMS – repetitive transcranial magnetic stimulation, SAE – serious adverse event, SCWTV – Stroop Color and Word Test*

Table 5-2: Summary of findings table: ECT versus ketamine in TRD

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty	Comments
	Risk with ketamine	Risk with ECT				
Overall mortality	Not pooled			181 (1)	⨁⨁⨁◯ Moderate	Only 1 RCT reported this outcome. 1/90 (1%) vs 0 patients during the 12 months follow-up.
Suicidal attempt	Not pooled			584 (2)	⨁⨁⨁◯ Moderate	1 RCT: 6/90 (7%) vs 4/91 (4%) of patients during 12 months follow-up. 1 RCT: 0/170 vs 0/195 patients at end of treatment, 0/70 (0%) vs 1/108 (1%) during 6 months follow-up.
Suicidal ideation	Not pooled			403 (1)	⨁⨁◯◯ Low	At end of treatment: 2/170 (1%) vs 4/195 (2%) and At 6-month FU: 1/70 (1%) vs 4/108 (4%)
Suicide score (BSSI or CSSRS)	1 RCT with 2 ketamine groups (oral and IM) mean score ranged from 3±3.25 and 2.7±1.35 at 24 hours, 1.53±2.09 and 1.66±1.37 at 2 weeks, 3.1±2.55 and 3.75±2.9 at 1 month. 1 RCT with IM ketamine mean score at end of treatment: 0.1±0.1 1-, 3- and 6-month FU: 0.6±0.1	MD 1 RCT: 24 hours after the first intervention: **0.01 and 0.21 lower** Second week during intervention: **0.31 lower and 0.5 lower** 1 month FU: **1.53 lower and 2.25 lower.** 1 RCT: End of treatment: **no difference** Month 1: **0.1 lower** Month 3 and 6: **0.1 higher**	Not estimable	442 (2)	⨁◯◯◯ Very low	Results were significant in one RCT only for 24 hours after the first intervention (p=0.045) and second week during intervention (p=0.033). Differences were non-significant at 1 month. The other study did not report p-values.
General functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Cognitive functioning (GSE-My score, SMCQ, HVLTR, WMS)	1 RCT: GSE-My score at end of treatment visit was 4.2±0.1 (high=good). SMCQ score at end of treatment visit was 0.2±1.4 (high=good). Change from baseline in HVLT-R T total score was 3.2±0.8 (high=good). 1 RCT: WMS mean score was 50.4±.4, p=0.5 at 1 week and 49.8±9.9, p=0.3 at 1 month (high=good).	MD 1 RCT (6 months follow-up): GSE-My score **1.1 lower** (from 0.9 to 1.2 lower). SMCQ score **9.0 lower** (from 5.1 to 13.0 lower). HVLT-R T total score **5.3 lower** (from 3.1 to 7.4 lower). 1 RCT (1 week to 1 month follow-up): WMS score **3.4 lower** at 1 week and **2 lower** at 1 month follow-up.	Not estimable	435 (2)	⨁◯◯◯ Very low	In the RCT with WMS score the results were non-significant. In the other RCT, the results were statistically significant (95% CI reported for the difference). None of the measurement instruments does have an MCID.

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty	Comments
	Risk with ketamine	Risk with ECT				
Quality of life	Mean change from baseline to post-treatment for the ketamine group was 12.3±1.0.	MD **0.6 higher** (from 2.1 lower to 3.4 higher)	Not estimable	403 (1)	⨁⨁◯◯ Low	Only one RCT reported this outcome. The result is statistically non-significant.
Response	532 per 1,000	543 per 1,000 (468 to 633)	RR 1.02 (0.88 to 1.19)	568 (3)	⨁⨁◯◯ Low	The systematic review by Menon et al. calculated RR using data from one of the studies which we could not find in the publication of the study. Menon stated that they contacted study authors for details in case of unclarities. We therefore used the data reported by Menon in our analysis.
Remission	407 per 1,000	395 per 1,000 (322 to 488)	RR 0.97 (0.79 to 1.2)	551 (2)	⨁⨁◯◯ Low	
Depression symptoms (HDRS, MADRS)	Mean post-treatment score across the ketamine group ranged from 10.9 to 16.9.	SMD **0.30 lower** (high=poor) (0.78 lower to 0.18 higher)	Not estimable	253 (4)	⨁⨁◯◯ Low	Small effect size.
Safety: serious adverse events	Not pooled			589 (2)	⨁⨁◯◯ Low	1 RCT: ≥1 SAE after initial treatment phase occurred in 4/170 (2%) vs 5/195 (3%) patients, while during 6-month follow-up period in 3/70 (4%) vs 8/108 (7%) patients. 1 RCT: ≥1 SAE occurred during the 12-month follow-up period in 23/90 (26%) vs 14/91 (15%), p=0.09

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, GSE-My -Global Self Evaluation of Memory, HVLT-R – Hopkins verbal Learning Test -Revised, MCID – minimal clinically important difference, MD – mean difference, RCT – randomised controlled trial, RR – risk ratio, SAE – serious adverse event, SMCQ – Squire Memory Complaint Questionnaire, SMD – standardised mean difference, WMS – Wechsler Memory Scale

Table 5-3: Summary of findings table: ECT plus antidepressants versus antidepressants in TRD

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty	Comments
	Risk with antidepressants alone	Risk with ECT plus antidepressants				
Mortality (suicide-related events)	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
General functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Cognitive functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Quality of life	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Response rate	428 per 1,000	779 per 1,000 patients (663 to 915)	RR 1.82 (1.55 to 2.14)	871 (13)	⨁⨁⨁◯ Moderate	
Remission rate	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Depression symptoms	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Safety: serious adverse events (somatisation)	Not reported	Not estimable	RR 0.79 (0.61-1.01)	710 (10)	⨁⨁⨁◯ Moderate	Risk with ECT was not estimable due to non-reporting of the baseline risk either in the intervention or in the control group.
Safety: serious adverse events (memory deterioration)	Not reported	Not estimable	RR 0.27 (0.03-2.4)	292 (4)	⨁◯◯◯ Very low	Risk with ECT was not estimable due to non-reporting of the baseline risk either in the intervention or in the control group.

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, RR – risk ratio

Table 5-4: Summary of findings table: ECT versus antidepressants in TRD

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty	Comments
	Risk with antidepressants	Risk with ECT				
Mortality (suicide-related events)	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
General functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Cognitive functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Quality of life	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Response rate	Not reported	Not estimable	RR 2.24 (1.51 to 3.33)	150 (3)	⨁⨁◯◯ Low	
Remission rate	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Depression symptoms	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Safety: serious adverse events (somtisation)	Not reported	Not estimable	RR 1.22 (0.69 to 2.17)	191 (3)	⨁⨁◯◯ Low	Risk with ECT was not estimable due to non-reporting of the baseline risk either in the intervention or in the control group.
Safety: serious adverse events (memory deterioration)	Not reported	Not estimable	RR 0.88 (0.41 to 1.88)	111 (2)	⨁⨁◯◯ Low	Risk with ECT was not estimable due to non-reporting of the baseline risk either in the intervention or in the control group.

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, RR – risk ratio

Table 5-5: Summary of findings table: ECT versus sham-ECT in TRS

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certaintyx	Comments
	Risk with sham-ECT	Risk with ECT				
Mortality (suicide-related events)	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
General Functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Cognitive functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Satisfaction and acceptability of treatment	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Response to treatment (reduction on the PANSS-P, 4 weeks follow-up)	20% reduction: 2 patients 30% reduction: 2 patients 40% reduction: 0 patients	20% reduction: no difference 30% reduction: **1 fewer** 40% reduction: **1 more**	Not pooled	23 (1)	⨁◯◯◯ Very low	Only one RCT reported this outcome. P-values were not reported.
Schizophrenia symptoms[68] (total BPRS score, follow-up: 4 weeks)	Mean decrease in BPRS score (high= poor) was 40.4.	MD **3.60 higher** (3.69 lower to 10.89 higher)	Not pooled	25 (1)	⨁◯◯◯ Very low	P-values were not reported. There is no established MCID for this scale.
Schizophrenia symptoms (total PANSS sore, follow-up up to 6 weeks)	Mean decrease in PANSS score (high= poor) was 9.37.	MD **2.89 higher** (17.22 lower to 11.44 higher)	Not pooled	23 (1)	⨁◯◯◯ Very low	No statistically significant difference (p=0.668) was found between the two groups. There is no consensus based MCID for this outcome, an analysis reported values between 14.02 to 31.50 as being clinically relevant[69], which is not reached in the study.
Schizophrenia symptoms (CGI-S score)	Mean decrease (high= poor) in CGI score was 0.94.	**MD** 0.12 point higher (0.90 lower to 0.66 higher)	Not pooled	23 (1)	⨁◯◯◯ Very low	No statistically significant difference was found between the two groups (p=0.908). 1 score increase or decrease has any meaningful change on the scale, therefore any score change lower than 1 has no clinical meaning.
Adverse event/ effect(s)-death	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.

Abbreviations: BPRS – Brief Psychiatric Rating Scale, CGI – Clinical Global Impression, CI – confidence interval, ECT – electroconvulsive therapy, MCID – minimal clinically important difference, MD – mean difference, PANSS – Positive and Negative Syndrome Scale

[68] Reported as "Mental state" in Sinclair (REF)

[69] The MCID for PANSS score was derived from Si et al (2021) [97]

Table 5-6: Summary of findings table: ECT plus antipsychotics (ziprasidone) versus clozapine plus antipsychotics (ziprasidone) in TRS

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty	Comments
	Risk with clozapine + ziprasidone	Risk with ECT + ziprasidone				
Mortality (suicide-related events)	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
General Functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Cognitive functioning	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Satisfaction and acceptability of treatment	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Response to treatment (4 weeks follow-up)	543 per 1,000	668 per 1,000	RR 1.23 (0.95 to 1.58)	162 (1)	⨁⨁◯◯ low	Only one RCT reported this outcome. Results were statistically non-significant (p=0.11)
Schizophrenia symptoms[70] (total BPRS score, follow-up: 4 weeks)	The mean BPRS- average score (high= poor) was 44.7.	MD 5.20 lower (7.93 to 2.47 lower)	Not estimable	162 (1)	⨁◯◯◯ very low	Only one RCT reported this outcome. Results were statistically significant (p<0.001) There is no established MCID for this scale.
Schizophrenia symptoms (total PANSS sore, follow-up up to 6 weeks)	See comment	See comment	See comment	See comment	See comment	Not included in the summary of findings in the systematic review (REF)
Schizophrenia symptoms (CGI score)	See comment	See comment	See comment	See comment	See comment	Not included in the summary of findings in the systematic review (REF)
Adverse event/ effect(s)-death	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.

Abbreviations: BPRS – Brief Psychiatric Rating Scale, CGI – Clinical Global Impression, CI – confidence interval, ECT – electroconvulsive therapy, MCID – minimal clinically important difference, MD – mean difference, PANSS – Positive and Negative Syndrome Scale

[70] Reported as "Mental state" in Sinclair et al. [76].

Table 5-7: Summary of findings table: ECT versus antipsychotics (flupentixol) in TRS

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with antipsychotics	Risk with ECT				
Mortality (suicide-related events)	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
General functioning (GAF)	The mean GAF-average score (high = good) was 30.1.	**MD 0.66** lower (3.6 lower to 2.28 higher)	Not estimable	30 (1)	⨁◯◯◯ very low	Statistically non-significant difference (p=0.66) MCID of 4 points was not reached
Cognitive functioning (MMSE)	The mean MMSE- average score (high=good) was 25.1.	MD 0.2 lower (3.7 lower to 3.3 higher)	Not estimable	30 (1)	⨁◯◯◯ very low	Statistically non-significant difference (p=0.91). There is no established MCID for this scale.
Satisfaction and acceptability of treatment	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Response to treatment (4 weeks follow-up)	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Schizophrenia symptoms[71] (total BPRS score, follow-up: 4 weeks)	The BPRS- average score (high = poor) was 44.3.	**MD 0.93** lower (6.95 lower to 5.09 higher)	Not estimable	30 (1)	⨁◯◯◯ very low	Statistically non-significant difference (p=0.76). There is no established MCID for this scale.
Schizophrenia symptoms (total PANSS sore, follow-up up to 6 weeks)	See comment	See comment	See comment	See comment	See comment	Not included in the summary of findings in the systematic review [76]
Schizophrenia symptoms (CGI score)	See comment	See comment	See comment	See comment	See comment	Not included in the summary of findings in the systematic review [76]
Adverse event/effect(s)-death	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.

Abbreviations *BPRS – Brief Psychiatric Rating Scale, CGI – Clinical Global Impression, CI – confidence interval, ECT – electroconvulsive therapy, MCID – minimal clinically important difference, MD – mean difference, PANSS – Positive and Negative Syndrome Scale*

[71] Reported as "Mental state" in Sinclair et al. [76]

Table 5-8: Summary of findings table: ECT plus standard care versus standard care in TRS

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with intervention				
Mortality (suicide-related events)	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
General functioning	The mean GAF average score (high = good) was 47.3.	**MD 10.66** higher (6.98 to 14.34 higher)	Not estimable	97 (2)	⨁◯◯◯ very low	Statistically significant difference (p<0.001). MCID of 4 points could be fulfilled.
Satisfaction and acceptability of treatment	23 per 1,000	27 per 1,000 (9 to 82)	RR 1.18 (0.38 to 3.63)	354 (3)	⨁◯◯◯ very low	Statistically non-significant difference (p=0.78)
Response to treatment (4 weeks follow-up)	308 per 1,000	635 per 1,000 (539 to 746)	RR 2.06 (1.75 to 2.42)	819 (9)	⨁⨁⨁◯ moderate	Response rate achieved according to definitions within the studies. Statistically significant difference (p<0.001)
Schizophrenia symptoms[72] (total BPRS score, follow-up: 4 weeks)	The mean BPRS average score (high = poor) was 33.4.	**MD 11.18** lower (12.61 lower to 9.76 lower)	Not estimable	345 (2)	⨁◯◯◯ low	Statistically significant difference (p<0.001) There is no established MCID for this scale.
Schizophrenia symptoms (total PANSS sore, follow-up up to 6 weeks)	The mean PANSS average score (high=poor) was 72.8.	**MD 24.06** lower (25.21 lower to 22.91 lower).	Not estimable	492 (7)	⨁◯◯◯ very low	Statistically significant difference (p<0.001) MCID of 14-31.5 points could be fulfilled.
Schizophrenia symptoms (CGI score)	See comment	See comment	See comment	See comment	See comment	Not included in the summary of findings in the systematic review (REF)
Adverse event/effect(s)-death	See comment	See comment	See comment	See comment	See comment	No studies reported this outcome, so there is no evidence to support or refute benefits of the intervention.
Adverse events/effect(s) – memory deterioration[73]	0 per 1,000	13 per 1,000 (1 to 219)	RR 27 (1.67 to 437.68)	72 (1)	⨁◯◯◯ very low	Statistically significant difference (p=0.02).

Abbreviations: BPRS – Brief Psychiatric Rating Scale, CGI – Clinical Global Impression, CI – confidence interval, ECT – electroconvulsive therapy, MCID – minimal clinically important difference, MD – mean difference, PANSS – Positive and Negative Syndrome Scale

[72] Reported as "Mental state" in Sinclair et al. [76]

[73] Reported as "Cognitive functioning" in Sinclair [76].

6 Discussion

Our review aimed to assess the clinical effectiveness and safety of ECT as mono-, combination or augmentation therapy for treating TRD and TRS, compared to standard care, consisting of pharmacotherapy and non-pharmacotherapy and their combinations.

Ziel: EKT vs. Standardtherapie (ST) (medikamentöse und nicht medikamentöse Behandlung)

Summary of evidence

Treatment-resistant depression

To assess the effectiveness and safety of ECT for treating TRD, our systematic review included three systematic reviews and two additional RCTs, amounting to 29 RCTs and involving 2,101 patients. The analysis involved ECT versus ketamine in 697 patients, ECT versus rTMS in 306 patients, and ECT versus various antidepressants in 1,098 patients. The diagnosis of participants varied, with TRD primarily in the ECT versus antidepressant studies, a mix of conditions in the ECT versus rTMS studies, and predominantly non-psychotic MDD in the ECT versus ketamine studies. The frequency of ECT administration across studies was typically 2-3 times per week, although the specific treatment durations and protocols varied. Many studies were unblinded, with follow-up periods ranging from one week to twelve months.

3 SRs und 2 RCTs (29 RCTs, 2101 Patient*innen)

Komparatoren: Ketamin, rTMS, Antidepressiva (AD)

No studies reported outcomes related to mortality or quality of life when comparing rTMS with ECT. Low to very low-quality evidence hinted that rTMS might be less effective than ECT in reducing suicide scores and symptoms of depression. While cognitive functioning improvements were observed with rTMS, this was based on a single study's report. Similarly, higher remission and response rates were noted with ECT, but these findings come from evidence of very low quality. Safety assessments indicated no significant adverse events reported in the studies, but this evidence is of low certainty as well.

EKT vs. rTMS: keine Studien zur Mortalität, QoL

mögliche Reduktion in Suizidalität und Depressionssymptome

Comparisons between ketamine and ECT showed no substantial differences, with moderate certainty in mortality and suicidality and low certainty in safety endpoints. Low certainty evidence indicated minor effects on depression symptoms favouring ECT and improved cognitive functioning for ketamine patients. Two studies had a non-inferiority design, aiming to evaluate if ketamine is non-inferior to ECT. However, their overall conclusions point in divergent directions, indicating inconclusive evidence. When focusing on specific outcomes analysed in the non-inferiority context, we found mixed results for remission rates with an overall non-significant conclusion. Additionally, when evaluating response rates, the analysis incorporated one superiority study and two non-inferiority studies; the superiority study found no significant effect. Meanwhile, the non-inferiority studies produced conflicting outcomes: one concluded that ketamine demonstrated non-inferiority, suggesting it was not less effective than ECT, while the other indicated ketamine's inferiority, favouring ECT over ketamine.

EKT vs. Ketamin: keine deutlichen Unterschiede bei Mortalität und Suizidalität, bei Depressionssymptome und kognitiver Funktion niedrige Vertrauenswürdigkeit der Evidenz

2 Nichtunterlegenheitsstudien zeigen keine eindeutigen Ergebnisse

In studies where ECT was added to antidepressant therapy, moderate certainty evidence indicated a notable improvement in response rates with ECT. However, the comprehensive assessment of the combination's benefits and risks remains unclear due to insufficient reporting of other critical effectiveness outcomes and statistically non-significant safety results regarding somatisation and memory deterioration with ECT. In studies where ECT as monotherapy was compared with antidepressants, low certainty evidence showed a considerable improvement in response rates. However, the assessment of safety events, specifically somatisation and memory deterioration, yielded inconclusive outcomes due to low certainty evidence and statistically non-significant results.

Verbesserungen beim Ansprechen der Therapie mit EKT verglichen mit AD; unzureichende Informationen zu entscheidenden Endpunkten

In summary, while some evidence suggests that ECT may offer significant improvements in response rates over antidepressants alone, the overall benefits and risks of ECT, particularly in comparison to other treatments such as ketamine and rTMS, cannot be conclusively determined from the available studies due to gaps in data on mortality, serious adverse events, cognitive and general functioning, and quality of life.

Ansprechen der Behandlung: mögliche Verbesserungen bei EKT

Treatment-resistant-schizophrenia

One systematic review and three additional RCTs (four publications) were included to assess the effectiveness and safety of ECT in TRS. In total, 18 RCTs involving 1,368 patients were included in the review. ECT as an augmentation to standard of care was compared to clozapine and standard of care (ziprasidone)(n=162), standard of care alone (n=1,137), and ECT alone was compared to sham-ECT (n=54) as well as standard of care alone (flupentixol) (n=30)[74]. The included participants were all diagnosed with treatment-resistant schizophrenia by international standards, including CCMD-2-R, CCMD-3, DSM-IV, and ICD-10. The treatment duration of the included studies ranged from two to 24 weeks. The treatment duration in the other studies was four weeks, eight weeks, or twelve weeks.

1 SR, 3 RCTs (4 Publikationen) (18 RCTs, 1368 Patient*innen)

EKT + ST vs. ST oder ST und Clozapin
EKT vs. ST oder Schein-EKT

Concerning the schizophrenia symptoms (assessed using the BPRS or PANSS), statistically significant differences between study groups were found only when ECT plus standard of care was compared to standard of care alone in favour of the intervention group. However, the overall certainty of evidence was low to very low. Furthermore, statistically significant differences were detected for the same comparison in the MMSE. Similar results between ECT and sham-ECT were achieved in response rate; ECT plus standard of care yielded statistically significantly more responders than standard of care alone. Safety outcomes were not statistically significantly different between groups. Still, it is essential to note that adverse events in both intervention groups varied. Adverse events in the ECT group include headaches (amongst others), while pharmaceuticals include, for example, constipation. Other outcomes and comparators did not show substantial differences between study groups.

Schizophreniesymptome: s.s. Unterschiede zugunsten EKT (+ ST vs. ST)

s.s. Unterschied MMSE kein s.s. Unterschied EKT vs. Schein-EKT

unterschiedliche Nebenwirkungen in den Studiengruppen

No information about overall mortality, suicidal attempts as well as suicide ideation could be retrieved from the included studies. In addition, no studies have reported on QoL. Patient satisfaction was assessed in three studies (ECT plus standard care vs standard care alone), resulting in no statistically significant differences between study groups.

keine Informationen zu Mortalität und Suizidversuchen, QoL

[74] One study had three arms (ECT + flupentixol, ECT alone, flupentixol alone).

To sum up, ECT may enhance response rates and improve schizophrenia symptoms, mainly when used as an augmentation to standard care. However, limited evidence exists for other outcomes and comparisons, and the available information is based on low to very low certainty of evidence. Despite potential positive effects, adverse events persist. This uncertainty prevents confirming the superiority of ECT over sham-ECT or standard care.

mögliche Verbesserung: Ansprechen der Behandlung, Symptome; limitierte Evidenz, niedrige Vertrauenswürdigkeit

Interpretation of findings

Various clinical practice guidelines recognise ECT as an established technology generally considered effective and safe. Nevertheless, a lack of clarity regarding its mechanism of action and robust evidence base raises concerns about its long-term effectiveness and its safety in general. The evidence base is predominantly composed of studies that are flawed and, in many cases, conducted a long time ago. The systematic review with antidepressant comparisons in depression and the systematic review on schizophrenia primarily included RCTs from the 2000s and early 2010s. The rTMS comparison studies were exclusively from the 2000s. In contrast, the studies comparing ketamine were more recent, dating from the late 2010s to the early 2020s.

Leitlinien beschreiben EKT als etablierte und sichere Technologie

aber: Mangel an Evidenz bezgl. Sicherheit

Less invasive treatment options like rTMS and ketamine emerged in the last decades, and they constitute the comparators in our review. Our findings align with other systematic reviews, highlighting the scarcity of evidence and a significant underreporting of safety outcomes, which obscures the treatment's risk-benefit assessment. Key safety concerns like potential brain damage and memory loss (also referred to as memory impairment, memory dysfunction, persistent or temporary memory loss, retrograde amnesia) lack both short-term and long-term reporting. It could also be frequently observed that even when cognitive functioning outcomes were reported, possible related safety events, like memory loss, were not reported. At the same time, it must be recognised that cognitive side effects are challenging to distinguish from cognitive impairments as a symptom of the underlying disease. Echoing NICE's two-decade-old conclusion [33], saying, "*Further research is urgently required to examine the long-term efficacy and safety of ECT, including its use as a maintenance therapy and its use in particular subgroups who may be at increased risk, for example, older people, children and young people, and during pregnancy. In addition to the use of appropriately validated psychometric scales, outcome measures should include user perspectives on the impact of ECT, the incidence and impact of important side effects such as cognitive functioning, and mortality.*" Additionally, we emphasize the importance of improving data quality and reporting of short-term serious safety events.

Erkenntnisse im Einklang mit der Schlussfolgerung des National Institute for Health and Care Excellence

Internal and external validity

The studies included in our analysis were typically characterised by small sample sizes and were open-label, with the majority presenting a high risk of bias. There was also a lack of uniformity in defining treatment response, and safety endpoints were infrequently reported. These factors collectively undermine the ability to draw robust conclusions from the data.

wenige Patient*innen, nicht-verblindetes Design, hohes RoB

The duration of follow-up periods was too short in most of the included studies to conclude whether the expected changes had a sustainable effect on patients' lives, especially in terms of symptom and functional outcomes, as well as the quality of life and adverse events. Moreover, the absence of established MCIDs in the field presents a challenge in determining whether the experienced changes were clinically meaningful.

Follow-Up Dauer zu kurz für Aussage zur Nachhaltigkeit der Therapie

The studies reviewed provided evidence on the use of antidepressants, ketamine, rTMS, and various pharmacotherapies, likely reflecting standard care options. However, the absence of evidence regarding psychotherapy in combination with or as an augmentation to other pharmaco- or non-pharmacotherapy interventions could significantly impact the perceived effectiveness of these treatments.

keine Studien, die Kombination oder Augmentation mit Psychotherapie vergleichen

ECT can be utilised in a broader range of populations than those included in our study, raising concerns about the generalisability of the findings. In the TRD studies, mean ages mostly ranged from the early 30s to mid-40s, though three studies included participants over 60. TRS studies scarcely presented older patients (over 60 years) who were not represented (only one study included patients between 18 and 74 years old). Therefore, it is not possible to conclude for old-aged TRS patients. Additionally, we could not find any systematic reviews comprising RCTs or RCTs focusing on adolescents in TRD or TRS, signalling a significant evidence gap. Consequently, our findings may not apply to children and adolescents in both indications.

EKT auch für andere Populationen geeignet → allgemeine Schlussfolgerung nicht möglich

Evidenzlücken zu Jugendlichen

Furthermore, some studies included patients with psychotic features while others did not, which could affect the ECT effectiveness since patients with psychotic features might have higher suicidal risks and more severe depressive symptoms [98]. Beyond suicides, increased mortality rates in TRD and TRS are also associated with natural causes, including cardiovascular and respiratory diseases, as well as metabolic syndrome [10, 25]. However, these long-term outcomes are notably absent in RCTs, even though they hold clinical significance.

Patient*innen mit und ohne psychotischen Symptomen inkludiert → Einfluss auf Wirksamkeit

Komorbiditäten als mögliche Todesursache

The variability in ECT protocols – such as the waveform of the electrical stimulus, the total number of sessions and frequency of administration, and electrode placement – may significantly influence treatment outcomes. These variations reflect clinical practice but challenge standardising and comparing study results. Additionally, the allowance of concomitant medications during trials can impact outcomes, although this also mirrors the complexity of real-world treatment scenarios. Modifications to treatment regimens within trials are another factor that can affect results. For instance, if ECT is administered in fewer or weaker sessions, it may not only alter effectiveness outcomes. However, it could also influence the type and frequency of adverse events, potentially not reflecting the full spectrum of what is observed in clinical practice. Using different anaesthetic agents in ECT can influence the seizure threshold and duration, affecting ECT's therapeutic outcomes. Recent research has turned towards measuring the effects of premedication and adjunct therapies, such as memory training techniques, on ECT, aiming to see if these mitigate adverse effects like headaches and improve cognitive functions, enhancing the overall effectiveness of ECT and patient well-being.

Unterschiede bei EKT-Protokollen

möglicher Einfluss von zusätzlichen Medikamenten, sowie unterschiedlich vielen Einheiten auf Effektivität und Nebenwirkungen

zusätzliche Therapien vor EKT zur Vermeidung von kognitiven Beeinträchtigungen

Ongoing research

The clinical landscape for depression treatment is evolving, with many novel therapies in clinical trials where ECT serves as a comparator. It will enhance our understanding of this well-established technology and contribute to the broader knowledge base in the field. Two larger-scale trials (enrolling over 400 and 1,500 patients) are underway, both on patients with depression (MDD and acute suicidal depression), expected to present high-quality evidence on ECT in comparison to ketamine, rTMS and drug therapy in terms of suicidal ideation, depression symptoms, response, and remission.

laufende Studien: EKT oft als Komparator für andere Interventionen

Limitations

We acknowledge certain limitations within our research. We encountered difficulties accessing all primary studies included in the systematic reviews, and some necessary data, such as event rates, was not available in the published literature. This limitation precluded us from calculating absolute risks for certain outcomes. Furthermore, we did not perform subgroup analyses for specific demographics, such as the elderly and adolescents, if studies included a certain proportion of them, and we did not examine differences in electrode placement (unilateral versus bilateral) or pulse types (brief versus ultrabrief). These factors are known to influence both the effectiveness and the side-effect profile of ECT and merit further investigation. Furthermore, our study did not encompass the use of ECT in continuation or maintenance therapy, mainly due to the heterogeneity in treatment protocols and the nature of evidence being limited by methodological constraints. Additionally, we excluded studies focusing on patients with bipolar depression unless they constituted a minor percentage of the study population. This exclusion was predicated on the distinct clinical features of bipolar depression and the tendency for such patients to be excluded from many research cohorts.

Limitationen:
kein Zugang zu allen Primärstudien aus den SRs

unterschiedliche Elektrodenplatzierungen wurden nicht untersucht

EKT als Erhaltungstherapie nicht untersucht

Exklusion von Studien mit Fokus auf Patient*innen mit bipolarer Depression

7 Conclusion

In Table 7-1 the scheme for evidence-based conclusion is displayed and the according choice is highlighted.

Table 7-1: Evidence-based conclusions

	Strong evidence for added benefit in routine use.
	Evidence indicates added benefit in specific indications.
X	Less robust evidence indicating an added benefit in routine use or in specific indications.
	No evidence or inconclusive evidence available to demonstrate an additional benefit of the intervention of interest.
	Strong evidence indicates that intervention is ineffective and or harmful.

Reasoning:

Moderate certainty evidence indicates that in TRD patients, adding ECT to antidepressants is more effective in improving clinical response without raising the risk of somatisation, in comparison to using antidepressants alone. Likewise, there is no elevated risk for memory deterioration associated with this combination. However, the certainty of the evidence regarding memory deterioration is low. Additionally, the currently available evidence is insufficient to prove the added benefit of ECT compared to rTMS, ketamine and antidepressants alone due to very low to low certainty of evidence. New study results may influence the effect estimate considerably.

TRD: mögliche verbesserte Ansprechrate bei gleicher Sicherheit mit EKT + AD

unzureichende Evidenz zum Vergleich mit anderen Therapien

Moderate certainty evidence indicates that in TRS patients, adding ECT to standard care is more effective in improving clinical response compared to standard care alone. The currently available evidence is insufficient to demonstrate that this combination is as safe as standard care. Further-more, evidence comparing the effectiveness and safety of adding ECT to antipsychotics versus the combination of clozapine with antipsychotics is lacking. Similarly, there is inadequate evidence to assess ECT's comparative effectiveness and safety against sham-ECT or antipsychotics alone.

TRS: mögliche verbesserte Ansprechrate mit EKT + ST, unzureichende Evidenz zur Sicherheit und zum Vergleich mit anderen Therapien

The re-evaluation is recommended the earliest after 2030 when potentially two larger scale (over 400 and 1,500 enrolled patients) RCTs will have been completed.

Reevaluierung: frühestens 2030 empfohlen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: ECT versus pharmacotherapy or non-pharmacotherapy: Systematic reviews

Author, year	Menon 2023 [99]	Song 2015 [65]	Erdos 2017 [100]	Sinclair 2019 [76]
Review aim	To compare depression rating outcomes with ketamine vs ECT in adults with major depressive episode (MDE) and to compare response and remission rates, number of sessions to response and remission, and adverse effects.	To assess the potential of ECT plus antidepressants compared with ECT alone by undertaking an indirect comparison meta-analysis.[75]	To assess the effectiveness and safety of repetitive transcranial magnetic stimulation (rTMS) in TRD compared with sham rTMS and ECT.	To assess the effects (benefits and harms) of ECT for people with treatment-resistant schizophrenia (TRS). To determine whether ECT produces a differential response in people (treated with unilateral compared with bilateral ECT, have had long or a short course of ECT, are given continuation or maintenance ECT, are diagnosed with well-defined TRS).
Population (diagnosis)	Adult patients with MDE	Adult patients with treatment-resistant depression (TRD)	TRD	TRS or related disorders (e.g. schizoaffective disorder, schizophreniform disorder)
Intervention (product)	ECT	ECT plus antidepressant/ECT alone	rTMS	ECT/ECT plus standard care
Comparator(s)	Ketamine	Antidepressant alone	ECT, sham-rTMS[76]	Sham-ECT, standard care, treatment with antipsychotics, non-pharmacological forms of treatment, placebo
Review outcomes	*Efficacy outcomes*: 1-week (or nearest) post-treatment depression ratings, 1-week (or nearest) study-defined response and remission rates, Number of sessions to treatment response and remission. *Safety outcomes*: Reported adverse effects.	*Efficacy outcomes*: Response rate *Safety outcomes*: Adverse reactions including memory deterioration and somatisation.	*Efficacy outcomes*: Response and remission rates, Mean difference in depression scores *Safety outcomes*: Cognitive impairment, Number of seizures, Other adverse events.	*Efficacy outcomes:* Response to treatment, Cognitive functioning, Satisfaction and acceptability of treatment, Mental state, General functioning, Service use *Safety outcomes:* Adverse effects.
Types of included studies	Parallel-group randomised trials (RCTs)	RCTs	RCTs	RCTs

[75] This is the objective as reported in the meta-analysis. However, the study has also included results for ECT + antidepressants or ECT alone versus antidepressants alone. Therefore, the objective from this report's perspective was to assess the efficacy and safety of ECT + antidepressants or ECT alone compared to antidepressants alone.

[76] Only the rTMS vs ECT part of the review is considered.

Author, year	Menon 2023 [99]	Song 2015 [65]	Erdos 2017 [100]	Sinclair 2019 [76]
Period searched	From inception until May 31, 2022	Search until November 21, 2014	The period of the search was limited to November 2014 to January 2017[77]	Search until August 4, 2017
Number of included studies, number of pts in total	5 278	17 1,098	6 266	15 1,285
List of included studies	Ekstrand et al. 2022 Ghasemi et al. 2014 Kheirabadi et al. 2019 Kheirabadi et al. 2020 Sharma et al. 2020	Folkerts et al. 1997 Qin et al. 2013 Ye and Tian 2013 Zhang et al. 2011 Hu et al. 2014 Huang et al. 2006 Jiang et al. 2010 Li et al. 2012 Li and Xu 2009 Niu et al. 2011 Shi et al. 2010 Tang et al. 2012 Wen et al. 2011 Xu et al. 2009 Yang et al. 2010 Zhou et al. 2014 Zhu et al. 2008	Eranti et al. 2007 Keshtkar et al. 2011 Grunhaus et al. 2003 Grunhaus et al. 2000 and Dannon et al. 2000 Rosa et al. 2006 Pidmore et al. 2000	Cai et al. 2008 Chanpattana et al. 1999 (3 publications) Chen et al. 2012 Goswami et al. 2003 (2 publications) Jiang et al. 2009 Jiang et al. 2013 Lin et al. 2014 Liu et al. 2010 Petrides et al. 2015 (5 publications) Wang et al. 2008 Wang et al. 2011 Wang et al. 2013 Yang et al. 2005 Zhang et al. 2010 Zhang et al. 2012
Quality of the included evidence	4 RCTs had high, or unclear risk of bias related to randomisation processes. All 5 RCTs had a high risk of bias related to deviations from intended interventions, given the lack of blinding of participants and treatment personnel and given that such deviations are likely to affect outcomes. 3 RCTs were judged to be at high risk of bias due to differences between groups on proportion of missing outcome data. 2 RCTs had high risk of bias in measurement of outcomes due to non-blinding of outcome raters. Finally, 2 RCTs were at high risk of bias in selection of reported results as they were unregistered/ retrospectively registered on a trial registry.	3 trials had selection bias, performance bias and detection bias. Only 1 trial performed appropriate blinding method to avoid performance and detection bias. 1 study did not perform an intention-to-treat (ITT) analysis to deal with drop-outs. Other potential bias resources did not exist in all trials. According to the assessment of risk of bias for each study, no study was classified into grade A for overall quality, 13 studies were rated as B grade and 4 studies were rated as C[78].	Overall, very low quality. High risk of bias of all included RCTs related to blinding. Unclear risk of bias in allocation concealment in all but one RCT. Unclear risk of bias in 1 RCT related to randomisation.	Most studies (14/15, 93.3%) were judged to be of high risk of bias due to issues related to the blinding of participants and personnel. 2/15 adequate sequence generation, 1/15 adequate allocation concealment, 1/15 double-blinded, 2/15 outcome assessors blinded, 11/15 complete outcome data, 11/15 appropriate reporting, 0/15 no other potential sources of bias.

[77] The start date of the search was chosen because this work is an update of another systematic review (Health Quality Ontario, 2016), whose search period lasted until November 2014.

[78] The summary risk of bias was considered low corresponding A grade (low risk in all domains), unclear corresponding B grade (unclear risk in 1 or more domains), or high corresponding C grade (high risk in 1 or more domains)

Author, year	Menon 2023 [99]	Song 2015 [65]	Erdos 2017 [100]	Sinclair 2019 [76]
Review findings (author conclusions)	A nonsignificant trend for superiority of ECT over ketamine for 1-week post-treatment depression ratings was found. In a sensitivity analysis excluding 3 methodologically weaker trials, ECT was significantly superior to ketamine for this outcome and was associated with significantly superior response and remission rates. Cognitive outcomes did not differ between ECT and ketamine trials.	Response rate can be improved in the ECT plus antidepressant (RR, 1.82; 95% CI, 1.55-2.14) and ECT alone group (RR, 2.24, 95% CI, 1.51-3.33) compared with antidepressant alone, respectively; adverse complications including memory deterioration and somatisation were not significantly increased except incidence of memory deterioration in ECT plus antidepressant in the 4th weeks after treatment (RR, 0.09, 95% CI, 0.02-0.49).	In comparison with ECT, the critical endpoints remission and response rates showed no statistically significant difference. However, the mean difference in depression scores was statistically and clinically significant favouring ECT. There was considerable heterogeneity in the trials, which can be explained by the variation of treatment parameters used in ECT application (unilateral or bilateral). Subgroup analysis for ECT electrode placement revealed that the subgroup of studies that used bilateral ECT in at least 40% of patients showed larger treatment effect than studies that used only unilateral or bilateral in less than 40% of patients.	Moderate-quality evidence indicates that relative to standard care, ECT has a positive effect on medium-term clinical response for people with TRS. However, there is no clear and convincing advantage or disadvantage for adding ECT to standard care for other outcomes. The available evidence was also too weak to indicate whether adding ECT to standard care is superior or inferior to adding sham-ECT or other antipsychotics to standard care, and there was insufficient evidence to support or refute the use of ECT alone. More good-quality evidence is needed before firm conclusions can be made.
Review limitations	Small number of eligible studies, small sample sizes in most studies, poor methodological quality of most studies, and high risk of bias in all. No study examined retrograde amnestic deficits, arguably the most problematic adverse effect of ECT.	Only a small number of eligible studies were included, and sample size was small in the studies. Some selection bias might have been introduced by not having searched non-English and Chinese databases and not having been able to include publications whose full-text was not available. In all of the trials included in the study, no study was classified as grade A and 4 studies were rated as grade C. Pooled results might be impaired due to the lack of standardisation in outcome measurement instruments across the included studies. The publication bias test was not conducted due to insufficient number of eligible studies for each outcome (subgroup).	The sample sizes of the RCTs were small, therefore, it is difficult to draw definitive conclusions about the true level of efficacy. The most serious limitation of the included studies is that only some of them reported on adverse events and only one study measured cognitive impairment, which is the most common adverse event in ECT therapy.	Comprehensive search strategies were developed, and the search was performed with no limitations on language, date, document type, or publication status. However, only included published data was included, so there is a possibility of publication bias. Nonetheless, two review authors independently screened studies and extracted data, therefore it is less likely that this process could have introduced bias.

Abbreviations: ECT – Electroconvulsive therapy, rTMS – repetitive Transcranial Magnetic Simulation, MDE – Major Depressive Episode, RCT – Randomized controlled trial, TRD – Treatment Resistant Depression, TRS – Treatment Resistant Schizophrenia

Table A-2: ECT versus rTMS for TRD: Results from randomised controlled trials (part 1)

Author, year	Abdel Latif 2020 [78]	Kesthkar 2011 [69] IRCT138902253930N1	Eranti 2007 [62] ISRCTN67096930
Country	Egypt	Iran	UK
Sponsor	NR	Shiraz University of Medical Sciences	NCCHTA, Guy's and St Thomas's Charitable Foundation, National Alliance for Research on Schizophrenia and Depression
Intervention: Treatment frequency, duration; Product; Pulse width; Electrode placement; Add-on/monotherapy/augmentation;	Bilateral ECT applied biweekly (4 to 8 sessions in total) with MECTA Q5000 Spectrum device (MECTA Corporation), ultrabrief pulse (pulse width of 0.3). Add-on therapy (antidepressants were allowed, anticonvulsants and benzodiazepines were not allowed)	Bilateral ECT applied three times weekly for 3 weeks and 1 day (10 sessions in total) with a MECTA device (MECTA Corp) in 27 patients and with a Thymatron System IV (Somatics, LLC) in 13 patients. Brief-pulse, (pulse width 1.4 ms; duration 1.25 s; frequency 80 Hz). Anaesthesia and muscle relaxants: thiopental as an anesthetic, and succinylcholine as a muscle relaxant, both administered intravenously.	Unilateral (18% of patients) and bilateral (81.8%) ECT twice weekly with Thymatron DGx device (Somatics) and Mecta SR2 (Mecta Corp.) Anaesthesia and muscle relaxants: methohexitone (0.75-1.0 mg/kg), and suxamethonium (0.5-1.0 mg/kg) The number of ECT treatments depended on the patients' responses as determined by the referring physicians. Add-on therapy.
Comparator: Treatment frequency, duration, total no. of sessions; Product; Trains, train duration, intertrain interval; Stimulation frequency; Pulses per session, total no. of pulses; Stimulation intensity (RMT); Electrode placement; Add-on/monotherapy/augmentation	rTMS: 25 sessions over 5 weeks, 5 sessions/week (30 min/session) Magstim Rapid 2 (Magstim Corporation), figure-8 coil Frequency of 10 Hz in 5-second trains at 120% RMT. 10 trains/session, 2000 pulses/session (in total 50,000 pulses) with a 10-second intertrain interval. Add-on therapy (antidepressants were allowed, anticonvulsants and benzodiazepines were not allowed)	rTMS: 10 sessions over 2 weeks Neuro-MS (Neurosoft), figure 8 coil 408 pulses/session, 4,080 total pulses Stimulation intensity: 90% RMT Unilateral, left DLPFC Add-on therapy	rTMS: 15 sessions over 3 weeks Magstim Super Rapid Stimulator, figure 8 coil Frequency of 10 Hz in 5-second trains at 110% RMT for 20 trains with a 55-second intertrain interval. 1,000 pulses/session (in total 15,000 pulses) Unilateral, left DLPFC Add-on therapy
Study design	Assessor-blinded RCT	Unblinded RCT	Multicentre assessor blinded RCT
Number of pts, **I vs C**	40 20 vs 20	73 40 vs 33	46 22 vs 24
Inclusion criteria	Average intelligence, right-handed, 18 to 55 years of age, diagnosed with MDD, single or recurrent episode, without psychotic features, according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR); scoring ≥19 on the Hamilton Rating Scale for Depression (HAM-D); and having failed to respond to multiple medication trials or urgently needing improvement, referred to ECT.	MDD according to DSM-IV	Referral by a psychiatrist for ECT, MDD diagnosis by the DSM-IV Axis I Disorders (SCID), right-handedness, >18 yrs

Author, year	Abdel Latif 2020 [78]	Kesthkar 2011 [69] IRCT138902253930N1	Eranti 2007 [62] ISRCTN67096930
Exclusion criteria	Comorbid psychiatric disorder, acute unstable medical condition, intracranial medical device, cochlear implant or prior brain surgery, epilepsy, or first degree family history of epilepsy, substance abuse within the past year, history of a manic or hypomanic episode, and/or psychosis outside mood episodes (schizoaffective disorder, postschizophrenia depression).	Previous rTMS, implanted device, history of seizure, bipolar disorder, substance abuse, history of significant head trauma, severe medication condition, previous nonresponse to ECT, pregnancy.	Metallic implants or foreign bodies, history of seizures, substance misuse in the previous 6 mo, medically unfit for general anaesthesia or ECT, ECT or rTMS in the previous 6 mo, dementia, other axis I diagnosis, inability to provide consent.
Study outcomes	HAM-D, Cognitive functioning	Depression score, Suicide behaviour, Safety	HAM-D, remission (HAM-D ≤8) at the end of treatment, Beck Depression Inventory-II and Visual analogue mood scales scores, Brief Psychiatric Rating Scale (BPRS) score, self-reported and observer-rated cognitive changes
Diagnosis	MDD	MDD	MDD referred for ECT
Age of patients (yrs) mean±SD, I vs C	31.65±10.05 vs 34.8±8.02, p=0.2	35.6 (8.1) vs 34.0 (9.9)	68.3 (13.4) vs 63.6 (17.3)
Sex m/f, I vs C	10/10 vs 9/11	8/32 vs 13/20	6/16 vs 8/16
Previous therapy, I vs C	ECT: 6/20 vs 4/20 Psychotropic medication: 11/20 vs 9/20	≥ 2 trials of antidepressants	Number of antidepressant failed in the current episode 1.7 vs 1.7 SSRI: 6 vs 5 Tricyclics: 2 vs 2 Venlafaxine: 10 vs 7 Mirtazapine: 4 vs 5 Lithium: 5 vs 6 Benzodiazepines: 3 vs 4 Zopiclone: 6 vs 3 Anticonvasculsant mood stabilizers: 2 vs 3 L-Tryptophan: 1 vs 0
Current therapy, I vs C	NR	NR	SSRI: 5 vs 6, Tricyclics: 2 vs 2, Venlafaxine: 7 vs 10, Mirtazapine: 5 vs 4, Lithium: 6 vs 5, Anticonvulsant: 3 vs 2, Benzodiazepines: 4 vs 3, Antipsychotics: 7 vs 7, Zopiclone: 3 vs 6, L-Tryptophan: 0 vs 1
Follow-up (months)	7 weeks	NR	6

Author, year	Abdel Latif 2020 [78]	Kesthkar 2011 [69] IRCT138902253930N1	Eranti 2007 [62] ISRCTN67096930
Loss to follow-up (disontinuation/drop out before analysis, disontinuation/ drop out during any point of the follow-up period), n (%), I vs C	3 (15) vs 1 (5)	NR	6 (27) vs 3 (12)
Outcomes			
Effectiveness			
Mortality (suicide-related events), n (%), I vs C ■ **Overall mortality** ■ **Suicidal attempt** ■ **Suicidal ideation** ■ **Suicide score,** mean±SD	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ HAM-*D suicide subscore* At baseline: 1.70±0.66 vs 1.15±0.37 At FU: 0.29±0.47 vs 0.37±0.5	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ *BDI-suicide subscore* At baseline: 1.4±1.0 vs 1.5±0.8 At FU: 0.5±0.7 vs 1.2±0.9 ■ *HDRS suicide subscore* At baseline: 2.3±1.1 vs 1.9±1.3 At FU: 0.3±0.5 vs 1.4±1.2	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ *Suicide score* NR
Depression symptoms (HAM-D, BDI, HDRS), mean score±SD, I vs C	*HAM-D* At baseline: 41.40±2.35 vs 40.5±1.36 At FU: 19.88±4.4 vs 23.36±6.19	*BDI* At baseline: 34.8±9.9 vs 34.0±9.6 At FU: 17.9±8.3 vs 26.5±9.2 *HDRS* At baseline: 25.8±6.1 vs 21.0±7.5 At FU: 8.4±6.1 vs 15.1±5.6	*BDI* At baseline: 37.8±10.5 vs 36.0±8.7 At FU: NR *HAM-D* At baseline: 24.8±5.0 vs 23.9±7.0 3-week FU: 10.7 vs 18.5
General functioning (GAF), mean score±SD, I vs C	NR	NR	NR
Cognitive functioning, mean score±SD, I vs C	*Digit Span Test* At baseline: 8.82±1.29 vs 8.79±0.86, p=0.62 At FU: 8.24 ± 1.44 vs 9.53±0.77, **p=0.02** *Stroop Color-Word Test-Victoria version* At baseline: Dots 22.8±5.71 vs 21.75±7.65, p=0.39 Words 29.8±8.03 vs 29±7.9, p=0.77 Colors 43.05±11.9 vs 39.15±10.3, P=0.25	NR	NR

Author, year	Abdel Latif 2020 [78]	Kesthkar 2011 [69] IRCT138902253930N1	Eranti 2007 [62] ISRCTN67096930
Cognitive functioning, mean score±SD, I vs C *(continuation)*	At FU: Dots 23.41±5.51 vs 20.16±6.62, p=0.02 Words 32.18±7.99 vs 27±7.65, p=0.03 Colors 47.88±12.75 vs 38.37±9.79, **p=0.01** *Color Trails Test* At baseline: Trial 1: 92.2±25.42 vs 79.6±31.55, p=0.2 Trial 2: 139.45±30.7 vs 116.4±43.56, **p=0.03** At FU: Trial 1: 98.06±30.64 vs 74.32±32.42, **p=0.009** Trial 2: 155.76±33.27 vs 110±41.50, **p=0.001** *Rey-Osterrieth Complex Figure Test* At baseline: Copy: 35.3±1.7 vs 35±1.14, p=0.6 Delay: 20.65±5.54 vs 19.05±3.68, p=0.47 At FU: Copy: 36±0 vs 36±0, p=1 Delay: 21.29±3.7 vs 23.37±3.76, p=0.09		
Quality of life, I vs C	NR	NR	NR
Satisfaction and acceptability of treatment (drop-outs from the study), n (%), I vs C	NR	Drop-outs: 10 (25) vs 5 (14) (due to AEs: 2 vs 2, Withdrew: 8 vs 3)	6 (13) pts discontinued
Response, n (%), I vs C	NR	NR	13 (59) vs 4 (17)
Remission/relapse, n (%), I vs C	NR	NR	13 (59) vs 4 (17) 6 mo FU: 6/12 (50) vs 2/4 (50)
Safety			
Overall complications, n (%), I vs C	NR	NR	*Columbia ECT SSES* At baseline: 14.2 vs 13.2 At FU: 6.7 vs 9.7
Major AE, n (%), I vs C	NR	Seizure or induced manic episodes: 0 vs 0	NR
Minor AE, n (%), I vs C	NR	Headache: 0 vs 1 (3)	NR

Abbreviations: AE – adverse event, BDI – Beck Depression Inventory, BPRS – Brief Psychiatric Rating Scale, C – comparator, DLPFC – dorsolateral prefrontal cortex, DSM-IV-TR – Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text revision, ECT electroconvulsive therapy, f – female, FU – follow-up, GAF – Global Assessment of Functioning, HAM-D – Hamilton Depression Rating Scale, HDRS – Hamilton Depression Rating Scale, Hz – Hertz, m – male, MDD – major depressive disorder, I – intervention, min – minute, n – number, NARSAD – National Alliance for Research on Schizophrenia and Depression, NCCHTA – National Coordinating Centre for Health Technology Assessment, NR – not reported, pts – patients, QoL – Quality of life, RCT – randomized controlled trial, RMT resting motor threshold, rTMS – repetitive transcranial magnetic stimulation, SCID – Structured Clinical Interview for DSM-IV, SD – standard deviation, SSES – Suicide Severity Rating Scale, SSRIs – selective serotonin re-uptake inhibitors, TRD – treatment-resistant depression, UK – United Kingdom, vs – versus, yrs – years.

Table A-2: ECT versus rTMS for TRD: Results from randomised controlled trials (part 2)

Author, year	Rosa 2006 [63]	Grunhaus 2003 [68]	Grunhaus 2000, Dannon 2002 [64]	Pridmore 2000 [70]
Country	Brazil	Israel	Israel	Australia
Sponsor	NR	NARSAD	NARSAD	NR
Intervention: Treatment frequency, duration; Product; Pulse width; Electrode placement; Add-on/monotherapy/augmentation	ECT with MECTA, SpECTrum 5000Q1 British model (MECTA Corporation), brief pulse. Treatment begun with right unilateral ECT. If there was no antidepressant response after 2 wk, bilateral ECT was performed. Anaesthesia and muscle relaxants: 100% oxygen, etomidate (1.0-1.5 mg/kg i.v.) and succinylcholine (0.5-1.25 mg/kg i.v.) and atropine (0.4-1.0 mg i.v.). Monotherapy	ECT twice weekly with MECTA SR-1 device, brief-pulse. Initially right unilateral in all patients, and patients could be switched to bilateral electrode placement if improvement was not observed by the 6th treatment. Anaesthesia and muscle relaxants: 100% oxygenation, methohexital (1 mg/kg) and succinylcholine (1 mg/kg). Add-on therapy: psychotropic medications were continued during the course of ECT.	ECT twice weekly with MECTA SR-1 device, brief-pulse. Anaesthesia and muscle relaxants: methohexital 0.75-1 mg/kg, and succinylcholine 0.5-1 mg/kg. Monotherapy	Unilateral ECT applied 3 days/week with Thymatron DGx and Thymapad electrodes (Somantics Inc.). Stimulus width at 0.5 ms. Anaesthesia and muscle relaxants: pre-oxygenation, intravenously 1-1.5 mg/kg methohexitone and suxamethonium. Add-on therapy: Patients were allowed to remain on their medication but no new medication was allowed and it was stopped when possible.
Comparator: Treatment frequency, duration, total no. of sessions; Product; Trains, train duration, intertrain interval; Stimulation frequency; Pulses per session, total no. of pulses, Stimulation intensity (RMT); Electrode placement; Add-on/monotherapy/augmentation	rTMS: 20 sessions over 4 weeks Magpro, figure 8 coil Frequency of 10 Hz in 10-second trains at 100% RMT for 25 trains with a 20-second intertrain interval. 2,500 pulses/session (in total 50,000 pulses) Unilateral, left DLPFC Monotherapy	rTMS: 20 sessions over 4 weeks Magstim, figure 8 coil Frequency of 10 Hz in 6-second trains at 90% RMT for 20 trains with a 30-second intertrain interval. 1,200 pulses/session (in total 24,000 pulses) Unilateral, left DLPFC Monotherapy (only lorazepam allowed)	rTMS: 20 sessions over 4 weeks Magstim, figure 8 coil Frequency of 10 Hz in 6-second trains at 90% RMT for 20 trains with a 30-second intertrain interval. 1,200 pulses/session (in total 24,000 pulses) Unilateral, left DLPFC Monotherapy (only clonazepam allowed)	rTMS: Mean no. of sessions: 12.2 Magstim, figure 8 coil Frequency of 20 Hz in 2-second trains at 100% RMT for 30-35 trains with a 28-second intertrain interval. Unilateral, left DLPFC Monotherapy
Study design	Assessor-blinded RCT	Unblinded RCT	Unblinded RCT	Assessor-blinded RCT
Number of pts, **I vs C**	35 15 vs 20	40 20 vs 20	40 20 vs 20	32 16 vs 16
Inclusion criteria	Referral by a psychiatrist for ECT, aged 18-65 yrs, unipolar MDD according to DSM-IV without psychotic symptoms, HAMD-17 ≥22	Diagnosis of unipolar major depression by DSM-IV, score of at least 18 on Hamilton Depression Rating Scale, 18 years or older, treatment resistant.	> 18 yrs, DSM-IV diagnosis of MDD, ≥ 18 scored on HRSD-17	TRD, DSM-IV diagnosis of MDD, right-handed, age 25-70, no history of epilepsy.
Exclusion criteria	History of epilepsy, past neurosurgery with metal clips, other neurological or psychiatric diseases, cardiac pacemakers, pregnancy.	Additional Axis I diagnoses, major depression with psychosis, major depression due to medical condition or substance abuse.	Additional Axis I diagnoses, history of seizures, no medical, neurological or neurosurgical disorder that would preclude the administration of rTMS or ECT.	Serious medical illness, intracranial metal objects, mood disorder due to medical condition or substance abuse, co-morbidity for mental disorder.

Author, year	Rosa 2006 [63]	Grunhaus 2003 [68]	Grunhaus 2000, Dannon 2002 [64]	Pridmore 2000 [70]
Study outcomes	Depressive symptom changes (HDRS), Visual Analogue Scale Clinical Global Impression, Response rate, Remission rate	Response rate defined as a decrease of at least 50% in HRSD score	HDRS General functioning (GAF)	HDRS, BDI, Remission, Visual Analogue ratings of mood
Diagnosis	Unipolar non-psychotic depression refractoriness referred to ECT	MDD referred for ECT	MDD referred for ECT due to nonresponse to antidepressant treatment and/or the diagnosis of psychotic MDD	Major depressive episode (MDE) and failed to respond to at least one course of medication.
Age of patients (yrs) mean±SD, I vs C	46.0 (10.6) vs 41.8 (10.2)	61.4 (16.6) vs 57.6 (13.7)	63.6 (15.0) vs 58.4 (15.7)	41.5 (12.9) vs 44.0 (11.9)
Sex m/f, I vs C	8/7 vs 8/12	5/15 vs 6/14	6/14 vs 8/12	3/13 vs 4/12
Previous therapy, I vs C	≥ 2 trials of antidepressants	≥ 1 course of antidepressant (adequate level for ≥ 4 w)	Previous ECT: 9 vs 6	Previous ECT: 3 vs 6
Current therapy, I vs C	The use of antidepressants, antipsychotics and mood stabilizers was not allowed during the treatment period. Benzodiazepines were used if necessary to treat anxiety and/or insomnia, and its use was computed as a covariable.	ECT: neuroleptics alone (4 patients), neuroleptics + antidepressants (6 patients), antidepressants alone (5 patients), neuroleptics + anticonvulsants (1 patient), 4 patients did not receive any additional medications.	SSRIs: 10 vs 11, Venlafaxine: 3 vs 7, Mirtazapine: 4 vs 2 Phenelzine: 2 vs 1, Antipsychotics + antidepressants: 6 vs 0 Valproic acid + antidepressants: 2 vs 2	Concurrent medication: 13 vs 12
Follow-up (months)	NR	NR	6	NR
Loss to follow-up (disontinuation/drop out before analysis, disontinuation/ drop out during any point of the follow-up period), n (%), I vs C	NR	NR	2 (4.6)	NR
Outcomes				
Effectiveness				
Mortality (suicide-related events), n (%), I vs C ■ **Overall mortality** ■ **Suicidal attempt** ■ **Suicidal ideation** ■ **Suicide score,** mean±SD	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ *Suicide score* NR	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ *Suicide score* NR	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ *Suicide score* NR	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ *Suicide score* NR

Author, year	Rosa 2006 [63]	Grunhaus 2003 [68]	Grunhaus 2000, Dannon 2002 [64]	Pridmore 2000 [70]
Depression symptoms (HAM-D, BDI, HDRS), mean score±SD, I vs C	*HDRS* At baseline: 32.1±5.0 vs 30.1±4.7 At FU: NR	*HDRS* At baseline: 25.5±5.9 vs 24.4±3.9 At FU: 13.2±6.6 vs 13.3±9.2	*HDRS* At baseline: 28.4±9.3 vs 25.8±6.1 At FU: 11.2±8.4 vs 15.4±7.5	*HDRS* Baseline: 25.8±3.6 vs 25.3±4.1 At FU: 8.3±7.5 vs 11.3±8.5 *BDI* At baseline: 31.8±6.6 vs 33.9±6.8 At FU: 9.6±8.9 vs 19.2±11.8
General functioning (GAF), mean score±SD, I vs C	NR	NR	At baseline: NR At 6-month FU: 72.8±12 vs 77.8±17.1	NR
Cognitive functioning, mean score±SD, I vs C	NR	NR	NR	NR
Quality of life, I vs C	NR	NR	NR	NR
Satisfaction and acceptability of treatment (drop-outs from the study), n (%), I vs C	5 (33) vs 2 (10) (due to 1 hypomania and 1 dissociative state in rTMS, 3 suspensions of the ECT treatment and 2 non-attendance in ECT)	NR	0 drop-outs	NR
Response, n (%), I vs C	6 (40) vs 10 (50)	12 (60) vs 11 (55)	4 week FU: 16 (80) vs 9 (45) 6 mo FU: 12 (4 vs 4 relapsed) vs 5	NR
Remission/relapse, n (%), I vs C	3 (20) vs 2 (10)	6 (30) vs 6 (30)	NR	11 (69) vs 11 (69)
Safety				
Overall complications, n (%), I vs C	NR	NR	NR	Side-effects rating scores at baseline: 7.9 (1.9) vs 8.1 (3.2) End of treatment: 5.3 (4.3) vs 3.9 (2.9)
Major AE, n (%), I vs C	NR	NR	Seizure: 0 vs 0	NR
Minor AE, n (%), I vs C	NR	Headache: 0 vs 3 (15) Device-related insomnia: 0 vs 2 (10)	Headache: 0 vs 5 (25)	NR

***Abbreviations**: AE – adverse event, BDI – Beck Depression Inventory, BPRS – Brief Psychiatric Rating Scale, C – comparator, DLPFC – dorsolateral prefrontal cortex, DSM-IV-TR – Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text revision, ECT electroconvulsive therapy, f – female, FU – follow-up, GAF – Global Assessment of Functioning, HAM-D – Hamilton Depression Rating Scale, HDRS – Hamilton Depression Rating Scale, Hz – Hertz, m – male, MDD – major depressive disorder, I – intervention, min – minute, n – number, NARSAD – National Alliance for Research on Schizophrenia and Depression, NCCHTA – National Coordinating Centre for Health Technology Assessment, NR – not reported, pts – patients, QoL – Quality of life, RCT – randomized controlled trial, RMT resting motor threshold, rTMS – repetitive transcranial magnetic stimulation, SCID – Structured Clinical Interview for DSM-IV, SD – standard deviation, SSES – Suicide Severity Rating Scale, SSRIs – selective serotonin re-uptake inhibitors, TRD – treatment-resistant depression, UK – United Kingdom, vs – versus, yrs – years.*

Table A-3: ECT versus ketamine in TRD: Results from randomised controlled trials

Author, year	Anand 2023 [59] NCT03113968 (ELEKT-D study)	Ekstrand 2022 [61]	Ghasemi 2014 [60]	Kheirabadi 2019 [79] IRCT201104092266N2	Kheirabadi 2020 [80] IRCT20090801002266N8
Country	U.S.	Sweden	Iran	Iran	Iran
Sponsor	Cleveland Clinic Foundation	Swedish Research Council, Crafoord Foundation, Skåne Regional Council, Königska Foundation, Lions forsknings foundation Skåne, OM Perssons donation foundation	Tehran University of Medical Sciences	Isfahan University of Medical Sciences	Esfahan University of Medical Sciences
Intervention/Product (pulse width, electrode placement, anaesthesia, duration of treatment, monotherapy/add-on therapy/augmentation)	ECT for three times per week for 3 weeks, right unilateral ultrabrief pulse (during trial it was allowed to switch to bilateral ECT) Anaesthesia: NR Add-on therapy (patients were allowed to continue with their previously prescribed medications)	ECT for three times per week for up to 12 sessions in total, pulse width 0,25-1, right unilateral (96% of sessions) Anaesthesia and muscle relaxants according to clinical routines Add-on therapy (concomitant medications were unrestricted. Drug adjustments were allowed)	3 ECT sessions every 48 hours, bilateral ECT using Thymatrone DGx (Somatics Inc). Anaesthesia: 0.5 mg atropine followed by 2-3 mg/kg thiopental intravenously; plus succinylcholine (0.5mg/kg) muscle relaxant Concurrent treatments: NR	ECT twice a week up to the complete remission of depressive symptoms, bilateral ECT using Thymatron® DGx (Somatics Inc) with 20-100 joules of electric energy. Anesthesia and muscle relaxants: thiopental 3 mg/kg, intravenously, plus atropine 0.25 mg and succinylcholine 20 mg muscle relaxant Concurrent treatments: NR.	ECT 6 to 9 sessions for 3 weeks, bilateral ECT using DGX machine. Electrical stimulus was first set at 20 joules and then was titrated. Anesthesia and muscle relaxants: succinylcholine. Add-on therapy (patients were allowed to continmue with their previuosly prescribed medications uncless contraindicated with ketamine or ECT)
Comparator	Ketamine twice per week for 3 weeks administered intravenously. 0.5 mg/kg infused over 40 min Add-on therapy (patients were allowed to continue with their previously prescribed medications)	Ketamine for three times weekly up to 12 infusions administered intravenously at a fixed dose of 0.5 mg/kg over 40 minutes	3 infusions of ketamine hydrochloride 0.5mg/kg intravenously over 45min	Ketamine hydrochloride twice a week up to the complete remission of depressive symptoms, 0.5 mg/kg infused over 40 min through an IV pump or a microdrip set Concurrent treatments: NR	Intramuscular (IM) ketamine: 0.5 mg/kg of racemic ketamine (R-ketamine) administered 6 to 9 times over 3 weeks (with a 2- to 3-day interval) Oral R-ketamine: 1mg/kg every 2 to 3 day up to 6 to 9 sessions during 3 weeks.
Study design	Unblinded prospective randomized open-label noninferiority controlled trial	Open-label multicentre noninferiority RCT	Assessor-blinded RCT	Blinded RCT	Open-label RCT
Number of pts randomised (number of pts having received the allocated treatment), I vs C	403 203 vs 200	199 (91 vs 95)[79]	18 9 vs 9	32 16 vs 16 (15 vs 16)[80]	45 15 vs 15 vs 15

[79] 13 patients were excluded after randomization due to erroneous inclusion and withdrawal from study. Therefore 186 patients received the allocated treatment.

[80] 1 patient in the ECT group did not get the allocated intervention due to extended seizure.

Author, year	Anand 2023 [59] NCT03113968 (ELEKT-D study)	Ekstrand 2022 [61]	Ghasemi 2014 [60]	Kheirabadi 2019 [79] IRCT201104092266N2	Kheirabadi 2020 [80] IRCT20090801002266N8
Inclusion criteria	Inpatients or outpatients referred to and eligible for ECT M/f ≥ 21 yrs ≤ 75 yrs Meet Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for major depressive episode (clinician's diagnostic evaluation and MINI International Neuropsychiatric Interview) Current depressive episode that has lasted a min. of 4 weeks Meet all criteria on symptom rating scales at screening: 1. Montgomery Asberg Depression Rating Scale (MADRS) score >20; 2. Young Mania Rating Scale (YMRS) of ≤ 5; 3. Montreal Cognitive Assessment (MoCA) of ≥18 ≥2 adequate trials of antidepressants or augmentation strategies during lifetime (adequate trial: 4 weeks of medication at the min. FDA approved dose. This equals to a trial rating of ≥3). Patient is willing and able to comply with scheduled visits.	Hospitalised patients, aged 18-85 years, diagnosed with unipolar depression according to the DSM-IV with a score of ≥20 on the MADRS, scheduled for ECT, proficient in Swedish and with an American Society of Anaesthesiologists physical status classification (ASA) 1-3	Patients aged 18-75 years experiencing a major depressive episode and scheduled to receive ECT and able to provide voluntary consent Diagnosis of major depressive disorder (MDD), currently in a major depressive episode, according to DSM-IV	19-59 years old, having no history of psychosis Having no drug abuse in the past 3 months Not pregnant or breastfeeding No serious physical conditions including liver, kidney, digestive, respiratory, cardiovascular, endocrine, neurologic, or hematologic diseases (based on medical counselling and paraclinical assessments) Not having untreated hypothyroidism	Informed consent Meet diagnostic criteria for major depression based on DSM V and candidate for ECT and also had one of the symptoms of suicidal ideation, treatment resistance, severe symptoms, and agitation Age between 18-70 years old
Exclusion criteria	Meet DSM-5 criteria for bipolar disorder, schizophrenia, schizophreniform disorder, schizoaffective disorder, mental retardation, or pervasive developmental disorder Meets any exclusion criteria for ECT or ketamine treatment as described in the clinical guidelines or according to investigator judgment Pregnancy or breast feeding Severe medical illness or severe neurological disorder Known ketamine allergy or taking a medication that may interact with ketamine Diagnosis of major depressive disorder with psychotic features during the current depressive episode Unable to give informed consent Was previously enrolled/randomized into the trial	Co-morbid conditions that could interfere with the treatment (e.g. primary psychosis) Habitual difficulties to speak, hear, remember or reason Treatment according to Compulsory Psychiatric Care Act Ongoing or recent (6 months) drug abuse Known allergy to the active substance Pregnant or breastfeeding Known cardiovascular disease (angina, acute/chronic congestive heart failure, moderly hypertension or tachyarrhythmia) Pathological conditions in central nervous system with risk of increased intracranial pressure Glaucoma Porphyria or thyroid disorder Ongoing severe infection	Lifetime diagnosis of primary psychotic disorder, manic or hypomanic episode, mental retardation, dementia, or mood disorder due to general medical condition Substance dependence or serious medical conditions	Having delirium following ketamine injection Unwillingness to continue participating in the study	Patients with a history of severe hepatic, cardiac, renal, or urologic diseases and those with a previous psychotic, manic, or hypomanic episode, substance abuse, and depression due to medical condition

Author, year	Anand 2023 [59] NCT03113968 (ELEKT-D study)	Ekstrand 2022 [61]	Ghasemi 2014 [60]	Kheirabadi 2019 [79] IRCT201104092266N2	Kheirabadi 2020 [80] IRCT20090801002266N8
Study outcomes	Response defined as a decrease from baseline of ≥ 50% in the 16-item Quick Inventory of Depressive Symptomatology-Self-Report Scale (QIDS-SR-16) score at last study visit Response defined as a decrease from baseline of ≥ 50% in the MADRS Remission according to the QIDS-SR-16 and MADRS Response and remission according to the Clinical Global Impression-Improvement (CGI-I) and Patient Global Impression-Improvement (PGI-I) Change in scores from baseline to end-of-treatment visit on the QIDS-SR16 and the MADRS; on Global Self-Evaluation of Memory (GSE-My), Squire Memory Complaint Questionnaire (SMCQ), Hopkins Verbal Learning Test-Revised (HVLT-R), QoL scale, and Clinician-Administered Dissociative States Scale (CADSS) Adverse events	Remission defined as a MADRS score ≤10 persisting over at least 2 subsequent treatment sessions or a min. of 5 days Response rate defined as a decrease of MADRS scores by ≥50% following a complete treatment series (range from 1 to 12 treatment sessions) Changes in MADRS Total number of sessions and number of sessions to remission Relapse defined as when a patient was considered to meet the criteria for depression Adverse events rated as very likely or probable to have causality to the received treatment	Depressive symptoms (Beck Depression Inventory/BDI, Hamilton Depression Rating Scale/HDRS) Response rate defined as patients with >50% reduction in depressive symptoms compared to baseline.	Changes in depression severity (HDRS) Changes in memory function (Wechsler Memory Scale/WMS) ECT or Ketamine complications	HDRS-17 at baseline, 24 hours, 1 week, 2 weeks, and 3 weeks within the intervention. Beck Scale for Suicidal Ideation (BSSI) at baseline, 24 hours, 1 week, 2 weeks, and 3 weeks within the intervention. Vital signs and adverse effects Satisfaction levels of patients for each method were recorded using Likert questionnaire
Age of patients (yrs) mean±SD (range), I vs C	47.1±14.1 vs 45.6±14.8	50±18 (20-85) vs 55±18 (18-84)	40±16.41 vs 35.22±13.63, p=0.51	36.4 ± 14.1 vs 41.7 ± 12.9, p>0.05	ECT: 41.6±15.44 IM Ketamine: 41.6±8.43 Oral Ketamine: 39.13±9.84 p=0.8
Sex m/f (n), I vs C	103/100 vs 94/106	33/58 vs 34/61	4/5 vs 4/5	33/66% vs 40/60%	ECT: 5/10 IM Ketamine: 6/9 Oral Ketamine: 8/7
Disease duration, I vs C	Mean age at onset of first episode of MD (yrs): 19.4±11.0 vs 19.7±11.5 Median no. of previous episodes of MD (IQR): 5 (2-18) vs 5 (2-16) Median duration of current episode of MD (months) (IQR): 24 (10-72) vs 24 (12-75)	Median duration (IQR) of current episode (weeks): 14 (8-14) vs 14 (8-28) Median no. (IQR) of previous episodes: 3 (1-6.5) vs 3 (1-7.5)	Mean age at onset of first episode (yrs): 30.78±17.51 vs 28.11±9.67, p=0.69 Mean length of current episode before admission (weeks): 9.22± 10.97 vs 8.77±8.91, p=0.92	NR	NR
Diagnosis, n (%), I vs C	*MDD with* Anxious features: 110 (54.2) vs 111 (55.5) Atypical features: 9 (4.4) vs 9 (4.5) Melancholic features: 31 (15.3) vs 28 (14.0) Coexisting condition (most common, diagnosed in >20%): Generalised anxiety: 113 (55.7) vs 113 (56.5)	*MDD* Single episode, moderate: 6 (7) vs 2 (2) Single episode, severe without psychotic features: 25 (27) vs 26 (27) Single episode, severe with psychotic features: 6 (7) vs 11 (12) Single episode, unspecified: 1 (1) vs 4 (4)	*MDD with* Anxiety disorder (OCD,GAD): 2 (22.2) vs 3 (33.3), p=0.59 Addiction: 1 (11.1) vs 0 (0), p=0.3 Bipolar disorder: 1 (11.1) vs 0 (0), p=0.3	*MDD* without psychotic features based on DSM IV-TR referred to ECT by a psychiatrist	*MDD* with one of the symptoms of suicidal ideation, treatment resistance, severe symptoms, and agitation. ECT vs IM ketamine vs Oral ketamine, P value

Author, year	Anand 2023 [59] NCT03113968 (ELEKT-D study)	Ekstrand 2022 [61]	Ghasemi 2014 [60]	Kheirabadi 2019 [79] IRCT201104092266N2	Kheirabadi 2020 [80] IRCT20090801002266N8
Diagnosis, n (%), I vs C *(continuation)*	Panic disorder: 42 (20.7) vs 33 (16.5) Post-traumatic stress: 50 (24.6) vs 38 (19.0) Social phobia: 57 (28.1) vs 56 (28.0) *Severity:* CGI-S: 5.2±0.6 vs 5.0±0.6 MADRS: 32.6±6.0 vs 32.3±6.2 QIDS-SR-16: 18.2±4.2 vs 17.9±4.1 Attempted suicide: 84 (41.4) vs 73 (36.5)	Recurrent, moderate: 13 (14) vs 13 (14) Recurrent, severe, without psychotic features: 31 (34) vs 31 (33) Recurrent, severe, with psychotic features: 8 (9) vs 7 (7) Recurrent, unspecified: 0 vs 1 (1) Mixed anxiety-depressive disorder: 1 (1) vs 0 Psychotic symptoms: 14 (15) vs 18 (19) Additional psychiatric diagnosis: 28 (31) vs 31 (33) Attempted suicide: 46 (51) vs 38 (40)	Personality disorder: 3 (33.3) vs 1 (11.1), p=0.57 Number of attempted suicide (mean, SD): 1.33±1.66 vs 0.77±1.48, p=0.46 BDI score (mean, SD): 42.44±9.53 vs 34.66±10.7, p=0.12 HDRS score (mean, SD): 35.88±6.47 vs 30.22±5.78, p=0.07		Personality disorders: 3 (20) vs 2 (13.3) vs 3 (23.1) P=0.792 Obsessive Compulsive Disorder: 1 (6.7) vs 1 (6.7) vs 2 (15.4) P=0.665 Anxiety Disorder: 4 (26.7) vs 5 (33.3) vs 5 (38.5) P=0.799
Previous therapies, n (%), I vs C	*ECT*: 21 (10.3) vs 23 (11.5) *Ketamine*: 8 (3.9) vs 14 (7.0)	*ECT:* 34 (37) vs 40 (42) *Psychotherapy:* 61 (69) vs 51 (55)	*Lithium*: 0 vs 1 (11.1) *Antidepressants*: SSRI: 5 (55.5) vs 4 (44.4) TCA: 2 (22.2) vs 1 (11.1) *Antipsychotics*: 2 (22.2) vs 1 (11.1) *Anticonvulsants*: 1 (11.1) vs 1 (11.1) *Benzodiazepines*: 5 (55.5) vs 2 (22.2)	NR	NR
Current therapy (at time of enrollment) n (%), I vs C	*Use of psychiatric medication:* Anticonvulsants: 51 (25.1) vs 54 (27.0) Atypical antidepressants: 92 (45.3) vs 90 (45.0) Atypical antipsychotics: 58 (28.6) vs 59 (29.5) Augmentation medications: 40 (19.7) vs 31 (15.5) Benzodiazepines: 63 (31.0) vs 60 (30.0) Serotonin-reuptake inhibitors: 75 (36.9) vs 58 (29.0) Serotonin- or norepinephrine-reuptake inhibitors: 70 (34.5) vs 67 (33.5) Tricyclic antidepressants: 10 (4.9) vs 13 (6.5)	*Mood stabilisers*: 15 (16) vs 9 (9) *Antidepressants*: 77 (85) vs 75 (79) *Anxiolytics*: 63 (69) vs 58 (61) *Antipsychotics*: 20 (24) vs 18 (19) *Central stimulants*: 1 (1) vs 1 (1) *Hypnotics*: 68 (75) vs 61 (64) *None*: 5 (6) vs 6 (6)	*Lithium*: 0 vs 1 (11.1) *Antidepressants*: SSRI: 7 (77.8) vs 5 (55.5) TCA: 4 (44.4) vs 2 (22.2) Trazodone: 1 (11.1) vs 2 (22.22) *Antipsychotics*: Olanzapine: 2 (22.2) vs 1 (11.1) Risperidone: 2 (22.2) vs 0 *Anticonvulsants*: Lamotrigine: 1 (11.1) vs 0 Valproate: 1 (11.1) vs 0 Carbamazepine: 1 (11.1) vs 1 (11.1) *Benzodiazepines*: 4 (44.4) vs 7 (77.8)	NR	ECT vs IM ketamine vs Oral ketamine *Serotonin Selective Reuptake Inhibitors (SSRIs):* 9 (60) vs 9 (60) vs 9 (64) *Serotonin norepinephrine reuptake inhibitors (SNRIs):* 1 (6.7) vs 6 (40) vs 2 (14.3) *Antipsychotics:* 8 (53.3) vs 8 (53.3) vs 7 (50)
Follow-up (months)	6	12	1 week	3	1
Loss to follow-up (discontinuation/drop-out before analysis, discontinuation/drop-out during any point of the follow-up period), n (%)	Drop-out (not having post-treatment scores) ECT: 2 Ketamine: 1	*Before 2 weeks:* ECT: 4 (4) (2 SAE, 1 AE, 1 non-compliance) Ketamine: 21 (22) (2 SAE, 10 AE, 8 drop-out, 1 non-compliance) *After 2 weeks:* ECT: 10; Ketamine: 15 *At 12 months:* ECT: 35; Ketamine: 51	0	ECT: 3 (19) Ketamine: 6 (37.5)	ECT: 3 (20) IM ketamine: 0 (0) Oral ketamine 3 (20)

Author, year	Anand 2023 [59] NCT03113968 (ELEKT-D study)	Ekstrand 2022 [61]	Ghasemi 2014 [60]	Kheirabadi 2019 [79] IRCT201104092266N2	Kheirabadi 2020 [80] IRCT20090801002266N8
Outcomes					
Effectiveness					
Mortality (suicide-related events), n (%) I vs C ■ **Overall mortality** ■ **Suicidal attempt** ■ **Suicidal ideation** ■ **Suicide score (BSSI, CSSRS)**	■ *Overall mortality* NR ■ *Suicidal attempt* After initial treatment phase: 0/170 vs 0/195 At 6-month FU: 0/70 vs 1/108 (0.9) ■ *Suicidal ideation* After initial treatment phase: 2/170 (1.2) vs 4/195 (2.1) At 6-month FU: 1/70 (1.4) vs 4/108 (3.7) ■ *Suicide score (CSSRS):* *At baseline:* 1.8 ± 0.1 vs 1.7 ± 0.1 *End of treatment:* 0.2 ± 0.1 vs 0.1 ± 0.1 *Month 1:* 0.6 ± 0.1 vs 0.6 ± 0.1 *Month 3:* 0.8 ± 0.1 vs 0.6 ± 0.1 *Month 6:* 0.8 ± 0.1 vs 0.6 ± 0.1	■ *Overall mortality (suicide)* 1/90 (1) vs 0/91 ■ *Suicidal attempt* 6/90 (7) vs 4/91 (4) ■ *Suicidal ideation* NR ■ *Suicide score* NR	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ *Suicide score* NR	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ *Suicide score* NR	■ *Overall mortality* NR ■ *Suicidal attempt* NR ■ *Suicidal ideation* NR ■ *Suicide score* Mean BSSI± SD ECT vs IM ketamine vs oral ketamine At baseline: 10.75±5.61 vs 8.1±5.61 vs 8±4.19, p=0.38 24 hours within the intervention: 5.66±3.98 vs 3±3.25 vs 2.7±1.35, **p=0.045** 1 week within the intervention: 4.33±3.65 vs 2±2.6 vs 2.16±1.33, p=0.065 2 weeks within the intervention: 3.91±3.47 vs 1.53±2.09 vs 1.66±1.37, **p=0.033** 3 weeks within the intervention: 3.75±4.6 vs 1.33±2.16 vs 1.25±1.13, p=0.069 After 1 week: 1.75±2.63 vs 1.86±2.64 vs 1.83±1.7, p=0.992 After 1 month: 4.25±4.45 vs 3.13±2.55 vs 3.75±2.9, p=0.688
General functioning (GAF, SDS), I vs C	NR	NR	NR	NR	NR
Cognitive functioning (MoCA, MMSE, TMT, RAVLT, ScoRS, WMS, HVLT-R T, SMCQ, GSE-My), mean score ± SD, I vs C	*GSE-My score at end of treatment visit* 3.2±0.1 vs 4.2±0.1 Difference (95% CI): -1.1 (-1.2 to -0.9) *SMCQ score at end of treatment visit* -8.8±1.5 vs 0.2±1.4 Difference (95% CI): -9.0 (-13.0 to -5.1) *Change from baseline in HVLT-R T total score* -2.1±0.8 vs 3.2±0.8 Difference (95% CI): -5.3 (-7.4 to -3.1)	NR	NR	*WMS* At baseline: 50.3±8.8 vs 42.9±8.2, p=0.8 At 1 week: 47±8.9 vs 50.4±.4, p=0.5 At 1 month: 47.8±9.5 vs 49.8±9.9, p=0.3	NR

Author, year	Anand 2023 [59] NCT03113968 (ELEKT-D study)	Ekstrand 2022 [61]	Ghasemi 2014 [60]	Kheirabadi 2019 [79] IRCT201104092266N2	Kheirabadi 2020 [80] IRCT20090801002266N8
Quality of life, mean score ± SD, I vs C	*Change from baseline in the 16-item QoL scale score* 12.9±1.1 vs 12.3±1.0 Difference (95% CI): 0.6 (-2.1 to 3.4)	NR	NR	NR	NR
Satisfaction and acceptability of treatment, mean score ± SD, I vs C	NR	*Hope of improvement (VAS score)* 6.3±2.7 vs 5.8±3.1, p=0.32 *Fear of negative outcomes (VAS score)* 4.2±3.0 vs 4.6±2.9, p=0.37	NR	NR	ECT vs IM ketamine vs oral ketamine Agreement: 3.33±0.65 vs 3.66±0.81 vs 3.9±0.86, p=0.24 Preference: 2.91±0.8 vs 3.6±0.5 vs 3.53±0.87, p=0.057 Motivation: 2.33±0.65 vs 2.86±0.83 vs 2.84±9, p=0.136 Satisfaction: 3.45±0.86 vs 3.8±0.67 vs 3.61±1.04, p=0.94
Remission/relapse, n (%), I vs C	*QIDS-SR-16-based remission* 34/170 (20.0) vs 63/195 (32.3) Difference (95% CI): -12.3 (-21.2 to -3.4) *MADRS-based remission* 37/170 (21.8) vs 74/195 (37.9) Difference (95% CI): -16.2 (-25.4 to -7.0)	*Relapse:* 36/56 (64) vs 31/44 (70), p=0.44 HR 0.83 [0.51, 1.34] *Remission*: 57/91 (63) vs 44/95 (46), **p=0.026** *Mean no. of treatments to remission* 6.0±2.3 vs 6.0±2.7, p=0.84	NR	NR	NR
Response to treatment (incl. time to onset of response), %, I vs C	*QIDS-SR-16-based response* 41.2 vs 55.4 Difference (95% CI): -14.2 (-24.2 to -3.9) *MADRS-based response* 41.4 vs 50.8 Difference (95% CI): -9.3 (-19.4 to 0.9)	*MADRS-based responders* 62 (56 patients) vs 56 (53 patients)[81]	*HDRS-based response* 1st treatment: 11.1 vs 77.8 2nd: 22.2 vs 77.8 3rd: 66.7 vs 88.9 72h post-treatment: 88.9 vs 100 1-week post-treatment: 88.9 vs 100 *BDI-based response* 1st treatment: 11.1 vs 44.4 2nd: 11.1 vs 55.6 3rd: 44.4 vs 77.8 72h post-treatment: 44.4 vs 77.8 1-week post-treatment: 77.8 vs 77.8	NR	NR

[81] As reported in Menon et al. [99] Supplementary appendix. The original publication by Ekstrand et al. [61] reported 9 (8 patients) versus 11 (10 patients), however these do not correspond with the rest of the publication. Therefore, we accepted the data reported by Menon, who explained in their publication that they contacted Ekstrand et al. for clarification.

Author, year	Anand 2023 [59] NCT03113968 (ELEKT-D study)	Ekstrand 2022 [61]	Ghasemi 2014 [60]	Kheirabadi 2019 [79] IRCT201104092266N2	Kheirabadi 2020 [80] IRCT20090801002266N8
Depression score (HAM-D, HDRS, MADRS, BDI, PHQ-9), mean score ± SD, I vs C	NR	MADRS: At baseline: 34.5±5.7 vs 33.1±6.3, p=0.11 Final FU: 12.2±11.1 vs 16.9±13.1, **p=0.009** Change in scores from baseline to FU: 22.4±11.4 vs 16.1±12.0, **p<0.001**	BDI: At baseline: 42.4±9.5 vs 34.7±10.7, p=0.12 1 week FU: 15.7±7.5 vs 10.9±7.5, p=0.19 Standardised mean difference (95% CI): 0.61 (-0.34 to 1.56)[82] HDRS: At baseline: 35.9±6.5 vs 30.2±5.8, p=0.07 1 week FU: 14±4.9 vs 9.5±5, p=0.07	HDRS: At baseline: 26.1±3.8 vs 24.6±2.4, p=0.3 At 1 week: 13.6±3.1 vs 16.9±3.3, p=0.5 At 1 month: 12.9±2.6 vs 19.4±1.5, p=0.3 At 2 months: 12.5±2.9 vs 21.1±1.6, p=0.1 At 3 months: 13.9±2.9 vs 22.6±1.8, p=0.4	HDRS: ECT vs IM ketamine vs oral ketamine At baseline: 21.83±4.63 vs 21±2.9 vs 21±2.73, p=0.789 24h within the intervention: 16±3.71 vs 14±2.4 vs 13.7±2, p=0.106 1 week within the intervention: 14.6±3.3 vs 13.26±2.9 vs 14.1±2.36, p=0.449 2 weeks within the intervention: 14±3.07 vs 11.66±4.35 vs 13.25±2.26, p=0.208 3 weeks within the intervention: 13.25±3.8 vs 10±4.85 vs 12.16±2.72, p=0.109 After 1 week: 9.5±5.35 vs 10.86±5.11 vs 12.83±3.18, p=0.23 After 1 month: 13.83±3.58 vs 16.2±3.12 vs 15.75±3.19, p=0.17
Safety					
Overall complications, n (%), I vs C	*≥1 AE in the initial treatment phase* 55/170 (32.4) vs 49/195 (25.1) *≥ 1 AE in the follow-up period* 10/70 (14.3) vs 17/108 (15.7)	*Patients experiencing ≥1 AE* 85/90 (94) vs 85/91 (93) *No. of AEs per patient* 7.8±5.4 vs 12.0±10.9, p<.001	No significant change in hemodynamic parameters including heart rate and blood pressure in both groups. Increase in systolic blood pressure as well as heart rate: 3 patients in the ketamine group. Hemodynamic parameters were not significantly altered in the ECT group.	Nausea: 9 (75) vs 3 (30) Headache: 12 (100) vs 6 (60) Dizziness: 11 (91.7) vs 10 (100) Muscle pain: 11 (91.7) vs 0 Joint Pain: 6 (50) vs 0 Orienation disorder: 4 (33.3) vs 0 Blurry vision: 0 vs 6 (60) Vertigo:0 vs 4 (40) Diplopia: 0 vs 4 (40) Numbness of half body: 0 vs 6 (60) Depersonalization: 0 vs 6 (60)	ECT vs IM ketamine vs oral ketamine: Dissociative symptoms: 0 (0) vs 15 (100) vs 8 (66.7) Nystagmus: 0 (0) vs 1 (6.3) vs 1 (8.3) Headache: 3 (25) vs 1 (6.7) vs 0 (0) Nausea: 1 (8.3) vs 0 (0) vs 0 (0) Muskoskeletal pain: 1 (8.3) vs 0 (0) vs 0 (0) Memory deficit: 9 (75) vs 0 (0) vs 0 (0)

[82] From Menon et al. [99].

Author, year	Anand 2023 [59] NCT03113968 (ELEKT-D study)	Ekstrand 2022 [61]	Ghasemi 2014 [60]	Kheirabadi 2019 [79] IRCT201104092266N2	Kheirabadi 2020 [80] IRCT20090801002266N8
Major AE, n (%), I vs C	*≥1 SAE in initial treatment phase* 4/170 (2.4) vs 5/195 (2.6) *Follow-up period* 3/70 (4.3) vs 8/108 (7.4)	*Patients experiencing ≥1 SAE* 23/90 (26) vs 14/91 (15), p=0.09 Amnesia: 26 (29) vs 8 (9), **p<0.001**	NR	NR[83]	NR
Minor AE, n (%), I vs C	*Initial treatment phase* Gastrointestinal AE: 9 (5.3) vs 13 (6.7 Muscle pain or weakness: 9/170 (5.3) vs 1/195 (0.5) Headache: 12/170 (7.1) vs 16/195 (8.2) Severe or prolonged hypertension: 4/170 (2.4) vs 6/195 (3.1)	*Most frequent AEs (>20% frequency in any study arm)* Euphoria: 0 vs 19 (21), **p<0.001** Dissociative symptoms: 14 (16) vs 55 (60), p<0.001 Anxiety: 16 (18) vs 41 (45), **p<0.001** Fatigue: 19 (21) vs 20 (22) Confusion: 22 (24) vs 23 (25) Vertigo: 22 (24) vs 63 (69), **p<0.001** Headache: 72 (80) vs 20 (22), **p<0.001** Blurred vision: 0 vs 18 (20), **p<.001** Diplopia: 2 (2) vs 28 (31), **p<0.001** Nausea: 23 (26) vs 25 (27) Dry mouth: 1 (1) vs 22 (24), **p<0.001** Muscle pain: 48 (53) vs 13 (14), **p<0.001**	NR	NR	NR
Procedure-related mortality, n (%), I vs C	0 vs 0	NR	NR	NR	NR

Abbreviations: AE – adverse event, BDI – Beck Depression Inventory, BSSI – Beck Scale for Suicidal Ideation, C – comparator, CADSS – Clinician-Administered Dissociative States Scale, CGI-I – Clinical Global Impression-Improvement, CGI-S – Clinical Global Impression–Severity, DSM – Diagnostic and Statistical Manual of Mental Disorders, ECT – Electroconvulsive therapy, F – female, FDA – Food and Drug Administration, GAF – Global Assessment of Functioning, GSE-My – Global Self Evaluation of Memory, HAMD-D – Hamilton Depression Rating Scale, HDRS – Hamilton Depression Rating Scale, HVLT-R – Hopkins Verbal Learning Test Revised, I – intervention, IM – intramuscular, IQR – interquartile range, , IV – intravenous, LPT – Lagen om psykiatrisk tvångsvård; Compulsory Psychiatric Care Ac, M – male, MADRS – Montgomery Asberg Depression Rating Scale, MD – major depression, MDD – major depressive disorder, MSSE – Mini-Mental State Examination, MoCA – Montreal Cognitive Assessment, n – number, NR – not reported, PGII – Patient Global Impression- Improvement, PHQ – Patient Health Questionnaire, pts -patients QIDS-SR – Quick Inventory of Depressive Symptomatology-Self report scale, Qol – quality of life, RAVLT – Rey Auditor Verbal Learning Test, RCT – randomized controlled trial, ScoRS – Schizophrenia Cognitive Rating Scale, SD – standard deviation, SDS – Sheehan Disability Scale, SMCQ – Squire Memory Complaint Questionnaire, SNRIs – Serotonin Norepinephrine Reuptake Inhibitors, SSRIs – Serotonin Selective Reuptake Inhibitors, TMT – Trail Making Test, TRD – treatment resistant depression, U.S – United States, v- versus, WMS – Wechsler Memory Scale, YMRS – Young Mania Rating Scale, yrs – years

[83] It is reported in the results section of the publication that "One case of extended seizure occurred in the ECT group". However, this adverse event was not reported in Table 2 "The comparison of the mean frequencies of side effects reported during the intervention in 22 patients with depression treated with ECT and intravenous ketamine", nor was it categorized in any other way. Furthermore, Figure 1 "Flow diagram of selection, allocation, and follow‑up of studied patients with depression treated with ECT and intravenous ketamine" shows a randomised participant not having received the ECT treatment due to extended seizure.

Table A-4: ECT vs sham-ECT, ECT vs clozapine for TRS: Results from randomised controlled trials

Author, year	Melzer-Riberio 2017 [73]	Melzer-Riberio 2020 [96]	Mishra 2022 [74]	Petrides 2019 [75]
Country	Brazil		India	USA
Sponsor/Funding	This study was not funded by any research grant, nor sponsored by any pharmaceutical company.	Elkis H: between 2018 and 2019 received research grants from Sao Paulo Research Support Foundation (FAPESP) and honoraria for participation as a member of advisory boards speaker or travel support pharmaceutical companies: Aché, Cristália, Daiichi-Sankyo, Janssen and Mantecorp-Hypera.	Intramural research grant: India vide grant from All India Institute of Medical Sciences (number: IMF/01/2018)	NR
Intervention/Product (pulse width, electrode placement, duration of treatment, monotherapy or add-on or augmentation)	ECT: 3 times per week, total of 12 sessions Product: MECTA SpECTrum 5000Q or a MECTA SpECTrum 4000Q Electrode placement: bitemporal Standard brief pulse stimulus threshold titration and dosing Anaesthesia: hypnotic induction with etomidate (0.15 to 0.3 mg/kg) or Propofol (1 to 2 mg/kg) Muscle relaxation: suxamethonium (0.5 mg/kg) with atropine 0,5 mg intravenously Augmentation strategy in patients with partial response to clozapine or super refractory schizophrenia		Acute ECT treatment: Six sessions over 2 weeks; afterwards: maintenance ECT: weekly sessions for 1 month, fortnightly for 2 months and monthly one for 3 months Electrode placement: bilateral, 1.5 times supra-threshold, brief pulse electrical stimulus under anaesthesia (thiopentone/propofol and succinylcholine) In advent of post-ECT agitation or confusion, injection lorazepam 4mg was given parenterally.	ECT (augmentation) + clozapine 3 times per week for the first 4 weeks, then twice weekly for the next 4 weeks. If patients met remission criteria before the completion of 8 weeks and showed a plateau in their improvement for two consecutive ratings, ECT was continued weekly through the end of 8 weeks. Electrode placement: bilateral Product: Thymatron-DGx Seizure threshold was determined at the first treatment. Dosing at subsequent treatments was given at 50% above threshold. Anaesthesia: glycopyrrolate (0.1 mg-0.2 mg), methohexital (0.5 mg/kg-1 mg/kg), and succinylcholine (0.5 mg/kg-1 mg/kg) Participants remained on the clozapine dose at which they entered the study
Comparator	Sham-ECT same setting and hypnotic sedation, but without muscle relaxation or electrical stimulus.		Clozapine 12.5 mg on the first day, followed by 12.5 mg twice daily on the second day, followed by 25 mg twice daily for the next 2 days and then an increment of 25 mg every two days till the target dose of 250-400 mg/day in two divided doses as per tolerability of the patients. The median stable dose of clozapine was 350 mg/day. Serum clozapine levels could not be estimated; however, the pill-count method was adopted to ensure compliance. The ongoing antipsychotic was gradually tapered and stopped over 1-2 weeks.	Clozapine only Participants remained on the clozapine dose at which they entered the study for 8 weeks. Concurrent use of other antipsychotic medications and antidepressants was allowed as long as they were taken at a stable dose for at least 12 weeks before entering the study. Lorazepam, up to 6 mg per day, or diphenhydramine, up to 100 mg, were used as needed for anxiety, agitation, or insomnia.

Author, year	Melzer-Riberio 2017 [73]	Melzer-Riberio 2020 [96]	Mishra 2022 [74]	Petrides 2019 [75]
Study design	Pilot, randomised, placebo-controlled, single blinded, single centre trial	Secondary analysis of a pilot study	Randomised, open-label, parallel-design clinical trial	Randomised single – blind study
Setting	NR		NR	Inpatient
Number of pts (randomised), I vs C	23 13 vs 10		60 30 vs 30	39 20 vs 19
Inclusion criteria	Between 18 and 55 years Both genders Fulfilled criteria for a DSM IV-TR diagnosis of schizophrenia or schizoaffective disorder based on clinical interview and follow-up of experienced psychiatrist Severity of symptoms: PANSS, CGI Generally patients were using clozapine at least for 6 months and had to have a total PANSS ≥ 60 and the CGI ≥ 4. Clozapine plasma levels should be equal or Higher than 350 ng/mL		Between 18 and 60 years Both genders Non response (<20% clinical improvement and significant functional impairment) despite trials with ≥2 different antipsychotics at doses ≥600 mg/day chlorpromazine-equivalent for ≥6-weeks were defined as TRS	Between 18 and 60 years Diagnosis of schizophrenia according to DSM-IV criteria Resistance to at least two antipsychotics, clozapine resistance A baseline BPRS score of at least moderate (score of 4) on one of the four psychotic items (hallucinatory behaviour, suspiciousness, conceptual disorganisation, and unusual thought content) of the psychotic symptom subscale or a score of 12 on these four items combined A clinical global impressions (CGI)-severity rating of at least moderate (score of 4) Capacity to give informed consent For women: negative pregnancy test and patient agreement to use a medically accepted form of contraception
Exclusion criteria	Evidence of any unstable clinical condition in the last three months before the inclusion in the study, ECT treatment for six months before the initiation of the study, Women were requested to use contraceptive methods.		History of clozapine, ECT, psychoactive-substance abuse, or any comorbid major medical condition, Pregnant or breastfeeding.	Schizoaffective disorder, disorder, current affective episode ECT within 6 months History of epilepsy, severe neurological or systemic disorder that could significantly affect cognition, behaviour, or mental status Psychoactive substance dependence (other than nicotine or caffeine) within 1 month prior to entering the study A score >18 on the 24-item Hamilton Depression Rating Scale (HAM-D) Clinical determination that mood stabilizers that could no be discontinued were necessary Affective disorders and prominent depressive symptoms Pregnancy.

Author, year	Melzer-Riberio 2017 [73]	Melzer-Riberio 2020 [96]	Mishra 2022 [74]	Petrides 2019 [75]
Study Outcomes	Response rate on psychotic symptoms (mean reduction at PANSS positive subscale Clinical improvement on other PANSS subscales and CGI		Change in PANSS scores over 6 months, Clinical response (>20% reduction in the PANSS-T, change in the scores of CGI-SCHI, MoCA and GAF), Number of patients requiring rescue medications and the adverse events reported in each group, Changes in regional cerebral perfusion	Response rate defined as ≥40% of improvement based on the psychotic symptom subscale, a CGI-severity r ating of mild or less (<3), and a CGI-improvement rating of much improved (≤2)
Age of patients (yrs), mean±SD, I vs C	36.63±9.95 vs 37.60±9.56, p=0.81		34.47±10.29 vs 35.80±10.36; p=0.62	35.70±2.27 vs 42.78±1.82; p=0.03
Sex m/f, (n), I vs C	9/4 vs 7/3		60:40 vs 57:43; p=0.99	15/5 vs 13/6
Disease duration (years), mean±SD, I vs C	Age (yrs) at first hospitalisation: 20.15 ± 5.92 vs 22.20 ± 8.51, p=0.5		9.6 ± 7.36 vs 12.8 ± 7.98; p=0.11	NR
Diagnosis	Schizophrenia with partial response to clozapine or super refractory schizophrenia (unsatisfactory response to clozapine using modified criteria: 1) at least 8 weeks treatment with clozapine with plasma levels of >350 micrograms/L and failure to improve by ≥20% in total BPRS score; 2) persistent psychotic symptoms as defined as ≥4 (moderate) on ≥2 to 4 positive symptoms items of the BPRS (18 items, graded 1-7); 3) current presence of at least moderately severe illness on the BPRS score (≥45) and a score of ≥4 (moderate) on the Clinical Global Impression Scale)		Treatment-resistant schizophrenia	Diagnosis of schizophrenia according to DSM-IV criteria Resistance to at least two antipsychotics, clozapine resistance
Previous therapies, mean±SD, I vs C	*Number of hospitalisations* 3.33 ± 2.74 vs 4.00 ± 1.32, p=0.51 *Clozapine dose (mg)* 532.69 (168.75) vs 505.00 (130.06), p=0.67 *Clozapine plasma levels (ng/ml)* 644.30 (253.71) vs 747.82 (397.66), p=0.45		NR	NR
Current therapy (at time of enrollment)	All patients were on clozapine either in monotherapy, or in combination with other psychotropic drugs such as antipsychotics, antidepressants or anticonvulsants		"The ongoing antipsychotics were continued at the same dose for ethical concerns."	Pharmacotherapy (no further details)
Follow-up (months)	4 weeks		24 weeks (after 6 weeks: M-ECT)	8 weeks (+ 8 weeks for clozapine non-responders)
Loss to follow-up (discontinuation/ drop out before analysis, discontinuation/drop-out during any point of the follow-up period), n (%), I vs C	1 (8%) (due to infectious orchitis) vs 3 (30%) (other reasons not related to the study)		2 (7%) vs 0	3 (15%) (refused further treatment, persistence of involuntary movements) vs 3 (16%) (refused to participate in rating assessment)
Outcomes				
Efficacy				
Overall survival, n (%), I vs C	13 (100%) vs 10 (100%)		NR	20 (100%) vs 19 (100%)
Suicidal attempt or ideation, n (%)	NR		NR	NR

Author, year	Melzer-Riberio 2017 [73]	Melzer-Riberio 2020 [96]	Mishra 2022 [74]	Petrides 2019 [75]
General functioning (GAF, bprs, SAS-SR), mean score±SD, I vs C	NR		*GAF* Baseline: 24.85 ± 1.09 vs 22.11 ± 1.5; p= 0.149 6 weeks FU: 53.08 ± 1.76 vs 30.59 ± 1.45; p <0.001 Baseline vs 6 weeks: p <0.001 vs p <0.001	*Executive Function* Baseline: Global Affective Flattening: 2.50 ± 1.36 vs 1.79 ± 1.65; p=0.1524 Global Alogia: 2.00 ± 1.56 vs 2.00 ± 1.56; p=0.9999 Global Avolition: 2.80 ± 0.95 vs 2.68 ± 1.42; p=0.7676 Global Asociality Anhedonia: 2.65 ± 1.18 vs 2.72 ± 1.13; p=0.8483 Percent change from baseline to final week: Global Affective Flattening: -27.45 vs 14.81; p=0.0585 Global Alogia: -1.08 vs 19.44; p=0.3435 Global Avolition: -9.51 vs 30.56; 0.1192 Global Asociality Anhedonia: -1.37 vs 36.11; p=0.1619 Percent change from baseline to week 4: Global Affective Flattening: -10.20 vs 23.06; p=0.2927 Globald Alogia: 20.42 vs -4.44; p=0.2538 Global Avolition: -6.67vs 9.09; p=0.1355 Global Asociality Anhedonia: -1.11 vs 20.83; p=0.1380
Cognitive functioning (MoCA, MMSE), mean±SD, I vs C	NR		*MoCA* Baseline: 19.08 ± 0.43 vs 19.22 ± 0.40; p=0.805 6 weeks FU: 20.27 ± 0.37 vs 20.07 ± 0.39; p=0.722 Baseline vs 6 weeks: p <0.001 vs p <0.001	*MMSE* Baseline: 22.6 ± 1.2 vs 22.2 ± 1.0; NR Week 9 FU: 23.1 ± 1.2 vs 23.4 ± 1.2; NR
Quality of life, I vs C	NR		NR	NR
Satisfaction and acceptability of treatment, I vs C	NR		NR	NR
Remission/relapse, n (%); I vs C	NR		Relapse or nonresponse: 2 vs 3[84]	Remission/nonresponse: 10 (50%) vs 19 (100%)

[84] It is unclear if the relapse/nonresponse took place within 6 weeks or afterwards.

Author, year	Melzer-Riberio 2017 [73]	Melzer-Riberio 2020 [96]	Mishra 2022 [74]	Petrides 2019 [75]
Response to treatment (time to onset of response, % reduction), I vs C	Response rates within trial duration: 20/% reduction on the PANSS-P: 2 vs 2 30/% reduction on the PANSS-P: 1 vs 2 40/% reduction on the PANSS-P: 1 vs 0		*PANSS –T* Baseline: 143.31 ± 2.58 vs 144.04 ± 3.26; p=0.862 6 weeks FU: 92.81 ± 2.11 vs 122.48 ± 3.24; p <0.001 Baseline vs 6 weeks: p <0.001 vs p <0.001	Response rates: 10/20 (50%) vs 0 (0%) met a priori response criteria 20% reduction on the BPRS: 12 vs 0 50% reduction on the BPRS: 9 vs 0 60% reduction on the BPRS: 6 vs 0 70% reduction on the BPRS: 3 vs 0
Service use (number of pts readmitted), I vs C	NR		NR	NR
Schizophrenia symptoms (PANSS, BPRS, SAPS, SANS, CGI), mean±SD, (95% CI), I vs C	*PANSS-Positive* Baseline: 19.31±3.57 vs ± 22.90±6.71 Post-treatment: 16.17±4.11 vs ± 19.14±6.28 p-values: Group: 0.121 Time: < 0.001 Interaction: 0.646 *PANSS-Negative* Baseline: 23.15±7.69 vs ± 29.00±7.62 Post-treatment: 23.42±5.82 vs 30.14±8.38 p- values: Group: 0.041 Time: 0.995 Interaction: 0.610 *PANSS-General* Baseline: 38.77±9.36 vs 44.90±9.33 Post-treatment: 35.17±7.61 vs 38.14±11.71 p- values: Group: 0.193 Time: 0.023 Interaction: 0.501	P1 Delusions: 3.92 ±1.44 vs 4.14 ± 1.57, (-1.08-0.78), p=0.756 P2 Conceptional disorganization: 1.75±0.87 vs 1.71 ± 1.25, (-0.97-0.89), p=0.934 P3 Hallucinatory behaviour: 2.92 ± 1.31 vs 4.29 ± 1.50, (-1.97- -0.00), p=0.048 P4 Excitement: 2.00 ± 1.04 vs 1.71 ± 1.25; (-1.19-0.67); p=0.587 P5 Grandiosity: 1.58 ± 1.08 vs 2.57 ± 1.13; (-1.87-0.07); p=0.070 P6 Suspiciousness: 3.17 ± 1.19 vs 3.29 ± 1,11; (-1.03-0.82); p=0.828 P7 Hostility: 1.42 ± 0.90 vs 1.43 ± 0.79; (-0.94-0.92); p=0.981 N1 Blunted affect: 3.75 ± 1.42 vs 4.29 ± 1.50; (-1.31-0.56); p=0.437 N2 Emotional withdrawal: 3.91[85] ± 0.94 vs 4.14 ± 1.77; (-1.12-0.77); p=0.718 N3 poor rapport: 3.17 ± 1.03 vs 4.14 ± 1.68; (-1.71-0.21); p=0.128 N4 Passive social withdrawal: 3.64[85] ± 1.21 vs 4.43 ± 1.13; (-1.64-0.30); p=0.177 N5 Difficulty in abstract thinking[86]: 3.67 ± 1.87 vs 4.71 ± 1.70; (-1.52-0.37); p=0.236	*PANSS –P* Baseline: 35.65 ± 4.87 vs 35.78 ± 5.2; p=0.93 6 weeks FU: 20.42 ± 0.74 vs 29.93 ± 0.82; p <0.001 Baseline vs 6 weeks: p <0.001 vs p <0.001 *PANSS –N* Baseline: 36.96 ± 6.35 vs 37.41 ±6.43; p=0.79 6 weeks FU: 26.23 ± 1.07 vs 32.56 ± 1.23; p <0.001 Baseline vs 6 weeks: p <0.001 vs p <0.001 *PANSS –G* Baseline: 70.69 ±9.69 vs 70.85 ±10.2; p=0.95 6 weeks FU: 46.15 ± 1.86 vs 60.00 ± 1.90; p <0.001 Baseline vs 6 weeks: p <0.001 vs p <0.001	*BPRS total*[87] Baseline: 45.68 ± 1.87 vs 46.42 ± 2.55 *BPRS psychotic symptom subscale score* Baseline: 16.58 ± 0.86 vs 16.89 ± 0.9 After 8 Weeks: p<0.0001 11.44 ± 1.06 vs 17.01 ± 1.06[88] *CGI* Baseline: 5.35 ± 0.02 vs 5.53 ± 0.22 After 8 weeks: 4.25 ± 0.24 Vs 5.47 ± 0.24[88] *SANS* on global measures for affective flattening: p=0.33 Alogia p=0.87 Avolition-apathy p=0.39 Anhedonia-associality p=0.18

[85] n=11

[86] SS in Baseline: 4,08 ± 1,24 vs 5,71 ± 1,11; **– 2.39- -0.33; 0.009**

[87] Available data extracted as reported in the study [75].

[88] Estimated by using a webplot digitizer.

Author, year	Melzer-Riberio 2017 [73]	Melzer-Riberio 2020 [96]	Mishra 2022 [74]	Petrides 2019 [75]
Schizophrenia symptoms (PANSS, BPRS, SAPS, SANS, CGI), mean±SD, (95% CI), I vs C *(continuation)*	*PANSS-Total* Baseline: 81.23±14.56 vs 96.80±19.27 Post-treatment: 74.75±12.17± vs 87.43±24.76 p- values: Group: 0.046 Time: 0.006 Interaction: 0.668 *CGI* Baseline: 5.23±0.60 vs 5.80±1.14 Post-treatment: 4.17±0.72 vs 4.86±1.46 p- values: Group: 0.149 Time: < 0.001 Interaction: 0.908	N6 Lack of spontaneity: 3.33 ± 1.30 vs 4.57 ± 0.98; (-2.02- -0.04); p=0.040 N7 Stereotyped thinking: 3.27[85] ± 1.62 vs 3.86 ± 1.07; (-1.36-0.54); p=0.401 G1 Somatic concern: 1.58 ± 1.16 vs 1.00 ± 0.00; (-1.57-0.33); p=0.201 G2 Anxiety: 2.50 ± 1.17 vs 2.57 ± 1.51; (-0.98-0.87); p=0.910 G3 Guilt feelings[89]: 1.83 ± 1.27 vs 1.29 ± 0.49; (-1.45-0.43); p=0.292 G4 Tension: 2.00 ± 1.13 vs 1.71 ± 1.25; (-1.18-0.68); p=0.605 G5 Mannerisms & posturing: 2.75 ± 1.36 vs 3.00 ± 1.29; (-1.12-0.74); p=0.695 G6 Depression: 2.00 ± 1.13 vs 2.00 ± 1.15; (-0.93-0.93); p=1.000 G7 Motor retardation: 2.58 ± 1.51 vs 2.29 ± 1.25; (-1.13-0.73); p=0.669 G8 Uncooperativeness[90]: 1.08 ± 0.29 vs 1.71 ± 0.95; (-2.02- -0.04); p=0.041 G9 Unusual though content: 1.92 ± 1.00 vs 2.29 ± 1.50; (-1.24-0.62); p=0.519 G10 Disorientation: 1.25 ± 0.87 vs 2.86 ± 1.46; (-2.48- -0.40); p=0.006 G11 Poor attention: 2.92 ± 1.08 vs 2.57 ± 1.13; (-1.25-0.61); p=0.505 G12 Lack of judgement & insight: 2.92 ± 1.38 vs 3.86 ± 1.86; (-1.55-0.35); p=0.216 G13 Disturbance of volition: 2.58 ± 1.00 vs 2.29 ± 0.95; (-1.23-0.64); p=0.537 G14: Poor impulse control: 1.50 ± 1.24 vs 1.57 ± 0.79; (-0.99-0.86); p=0.894 G15 Preoccupation: 2.67 ± 1.37 vs 3.29 ± 1.38; (-1.39-0.49); p=0.348 G16: Active social avoidance: 3.33 ± 1.23 vs 3.86 ± 1.57; (-1.33-0.55); p=0.417	*PANSS-T* Baseline: 143.31±14.13 vs 144.04±17.85; p=0.86 6 weeks FU: 92.81±2.11 vs 122.48±3.24; p<0.001 Baseline vs 6 weeks: p <0.001 vs p <0.001 *CGI-SCH-S* Baseline: 6.192±0.49 vs 6.185±0.6; p=0.96 6 weeks FU: 3.69 ± 0.11 vs 5.11 ± 0.13; p <0.001 Baseline vs 6 weeks: p <0.001 vs p <0.001 *CGI-SCH-I* Baseline: 2.27 ± 0.12 vs 3.29 ± 0.10; p <0.001 6 weeks FU: 2.04 ± 0.14 vs 2.67 ± 0.13; p=0.002 Baseline vs 6 weeks: NR	

[89] SS in Baseline: 2.75 ± 1.54 vs 1.29 ± 0.49; **-2.14- -0.14; 0.025**

[90] SS in Baseline: 1.42 ± 0.79 vs 2.29 ± 0.95; **-1.02 -2.01- -0.03; 0.042**

Author, year	Melzer-Riberio 2017 [73]	Melzer-Riberio 2020 [96]	Mishra 2022 [74]	Petrides 2019 [75]
Safety				
Overall complications, n (%), I vs C	NR		No profound adverse effects could be reported.	Recurrence of preexisting involuntary "jerky" movements (concerns were not substantiated by electroencephalographic studies): 1 (5%) vs 0
Major AE, n (%), I vs C	NR		NR	NR
Minor AE, n (%), I vs C	NR		Headache: 12 (40%) vs 0 Sialorrhea: 0 vs NA ("most patients") Constipation: 0 vs18 (60%) Cognitive deficits: 2 (7%) vs 0	Mild confusion: 2 vs 0
Procedure-related mortality, n (%)	NR		NR	NR

Abbreviations*: AE – adverse event, BPRS – Brief Psychiatric Rating Scale, C – comparator, CGI – Clinical Global Impression, CGI-SCH – Clinical Global Inventory Schizophrenia Scale, CGI-SCH-I – Clinical Global Inventory Schizophrenia improvement score, CGI-SCH-S – Clinical Global Inventory Schizophrenia severity score, DSM – Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text revision, ECT – Electroconvulsive therapy, F – female, FAPESP – Sao Paulo Research Support Foundation, GAF – Global Assessment of Functioning, I – intervention, M – male, M-ECT – maintenance electroconvulsive therapy, MoCA – Montreal Cognitive Assessment, n – number, NR – not reported, PANSS – Positive and Negative Syndrome Scale, pts –patients, RAVLT – Rey Auditor Verbal Learning Test, rTMS – repetitive transcranial magnetic stimulation, SANS – Scale for the Assessment of Negative Symptoms, SAPS – Scale for the Assessment of Positive Symptoms,ScoRS – Schizophrenia Cognitive Rating Scale, SD – standard deviation, TRS – treatment resistant schizophrenia, TMT – Trail Making Test, yrs – years*

Risk of bias tables and GRADE evidence profile

Table A-5: Risk of bias – study level (systematic reviews), see [52]

SR	Domain				Question			Risk of bias in the review
	1. specification of study eligibility criteria	2. methods used to identify and/or select studies	3. methods used to collect data and appraise studies	4. synthesis and findings	A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	B. Was the relevance of identified studies to the review's research question appropriately considered?	C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	
Menon 2023 [99]	Low	Unclear	Low	Low	PN	PY	PY	Low
Song 2015 [65]	Low	Low	Low	Low	Y	PY	Y	Low
Sinclair 2019 [76]	Low	Low	Low	Low	Y	Y	Y	Low

Abbreviations: PN – probably not, PY – probably yes, SR – systematic review, Y – yes

Table A-6: Risk of bias – outcome and study level (randomised studies), see Cochrane RoB 2.0 [53]

Trial	Endpoints	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Abdel Latif 2020 [78]	Depression score, cognitive functioning	Some concern[91]	Some concern[92]	High[93]	High[94]	Some concern[95]	High
Anand 2023 [59]	Response to treatment, remission, cognitive functioning, quality of life	Low	Low	Low	High[96]	Low	High
Melzer,-Riberio 2017 & 2020 [73, 96]	Response rate on psychotic symptoms, clinical improvement	Some concern[97]	Some concern[98]	Low	Some concern[99]	Some concern[100]	High
Mishra 2022 [74]	PANSS Scores	Low	Some concern[101]	Low	Low	Low	Some concern
Petrides 2019 [75]	Response rate (improvementon the psychotic symptom subscale), CGI Improvement	High[102]	High[103]	High[104]	Low	High[105]	High
Menon 2023 [99]							
Ekstrand 2022 [61]	Overall study	Some concern	High	High	High	Low	High
Ghasemi 2014 [60]	Overall study	High	High	Low	Low	High	High
Khierabadi 2019 [79]	Overall study	High	High	High	Low	Low	High
Khierabadi 2020 [80]	Overall study	High	High	High	High	Low	High

[91] No information concerning allocation sequence concealment.

[92] Patients and carers were not blinded.

[93] High drop-out rate; no sensitivity analysis; discontinuation could be related to participants' health status and their received treatment.

[94] Measurement of the outcome has differed between groups; no blinding in post-intervention assessments.

[95] Pre-specified analysis plan was not available.

[96] Measurement of the outcome could have differed between groups, assessors not blinded, assessment of the outcome could have been influenced by knowledge of intervention received.

[97] No information concerning allocation sequence concealment.

[98] Patients and carers were not blinded.

[99] No information concerning differences in measurement of the outcome between intervention groups.

[100] Deviations from pre-specified analysis plan.

[101] Patients and carers not blinded.

[102] No information concerning allocation sequence, statistically significant difference in baseline characteristics.

[103] Patients and carers were not blinded.

[104] Data for the outcomes were not available for all or nearly all participants randomized.

[105] Results were assessed on the basis of the results from multiple eligible outcome measurements and analyses.

Table A-7: Risk of bias – study level (randomised studies), see risk of bias tool 1 [101]

Trial	Random Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall risk of bias
Song 2015 [65]								
Folkerts 1997	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Hu 2014	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Huang 2006	High	High	High	High	Low	Low	Low	High
Jiang 2010	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Li 2009	High	High	High	High	Low	Low	Low	High
Li 2012	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear
Niu 2011	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Qin 2013	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Shi 2010	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Tang 2012	Unclear	Unclear	Unclear	Unclear	High	Low	Low	High
Wen 2011	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Xu 2009	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Yang 2010	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Ye 2013	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Zhang 2011	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Zhou 2014	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Zhu 2008	High	High	High	Unclear	Low	Low	Low	High
Erdos 2017 [100]								
Kesthkar 2011	Low	Unclear	High	High		Low	High	High
Eranti 2007	Low	Low	High	High		Low	Low	High
Rosa 2006	Low	Unclear	High	High		High	Low	High
Grunhaus 2003	Low	Unclear	High	High		Low	Low	High
Grunhaus 2000 & Dannon 2002	Low	Unclear	High	High		Low	Low	High
Pridmore 2000	Unclear	Unclear	High	High		Low	Low	High

Trial	Random Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall risk of bias
Sinclair 2019 [76]								
Chai 2008	Unclear	Unclear	High	Unclear	Low	Low	Low	High
Chanpattana 1999	Unclear	Unclear	High	Low	Unclear	Low	Low	High
Chen 2012	Unclear	Unclear	High	Unclear	Low	Low	Low	High
Goswami 2003	Low	Low	Low	Unclear	Unclear	High	Low	High
Jiang 2009	Low	Unclear	High	Unclear	Low	Low	Low	High
Jiang 2013	Unclear	Unclear	High	Unclear	Low	Low	Low	High
Lin 2014	Unclear	Unclear	High	Unclear	Low	Low	Low	High
Liu 2010	Unclear	Unclear	High	Unclear	Low	High	Low	High
Petrides 2015	Unclear	Unclear	High	Low	Unclear	Low	Low	High
Wang 2008	Unclear	Unclear	High	Unclear	Low	Unclear	Low	High
Wang 2011	Unclear	Unclear	High	Unclear	Low	Unclear	Low	High
Wang 2013	Unclear	Unclear	High	Unclear	Unclear	Low	Low	High
Yang 2005	Unclear	Unclear	High	Unclear	Low	Low	Low	High
Zhang 2010	Unclear	Unclear	High	Unclear	Low	Low	Low	High
Zhang 2012	Unclear	Unclear	High	Unclear	Low	Low	Low	High

Table A-8: Evidence profile: efficacy and safety of ECT versus rTMS in TRD

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[106]	ECT	rTMS	Relative (95% CI)	Absolute (95% CI)	
Overall mortality (suicide-related events), suicidal attempt, suicidal ideation											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Suicide score (difference in mean scores on HAM-D/HDRS or BDI subscale, follow-up: 7 weeks)											
2 [69, 78]	Randomised trial	Serious[a]	Not serious	Serious[b]	Serious[c]	None	60	53	Not estimable	**MD** 1 RCT (HAM-D): 0.63 points greater reduction in the score. 1 RCT (HDRS and BDI): 1.5 points greater reduction in the score (HDRS) and 0.6 scores greater reduction (BDI).	⨁◯◯◯ Very low
Cognitive functioning (difference in mean scores on DSP, SCWTV dots, words&colors, CTT trial 1&trial 2, ROT copy&delay, follow-up: 7 weeks)											
1 [78]	Randomised trial	Serious[f]	Not serious	Serious[b]	Serious[c]	None	20	20	Not estimable	**MD** DSP: 1.32 lower (1.25 to 1.39 lower) SCWTV dots: 2.20 higher (1.74 to 2.66 higher); words: 4.38 higher (4.27 to 4.49 higher); colors: 5.6 higher (5.17 to 6.03 higher) CTT trial 1: 11.14 higher (8.82 to 13.46 higher); trial 2: 22.71 higher (21.27 to 24.15 higher) ROT copy: 0.30 lower (0.60 higher to 1.20 lower); delay: 3.67 lower (2.86 to 4.48 lower)	⨁◯◯◯ Very low
General functioning[107], quality of life											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Response rate (follow-up: end of treatment)											
3 [100]	Randomised trial	Serious[g]	Serious	Not serious	Serious[c]	None	62	64	RR 1.72 (0.95 to 3.11)	270 more per 1,000 (from 19 fewer to 791 more)	⨁◯◯◯ Very low
Remission rate (follow-up: end of treatment)											
3 [100]	Randomised trial	Serious[h]	Serious	Not serious	Serious[c]	None	58	60	RR 1.44 (0.64 to 3.23)	154 more per 1,000 (from 126 fewer to 781 more)	⨁◯◯◯ Very low

[106] Publication bias, large effect, plausible confounding, dose response gradient.

[107] General functioning was reported in one study [64] but without any baseline data.

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[106]	ECT	rTMS	Relative (95% CI)	Absolute (95% CI)	
Depression score (difference in mean scores on HAM-D or HDRS, follow-up: 4 to 7 weeks)											
5[108] [64, 68-70, 78]	Randomised trial	Serious[d]	Not serious	Not serious	Serious[e]	None	116	109	Not estimable	**MD** 5.85 lower (from 2.34 to 9.37 lower)	⨁⨁◯◯ Low
Serious adverse event: seizures											
2 [100]	Randomised trial	Serious[i]	Not serious	Not serious	Serious[c]	None	60	53	Not pooled	No seizures occurred in any of the studies.	⨁⨁◯◯ Low

Abbreviations: CI – confidence interval, CTT – Color Trails Test, DSP – Digit Span Test, ECT – electroconvulsive therapy, HAM-D/HDRS – Hamilton Depression Rating Scale, MD – mean difference, rTMS – repetitive transcranial magnetic stimulation, RR – relative risk, ROT – Rey-Osterrieth Complex Figure Test, SCWTV – Stroop Color-Word Test-Victoria version

Comments:

[a] *High overall risk of bias due to non-blinding of participants and personnel and no available pre-analysis plan in both studies, as well as high drop-out rate, no sensitivity analysis, and potentially different measurement of the outcomes between groups in one study.*

[b] *Surrogate endpoint.*

[c] *Low number of studies with very small sample size.*

[d] *High overall risk of bias in all studies due to non-blinding of participants and personnel in all studies, unclear risk for allocation concealment in all studies, unclear risk for randomisation in study, no available pre-analysis plan in two studies, as well as high drop-out rate, no sensitivity analysis, and potentially different measurement of the outcomes between groups in one study.*

[e] *Small sample size.*

[f] *High overall risk of bias due to non-blinding of participants and personnel, no available pre-analysis plan, high drop-out rate, no sensitivity analysis, and potentially different measurement of the outcomes between groups.*

[g] *High risk of bias of all included studies due to non-blinding of participants and personnel in all studies, and unclear risk of bias for allocation concealment in one study.*

[h] *High risk of bias of all included studies due to non-blinding of participants and personnel in all studies, and unclear risk of bias for allocation concealment and randomisation in one study.*

[i] *High overall risk of bias in the included studies due to non-blinding of participants and personnel, unclear allocation concealment in both studies, as well as non-available pre-analysis plan in one study.*

Sources: If the systematic review by Erdos et al. [100]) is cited, the results are presented from the original review unchanged.

[108] Only those studies were included in the meta-analysis, in which the rTMS treatment complied with the safety standards for rTMS.

Table A-9: Evidence profile: efficacy and safety of ECT versus ketamine in TRD

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[109]	ECT	Ketamine	Relative (95% CI)	Absolute (95% CI)	
Overall mortality (suicide-related events, follow-up: 12 months)											
1 [61]	Randomised trial	Not serious	Not serious	Not serious	Serious[a]	None	90	91	Not pooled	1 (1%) vs 0 patients during 12 months follow-up.	⨁⨁◯◯ Moderate
Suicidal attempt (events, follow-up: from 6 to 12 months)											
2 [59, 61]	Randomised trial	Not serious	Not serious	Not serious	Serious[a]	None	293	291	Not pooled	1 RCT: 6/90 (7%) vs 4/91 (4%) of patients during 12 months follow-up. 1 RCT: 0/170 vs 0/195 patients at end of treatment, 0/70 (0%) vs 1/108 (1%) during 6 months follow-up.	⨁⨁◯◯ Moderate
Suicidal ideation (events, follow-up: 6 months)											
1 [59]	Randomised trial	Serious[b]	Not serious	Not serious	Serious[a]	None	203	200	Not pooled	At end of treatment: 2/170 (1%) vs 4/195 (2%) and At 6-month FU: 1/70 (1%) vs 4/108 (4%)	⨁⨁◯◯ Low
Suicidal score (difference in BSSI or CSSRS, follow-up: from 1 to 6 months)											
2 [59, 80]	Randomised trial	Serious[b,c]	Not serious	Serious[d]	Serious[a]	None	215	227	Not estimable	**MD** 1 RCT (BSSI) (with 2 comparators, i.e. oral and IM ketamine): 24 hours after the first intervention 0.01 and 0.21 lower score, second week during the intervention 0.31 and 0.5 lower and at 1 month follow-up 1.53 and 2.25 lower score (high=poor). 1 RCT (CSSR): at end of treatment no difference, at 1 month follow-up 0.1 lower score, at 3 and 6 months follow-up 0.1 higher score (high=poor).	⨁◯◯◯ Very low
Cognitive functioning (difference in GSE-My score, SMCQ score, HVLT-R T toal score, WMN scale, follow-up: 1 week to 6 months)											
2 [59, 79]	Randomised trial	Serious[b,c]	Not serious	Serious[d]	Serious[a]	None	219	216	Not estimable	1 RCT (6 months follow-up): GSE-My score **MD** 1.1 lower (from 0.9 to 1.2 lower). SMCQ score **MD** 9.0 lower (from 5.1 to 13.0 lower). HVLT-R T total score **MD** 5.3 lower (from 3.1 to 7.4 lower). 1 RCT (2 months follow-up): WMS MD 3.4 points lower at 1 week and 2 points lower at 1 month follow-up. The changes were non-significant.	⨁◯◯◯ Very low

[109] Publication bias (undetected/strongly suspected), Large effect (no/large/very large), Plausible confounding (no/would reduce demonstrated effect/would suggest spurious effect), Dose response gradient (no/yes)

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[109]	ECT	Ketamine	Relative (95% CI)	Absolute (95% CI)	
General functioning											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quality of life (difference in 16-item QoL scale score, follow-up: 6 months)											
1 [59]	Randomised trial	Serious[b]	Not serious	Not serious	Serious[a,e]	None	203	200	Not estimable	**MD** 0.6 scores higher (from 2.1 lower to 3.4 higher) (high=good).	⨁⨁◯◯ Low
Response (follow-up: from 1 to 3 weeks)											
3 [59-61]	Randomised trial	Serious[b,c]	Not serious	Not serious	Serious[a,e]	None	269	299	RR 1.02 (0.88 to 1.19)	11 more per 1,000 (from 64 fewer to 101 more)	⨁⨁◯◯ Low
Remission (follow-up: from end of treatment to 4 weeks)											
2 [59, 61]	Randomised trial	Serious[b,c]	Not serious	Not serious	Serious[a,e]	None	261	290	RR 0.97 (0.79 to 1.2)	12 fewer per 1,000 (from 85 fewer to 81 more)	⨁⨁◯◯ Low
Depression score (difference in HDRS or MADRS, follow-up: from 1 week to 3 months)											
4 [60, 61, 79, 80]	Randomised trial	Serious[c]	Not serious	Not serious	Serious[a,e]	None	124	129	Not estimable	**SMD** 0.30 score lower (high=poor) (0.78 lower to 0.18 higher)	⨁⨁◯◯ Low
Serious adverse events (follow-up: from 1 week to 12 months)											
2 [59, 61]	Randomised trial	Serious[b,c]	Not serious	Not serious	Serious[a]	None	294	295	Not pooled	1 RCT: ≥1 SAE after initial treatment phase occurred in 4/170 (2%) vs 5/195 (3%) patients, while during 6-month follow-up period in 3/70 (4%) vs 8/108 (7%) patients. 1 RCT: ≥1 SAE occurred during the 12-month follow-up period in 23/90 (26%) vs 14/91 (15%), p=0.09	⨁⨁◯◯ Low

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, HAM-D – …, HDRS – …., MD – mean difference, RR – relative risk,

Comments:

[a] *Low number of studies with very low sample size.*

[b] *High overall risk of bias of the included study because the measurement of the outcome could have differed between the two groups and the assessors not being blinded, the assessment of the outcome could have been influenced by knowledge of the intervention.*

[c] *High overall risk of bias due to high or unclear risk of bias in the randomisation process, blinding of participants and personnel, missing outcome data, and measurement of the outcome.*

[d] *Surrogate endpoint.*

[e] *Confidence interval is wide.*

Table A-10: Evidence profile: efficacy and safety of ECT plus antidepressant versus antidepressant in TRD

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[110]	ECT plus antidepressant	Antidepressant	Relative (95% CI)	Absolute (95% CI)	
Overall mortality (suicide-related events), suicidal attempt, suicidal ideation, suicide score											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Depression score, quality of life, general functioning, cognitive functioning, remission rate											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Response rate (follow-up: 4 to 8 weeks)											
13 [65]	Randomised trial	Serious[a]	Not serious	Not serious	Not serious	None	436	435	RR 1.82 (1.55 to 2.14)	351 more per 1,000 (235 more to 487 more)	⨁⨁⨁◯ Moderate
Serious adverse events: somatisation (follow-up: 4 to 8 weeks)											
10 [65]	Randomised trial	Serious[a]	Not serious	Not serious	Not serious	None	354	356	RR 0.79 (0.61 to 1.01)	Not estimable due to non-reporting of the baseline risk either in the intervention or in the control group.	⨁⨁⨁◯ Moderate
Serious adverse events: memory deterioration (follow-up: 4 weeks)											
4 [65]	Randomised trial	Serious[b]	Serious[c]	Not serious	Serious[d]	None	145	147	RR 0.27 (0.03 to 2.40)	Not estimable due to non-reporting of the baseline risk either in the intervention or in the control group.	⨁◯◯◯ Very low

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, MD – mean difference, NA – not applicable, RR – relative risk

Comments:

[a] *Unclear risk of bias for randomisation, allocation concealment and blinding in the majority of studies (two and one study with high risk of bias for response rate and somatisation, respectively)*

[b] *Unclear risk of bias in the included studies for randomisation, allocation concealment and blinding.*

[c] *Heterogeneity among the included studies.*

[d] *Low number of studies with low patient numbers. Wide confidence interval.*

Sources: when the systematic review by Song et al. [65] is cited, results are presented unchanged.

[110] Publication bias (undetected/strongly suspected), Large effect (no/large/very large), Plausible confounding (no/would reduce demonstrated effect/would suggest spurious effect), Dose response gradient (no/yes)

Table A-11: Evidence profile: efficacy and safety of ECT versus antidepressants in TRD

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[111]	ECT	Antidepressant	Relative (95% CI)	Absolute (95% CI)	
Overall mortality (suicide-related events), suicial attempt, suicidal ideation, suicide score											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Depression score, quality of life, general functioning, cognitive functioning, remission rate											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Response rate (follow-up:4 weeks)											
3 [65]	Randomised trial	Serious[a]	Not serious	Not serious	Serious[b]	None	78	72	RR 2.24 (1.51 to 3.33)	Not estimable due to non-reporting of the baseline risk either in the intervention or in the control group.	⨁⨁◯◯ Low
Serious adverse events: somatisation (follow-up: from 4 to 8 weeks)											
3 [65]	Randomised trial	Serious[a]	Not serious	Not serious	Serious[b,c]	NA	97	94	RR 1.22 (0.69 to 2.17)	Not estimable due to non-reporting of the baseline risk either in the intervention or in the control group.	⨁⨁◯◯ Low
Serious adverse events: memory deterioration (follow-up:4 weeks)											
2 [65]	Randomised trial	Serious[a]	Not serious	Not serious	Serious[b,c]	NA	57	54	RR 0.88 (0.41 to 1.88)	Not estimable due to non-reporting of the baseline risk either in the intervention or in the control group.	⨁⨁◯◯ Low

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, MD – mean difference, NA – not applicable, RR – relative risk

Comments:

[a] *Unclear risk of bias in the included studies for randomisation, allocation concealment and blinding.*

[b] *Few studies with very low number of patients.*

[c] *Wide confidence interval.*

Sources: when the systematic review by Song et al. [65] is cited, results are presented unchanged.

[111] Publication bias (undetected/strongly suspected), Large effect (no/large/very large), Plausible confounding (no/would reduce demonstrated effect/would suggest spurious effect), Dose response gradient (no/yes)

Table A-12: Evidence profile: efficacy and safety of ECT versus sham-ECT in TRS

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[112]	ECT	Sham ECT	Relative (95% CI)	Absolute (95% CI)	
Response rate (4 weeks follow-up)											
1 [73, 96]	Randomised trial	Serious[a]	Not serious	Not serious	Serious[b]	NA	13	10	Not pooled	20/% reduction on the PANSS-P: 2 vs 2 patients 30/% reduction on the PANSS-P: 1 vs 2 patients 40/% reduction on the PANSS-P: 1 vs 0 patients	⨁◯◯◯ Very low
Cognitive functioning, general functioning, quality of life, satisfaction and acceptability of treatment, remission rate											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Schizophrenia symptoms[113] (total BPRS score, follow-up: 4 weeks)											
1 [76]	Randomised trial	Not serious	Not serious	Serious[c]	Serious[b,d]	NA	NR[114]	NR	Not estimable	**MD** 3.60 higher (3.69 lower to 10.89 higher)	⨁◯◯◯ Very low
Schizophrenia symptoms (total PANSS score or CGI score, follow-up 4 weeks)											
1 [73, 96]	Randomised trial	Serious[a]	Not serious	Serious[c]	Serious[b,d]	NA	13	10	Not pooled	Total PANSS score: **MD** 2.89 higher (17.22 lower to 11.44 higher) CGI score: **MD** 0.12 point higher (0.90 lower to 0.66 higher)	⨁◯◯◯ Very low
Adverse event/effect(s) – death											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, MD – mean difference, NA – not applicable,

Comments:

[a] *High overall risk of bias of the included study/studies.*

[b] *Low number of studies with very low number of patients.*

[c] *Scores from scale were employed as a surrogate index of the intended outcome.*

[d] *Wide confidence intervals.*

Sources: when the systematic review by Sinclair et al. [76] was referenced, the results from the review were presented unchanged.

[112] Publication bias (undetected/strongly suspected), Large effect (no/large/very large), Plausible confounding (no/would reduce demonstrated effect/would suggest spurious effect), Dose response gradient (no/yes)

[113] Reported as "mental state" in Sinclair et al. [76].

[114] The total number of included patients was 25. The number of patients per study arm was not reported.

Table A-13: Evidence profile: efficacy and safety of ECT plus antipsychotics (ziprasidone) versus clozapine plus antipsychotics (ziprasidone) in TRS

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[115]	ECT	Sham ECT	Relative (95% CI)	Absolute (95% CI)	
Response rate (4 weeks follow-up)											
1 [76]	Randomised trial	Serious[a]	Not serious	Not serious	Serious[b,d]	NA	81	81	RR 1.23 (0.95 to 1.58)	668 per 1,000 (516 to 858)	⨁⨁◯◯ Low
Cognitive functioning, general functioning, quality of life, satisfaction and acceptability of treatment, remission rate											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Schizophrenia symptoms (total BPRS score, follow-up: 4 weeks)											
1 [76]	Randomised trial	Serious[a]	Not serious	Serious[c]	Serious[b,d]	NA	81	81	Not estimable	MD 5.20 lower (7.93 to 2.47 lower)	⨁◯◯◯ Very low
Adverse event/effect(s) (total TESS score, follow-up: 8 weeks)											
1 [76]	Randomised trial	Serious[a]	Not serious	Serious[c]	Serious[b]	NA	81	81	Not estimable	MD 1.1 lower (1.4 lower to 0.8 lower)	⨁◯◯◯ Very low
Adverse event/effect(s) – death											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, MD – mean difference, NA – not applicable, RR – relative risk

Comments:

[a] *High overall risk of bias of the included study/studies (high risk of bias for blinding of participants and personnel).*

[b] *Low number of studies with very low number of patients.*

[c] *Scores from scale were employed as a surrogate index of the intended outcome.*

[d] *Wide confidence intervals.*

Sources: when the systematic review by Sinclair et al. [76] was referenced, the results from the review were presented unchanged.

[115] Publication bias (undetected/strongly suspected), Large effect (no/large/very large), Plausible confounding (no/would reduce demonstrated effect/would suggest spurious effect), Dose response gradient (no/yes)

Table A-14: Evidence profile: efficacy and safety of ECT versus antipsychotics (flupenthixol) in TRS

Certainty assessment							Summary of findings					
							Number of patients		Effect			Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[116]	ECT	Sham ECT	Relative (95% CI)	Absolute (95% CI) Risk with sham ECT	Absolute (95% CI) Risk with ECT	
Satisfaction and acceptability of treatment, quality of life, response rate, remission rate												
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
General functioning (GAF, follow-up: 6 months)												
1 [76]	Randomised trial	Serious[a]	Not serious	Serious[b]	Serious[c,d]	NA	15	15	Not estimable	**MD 0.66** lower (3.6 lower to 2.28 higher)		⨁◯◯◯ Very low
Cognitive functioning (MMSE, follow-up: 6 months)												
1 [76]	Randomised trial	Serious[a]	Not serious	Serious[b]	Serious[c,d]	NA	15	15	Not estimable	**MD 0.2** lower (3.7 lower to 3.3 higher)		⨁◯◯◯ Very low
Schizophrenia symptoms (total BPRS score, follow-up: 6 months)												
1 [76]	Randomised trial	Serious[a]	Not serious	Serious[b]	Serious[c,d]	NA	15	15	Not estimable	**MD 0.93** lower (6.95 lower to 5.09 higher)		⨁◯◯◯ Very low
Adverse event/effect(s) – death												
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, MD – mean difference, NA – not applicable, RR – relative risk

Comments:

[a] *High overall risk of bias of the included study/studies (high risk of bias for blinding of participants and personnel).*

[b] *Scores from scale were employed as a surrogate index of the intended outcome.*

[c] *Low number of studies with very low number of patients.*

[d] *Wide confidence intervals.*

Sources: when the systematic review by Sinclair et al. [76] was referenced, the results from the review were presented unchanged.

[116] Publication bias (undetected/strongly suspected), Large effect (no/large/very large), Plausible confounding (no/would reduce demonstrated effect/would suggest spurious effect), Dose response gradient (no/yes)

Table A-15: Evidence profile: efficacy and safety of ECT plus standard care versus standard care in TRS

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[116]	ECT	Sham ECT	Relative (95% CI)	Absolute (95% CI)	
Response rate (follow-up: 8 to 12 weeks)											
9 [76]	Randomised trial	Serious[a]	Not serious	Not serious	Not serious	NA	410	409	RR 2.06 (1.75 to 2.42)	327 more per 1,000 (from 231 to 438 more)	⨁⨁⨁◯ Moderate
Satisfaction and acceptability of treatment (follow-up: 8 to 12 weeks)											
3 [76]	Randomised trial	Serious[a]	Not serious	Not serious	Serious[c,d]	NA	177	177	RR 1.18 (0.38 to 3.63)	4 more per 1,000 (from 9 less to 83 more)	⨁◯◯◯ Very low
General functioning (GAF, follow-up: 12 weeks to 6 months)											
2 [76]	Randomised trial	Serious[a]	Serious[e]	Serious[b]	Serious[f]	NA	47	50	Not estimable	**MD 10.66** higher (6.98 to 14.34 higher)	⨁◯◯◯ Very low
Cognitive functioning, remission rate											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Schizophrenia symptoms (total BPRS score, follow-up: 4 weeks)											
2 [76]	Randomised trial	Serious[a]	Not serious	Serious[b]	Not serious	NA	173	172	Not estimable	**MD 11.18** lower (12.61 lower to 9.76 lower)	⨁⨁◯◯ Low
Schizophrenia symptoms (total PANSS score, follow-up up to 6 weeks)											
7 [74, 84, 87, 90, 92-94]	Randomised trial	Serious[a]	Serious[e]	Serious[b]	Not serious	NA	245	247	Not estimable	**MD 24.06** lower (25.21 lower to 22.91 lower).	⨁◯◯◯ Very low
Adverse event/effect(s) – death											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Adverse events[117] (memory deterioration, follow-up: 3 to 4 weeks)											
1 [76]	Randomised trial	Serious[a]	Not serious	Serious[b]	Serious[c]	NA	36	36	RR 27 (1.67 to 437.68)	13 more per 1,000 (from 1 to 219 more)	⨁◯◯◯ Very low

Abbreviations: CI – confidence interval, ECT – electroconvulsive therapy, MD – mean difference, NA – not applicable, RR – relative risk

Comments:

[a] *High overall risk of bias of the included study/studies (high risk of bias for blinding of participants and personnel).*

[b] *Scores from scale were employed as a surrogate index of the intended outcome.*

[c] *Low number of studies with low event rate.*

[d] *Wide confidence interval.*

[e] *High heterogeneity between studies.*

[f] *Low number of studies with small sample size.*

Sources: when the systematic review by Sinclair et al. [76] was referenced, the results from the review were presented unchanged.

[117] Reported as „cognitive functioning" in Sinclair et al. [76].

Applicability table

Table A-16: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	**Depression:** The general characteristics if the enrolled patients were homogenous in terms of age as the mean age in most studies ranged between early 30s to mid-40s. Only 3 studies had a mean age above 60 years old. We could not identify any RCTs or SR with RCTs including children and adolescents. Moreover, the mean depression scores were consistent across studies comparing ECT to ketamine ranging between 26-35 and in studies comparing ECT to rTMS ranging between 26-40. The diagnosis criteria were not consistent across studies as some studies included patients who failed one or more lines of previous therapy while others included patients who failed at least two lines. Some studies included patients who previously received ECT while others did not. The number of previous failed treatments might influence the effectiveness of ECT. Furthermore, some studies included patients with psychotic features while others did not. This could affect the ECT effectiveness since patients with psychotic features might have higher suicidal risks and more severe depressive symptoms. **Schizophrenia:** The mean age of participants ranged from 19 to 46, indicating a broader age range of included patients. Older patients (over 60 years) were not represented in the studies (only one study including patients between 18-74 years old). We could not identify studies including children and adolescents. All participants were diagnosed with TRS based on international standards.
Intervention	**Depression:** The frequency and duration of ECT in most studies was consistent with the recommended practice which was given 2-3 times per week for 6-12 session or till complete remission. Only one study administered ECT for only 3 sessions. Regarding the electrode placement, most studies used bilateral placement which is associated with the greatest antidepressant efficacy and quickest speed of response, but may cause the most memory impairment, some studies allowed switching from unilateral to bilateral if no response was detected. Three studies used unilateral electrode placement. The choice of electrode placement could affect the effectiveness as well as the adverse reactions of ECT. ECT was used as combination with other types of medications rather than monotherapy in most studies, this might have an impact on the efficacy of ECT by having lower relapse rates. Some studies used ultrabrief pulse while others used brief pulse ECT but in the vast majority it's not reported (76%). The choice of pulse might affect the efficacy and the adverse reaction of ECT as brief pulse is considered standard due to its efficacy compared with ultra-brief pulse; however, ultra-brief pulse is a reasonable alternative based upon its superior tolerability. **Schizophrenia:** The frequency and duration of ECT in most studies was consistent with the recommended practice. Most studies administered ECT 3 times per week for two to four weeks (6-12 sessions). Some studies used a longer duration (14-20 sessions). Regarding the electrode placement, it was only reported in some studies, and it was bilateral which might have an impact on the adverse reactions but usually it is associated with better efficacy. All included studies used ECT plus standard care, with only one arm in one study ECT as sole intervention.
Comparators	**Depression:** The choice of comparators was based on the latest guidelines. The choice included pharmacotherapies (antidepressants, lithium, ketamine and antipsychotics) as well as non-pharmacotherapy including rTMS and psychotherapy. We have not identified any RCTs comparing ECT with psychotherapy alone or in combination. We also could not identify studies comparing ECT with antipsychotics. The included studies present evidence on antidepressants, ketamine, and rTMS, likely representing the available standard of care options. However, the lack of evidence on the use of psychotherapy might influence the perceived treatment effect of these treatments considerably. **Schizophrenia:** The choice of comparators was based on the latest guidelines. The choice included pharmacotherapies (clozapine, flupenthixol, and chlorpromazine) as well as non-pharmacotherapy including cognitive therapy and psychotherapy. We could not identify any RCTs comparing ECT with psychotherapy or cognitive therapy alone or in combination. The included studies present evidence on various pharmacotherapies, potentially reflecting the available standard of care options. However, the lack of evidence on the use of psychotherapy and cognitive therapy might influence the perceived treatment effect of these treatments considerably.

Outcomes	**Depression:** Primary outcomes in the reviewed studies included changes in depression scores, remission, and response rates. However, critical data on mortality, suicidal attempts, and ideation were seldom reported. Additionally, quality of life was assessed in only one study, and adverse events were rarely reported on. Given the higher prevalence of suicide risk among TRD patients and its life-threatening nature, the lack of measurement of suicidal behaviour and ideation significantly impedes the evaluation of clinical benefits in this context. The length of follow-up periods varied for the various outcomes and for the various comparators. Short-term efficacy was measured in the studies, but longer-term follow-up was absent for depression score, cognitive and general functioning, quality of life, as well as memory deterioration (adverse event) in the rTMS and in the antidepressant comparisons. **Schizophrenia:** Response to treatment and schizophrenia symptoms were the outcomes reported most frequently. Critical outcomes such as mortality and suicidal attempts or ideation were not reported. Moreover, important outcomes such as quality of life was not reported and data on adverse events was scarce. The length of follow-up periods varied for the various outcomes and for the various comparators. Short-term efficacy was measured in the studies, but longer-term follow-up was absent for schizophrenia symptom scores, cognitive functioning, quality of life and remission rates in the sham-ECT, the standard of care and the antipsychotics plus clozapine comparisons.
Setting	**Depression:** All but one study on antidepressants versus ECT were conducted in China. Ketamine and rTMS comparative studies were conducted in Germany, the United States, United Kingdom, Sweden, Iran, Egypt, Brazil, Israel and Australia, representing a broad range of geographical regions. At the same time, there is no reason to suspect that the aetiology of MDD and TRD is substantially different in the various regions. It was not reported in the majority of studies if the intervention took place as inpatient or outpatient treatment. When reported, the clinical setting used in the studies reflects the setting in which the intervention will be typically used. **Schizophrenia:** Most participants were recruited from China. Others were from Brazil, United States, Thailand and India. There is no reason to suspect that the aetiology of TRS is substantially different from other countries. The setting in the included studies was inpatient (hospital), only one study reporting both in- and outpatient use. This reflects the setting in which the intervention will be typically used.

List of ongoing randomised controlled trials

Table A-17: List of ongoing randomised controlled trials with ECT

Identifier/Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT03272698	Treatment-resistant depression (TRD)	Ketamine	Ketamine-ECT	Number of treatments required to reach remission as defined by a reduction of MADRS score to <10, assessed up to 4 weeks.	December 30th, 2024	University of Saskatchewan
NCT06034821	Acute suicidal depression	Ketamine	ECT	Beck Scale for Suicidal Ideation (BSSI)	January 1st, 2030	Brigham and Women's Hospital
CTRI/2024/01/061652	Major depressive disorder (MDD), recurrent severe without psychotic features	ECT	Ketamine	Neurocognitive side effects 1 week and 1-month post-treatment	NR	Department of Psychiatry Sion hospital
CTRI/2024/01/060984	MDD, single episode and recurrent, moderate MDD single episode, severe without psychotic features	Ketamine	ECT	Change in MADRS score at 1-week post-treatment	NR	Dr Susanta Kumar Padhy
CTRI/2023/06/053779	MDD, recurrent severe without psychotic features	Ketamine	ECT	Efficacy and safety	NR	Lavanya Seth
CTRI/2022/11/047630	Bipolar disorder MDD single episode and recurrent, severe without psychotic features	Ketamine	ECT	50% reduction in HDRS-17 over a course of 3 interventions	NR	Kles Academy of Higher Education and Research
CTRI/2021/07/035210	MDD single episode, severe without psychotic features	Ketamine	ECT	Scores on the BSSI	NR	Central Institute of Psychiatry Ranchi
CTRI/2020/08/027340	MDD TRD	ECT	Ketamine	Response to treatment (at least 50% improvement of QIDS-SR-16 score)	Mat 31st, 2020	Ahana hospitals LLP
CTRI/2019/09/021184	Bipolar disorder MDD	Ketamine	ECT	Antidepressant effects	April 30th, 2018	National Institute of Mental Health and Neurosciences Bengaluru
IRCT20090801002266N8	MDD, recurrent severe without psychotic features	IV Ketamine Oral Ketamine ECT	IV Ketamine Oral Ketamine ECT	Depression score on HDRS-17	NR	Esfahan University of Medical Sciences
NCT05047159	MDD	Drug therapy rTMS with drug therapy ECT with drug therapy Light therapy with drug therapy	Drug therapy rTMS with drug therapy ECT with drug therapy Light therapy with drug therapy	Change of the HAMD-17 score Response rate Remission rate	March 30th, 2024	Shanghai Mental Health Center

Identifier/Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
ChiCTR2000039393	MDD	Antidepressants Modified ECT rTMS	Antidepressants Modified ECT Sham-rTMS	HAMD	NR	ongji Hospital of Tongji University
CTRI/2021/05/033775	Schizophrenia	ECT	Sham-ECT	At least 40% improvement in SAPS scores	NR	Department of Psychiatry National Institute of Mental Health and Neuro Sciences
IRCT20221224056914N1	MDD single episode, severe without psychotic features	ECT rTMS tDCS one of the drugs of the SSRI class with an antidepressant dose	ECT rTMS tDCS one of the drugs of the SSRI class with an antidepressant dose	Depression score on Beck scale (BDI score)	NR	Zanjan University of Medical Sciences
CTRI/2018/06/014545	MDD, recurrent severe without psychotic features TRD	ECT	tDCS	Response to treatment (at least 50% improvement in BDI score)	December 31st, 2018	
NCT05054699	MDD Bipolar depression	MST	ECT	Depressive symptoms score on HDRS-17, Biographical memory as score on the AMT	June 1st, 2024	University of Sao Paulo
NCT03191058	Unipolar Depression TRD	MST	ECT	Symptom severity as measured by the HDRS-24 Cognitive adverse effects (measured by the AMT)	July, 2024	University of Texas Southwestern Medical Center
NCT04441008	MDD Suicidal patients	aiTBS	ECT	Retention rate at completion	December, 2025	University of Iowa
NCT03711019	Bipolar depression Unipolar depression TRD	MST	Unilateral ultrabrief ECT Bitemporal ECT	Difference in HDRS-24 scores at 6 months Cognitive adverse effects (measured by the AMT)	March, 2024	University of British Columbia, Shores Centre for Mental Health Sciences, Brain Canada
CTRI/2021/05/033784	MDD single episode and recurrent	tDCS	ECT	Improvement in HAMD-17 scale. Score of more than or equal to 50% from baseline	NR	Department of Psychiatry National Institute of Mental Health and Neuro Sciences
CTRI/2021/09/036693	Bipolar disorder MDD Other depressive disorders	FEAST	ECT	Effectiveness	NR	GMC Patiala

Abbreviations: aiTBS – accelerated intermittent theta burst, AMT – Autobiographical Memory Test, BDI-Beck's Depression Inventory, ECT – electroconvulsive therapy, FEAST – focal electrically-administered seizure therapy, HAM-D/HDRS -Hamilton Depression Scale, IV – intravenous, MADRS – Montgomery-Asberg Depression Rating Scale, MDD – major depressive disorder, MST – magnetic seizure therapy, NR – not reported, SAPS- Scale for the Assessment of Positive Symptoms, SSRI-Selective Serotonin Reuptake Inhibitor, tDCS- transcranial direct current stimulation, TRD – treatment-resistant depression, QIDS-SR- Quick Inventory of Depressive Symptomatology-Self-Report, rTMS – repetitive transcranial magnetic stimulation, RUL-UB-right unilateral ultrabrief pulse.

Research questions

Table A-18: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table A-19: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and in what context and level of care is it?
B0008	What kind of special premises are needed to use the technology?
B0009	What supplies are needed to use the technology?
A0021	What is the reimbursement status of the technology?

Table A-20: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?

Table A-21: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?

Outcomes scales and measures

Table A-22: Outcome measures and scales

Name of measurement instrument	Description
Depression and schizophrenia	
Functional outcomes: General functioning	
Global Assessment of Functioning (GAF) [102]	Rates how serious a mental illness may be. It measures how much a person's symptoms affect their day-to-day life on a scale of 0 to 100. Higher scores indicate better functioning. Regarding MCID, there is no consensus based, internationally accepted threshold but one study suggested using 4 as the MCID [103].
Sheehan Disability Scale (SDS) [104]	Assesses functional impairment in three inter-related domains: work/school, social and family life on a 10-point visual analogue scale. There is no recommended cut off score. Higher scores indicate greater impairment in functioning.
Social Adjustment Scale-Self Report (SAS-SR) [105]	Assesses role performance in the past 2 weeks across six domains: work/school role, social/leisure time, family outside the home, primary relationship, parental role, and family unit. Each item is rated on a 5-point scale. Higher scores indicate greater impairment in functioning.
Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [106]	Self-report measure designed to enable investigators to easily obtain sensitive measures of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. Higher scores indicate greater life satisfaction and enjoyment.
Functional outcomes: Cognitive functioning	
Montreal Cognitive Assessment (MoCA) [107]	Simple test that can detect mild cognitive impairment and the early onset of dementia. It does so based on 11 questions that evaluate seven domains of cognitive function. The MoCA has a maximum score of 30, and anything below 24 is a sign of cognitive impairment
Trail Making Test (TMT) [108]	Involves visual scanning and working memory. The TMT has two parts: the TMT-A (rote memory) and TMT-B (executive functioning). It is scored by how long it takes to complete the test. An average score for TMT-A is 29 seconds and a deficient score is greater than 78 seconds. For TMT-B, an average score is 75 seconds, and a deficient score is greater than 273 seconds.
Rey Auditory Verbal Learning Test (RAVLT) [109]	Evaluates a wide diversity of functions: short-term auditory-verbal memory, rate of learning, learning strategies, retroactive, and proactive interference, presence of confabulation of confusion in memory processes, retention of information, and differences between learning and retrieval Participants are given a list of 15 unrelated words repeated over five different trials and are asked to repeat. Another list of 15 unrelated words is given and the participant must again repeat the original list of 15 words and then again after 30 minutes.
Digit Span Test (DSP) [110, 111]	Subjects are asked to repeat a sequence of numbers to the examiner in order (forward span) and in reverse order (backward span). This test is used to assess selective attention and working memory. Scores are based on digits forward, digits backwards, and total score, with higher scores indicating better performance.
Stroop Color Word Test-Victoria version (SCWT) [112]	A measure of executive function commonly used in neuropsychological evaluation. This test uses three conditions that consist in naming the color of dots, of neutral words, and of color words printed in incongruent colors. Each condition contains 24 items. The score is the time in seconds, with higher scores indicating worse performance.
Color Trails Test (CTT) [113]	A language-free version of the TMT that was developed to allow for broader cross-cultural assessment of sustained attention and divided attention in adults. Subjects first rapidly connect circles numbered 1 to 25 in sequence, and then again rapidly connect the circles in sequence but alternate between pink and yellow circles. Scoring is done in terms of the time in seconds required for each part of the test; the shorter the time, the better the score.
Rey-Osterrieth Complex Figure Test (ROT) [114]	Evaluates visuo-constructional ability and non-verbal memory in clinical practice and research. It includes immediate copy and delayed recall. Subjects copy complex geometric shapes and then reproduce them from memory. Higher scores indicate a more efficient planning and strategic approach to making the copy.
Schizophrenia Cognition Rating Scale (ScoRS) [115]	An interview-based measure of cognitive impairment with questions aimed at the degree to which this impairment affects day-to-day functioning. It consists of seven cognitive domains and includes 20 items. Each item is rated on a scale ranging from 1-4 with higher scores reflecting a greater degree of impairment.
Global Self Evaluation of Memory (GSE-My) [116]	Self-reported scale of global memory. Likert-like scale from one to seven with "one" indicating extreme negative effect and "seven' indicating extreme positive effect.
Squire Memory Complaint Questionnaire (SMCQ) [59]	Self-report of memory complaints questionnaire which can differentiate between before and after ECT. Range -72 - +72. Higher scores indicating better memory function.

Name of measurement instrument	Description
Hopkins verbal Learning Test – Revised (HVLT-R) [117]	A verbal memory task with 12 words learned over three trials, with the correct words summed. The total range is 0-36. The Delayed Recall score is the number of correct words recalled after a 20-25-minute delay range: 0-2. Higher values indicate better performance.
Wechsler Memory Scale (WMS) [118]	Contains index scores and subtest scores to describe different aspects of memory function. It assesses visual and auditory memory functions in a comprehensive manner, includes immediate and delayed memory subscales to verify deficits of short-term memory and long-term memory and is appropriate for illiterate people. Higher index score and subtest scaled score indicate better memory function.
Mini-Mental State Examination (MMSE) [119]	A clinician-administered rating measure used to assess mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment
Symptom outcomes	
Clinical Global Impression (CGI) [120, 121]	Clinician-rated measure of global symptom severity and treatment response for patients with mental disorders. CGI has two components—the CGI-Severity, which rates illness severity, and the CGI-Improvement, which rates change from the initiation (baseline) of treatment. Higher scores indicate more severe symptoms. CGI-I of "minimally improved" is considered the clinical gold standard for minimum clinically important difference [122].
Patient Global Impression (PGI) [123, 124]	Self-report measure of change in clinical status (PGI-C), disease severity (PGI-S) or disease improvement (PGI-I). Higher scores indicate more severe symptoms.
Quality of life	
Quality of Life Scale (QoLS-16) [125]	Self-reported 16-item questionnaire which measures quality of life in six domains: material and physical well-being, relationships with other people, social, community and physical activities; personal development and fulfilment; recreation; and independence. Higher score indicates higher quality of life.
Suicide-related outcomes	
Beck Scale for Suicidal Ideation (BSSI) [126]	Self-reported 19-item scale preceded by five screening items intended to assess a patient's thoughts, plans and intent to commit suicide. All 24 items are rated on a three-point scale (0 to 2), total scores could range from 0 to 48. No specific cut-off scores exist to classify severity or guide patient management. Increasing scores reflect greater suicide risk.
Columbia – Suicide Severity Rating Scale (C-SSRS) [127]	The scale was designed to distinguish between suicidal ideation and suicidal behaviour. It consists of 18 items and has been shown to predict suicide attempts in both suicidal and non-suicidal individuals. The scale is a validated instrument to evaluate the severity of suicidal ideation, the intensity of ideations, and the history of suicide attempts.
Subscore on the BDI, HAM-D/HDRS scales	A single item on the scale related to suicidal thoughts.
Depression	
Symptom outcomes	
Hamilton Rating Scale for Depression (HAM-D or HDRS) [128, 129]	Clinician administered scale that is used to assess severity of, and change in, depressive symptoms. Each section of the HAM-D has a rating scale, some ranging from 0-4 and others ranging from 0-2. Lower numbers do align with milder symptoms. Regarding MCID, there is no consensus based, internationally accepted threshold. However, it was reported that MID estimates are likely to be between 3 and 5 points [130].
Montgomery Asberg Depression Rating Scale (MADRS) [131]	Clinician administered measure of depression severity. It consists of 10 items; each item is rated on a 0-6 scale, resulting in a maximum total score of 60 points, with higher scores indicative of greater depressive symptomology. Regarding MCID, there is no consensus based, internationally accepted threshold. However, it was reported that MID estimates are likely to be between 1.6 and 1.9 [122].
Patient Health Questionnaire (PHQ-9) [132]	Self-administered by patients and verified by clinicians. Multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. Higher scores indicate more severe depressive symptoms. Regarding MCID, there is no consensus based, internationally accepted threshold. However, it was reported that MCID estimates ranged between 2-4.8 with a final threshold of 3 [133].
Quick Inventory of Depressive Symptomatology-Self-Report Scale (QIDS-SR) [134]	A self-reported 16-item questionnaire to assess the severity of depressive symptoms. Scores range from 0 to 27 with scores of 5 or lower indicative of no depression, scores from 6 to 10 indicating mild depression, 11 to 15 indicating moderate depression, 16 to 20 reflecting severe depression, and total scores greater than 21 indicating very severe depression. Regarding MCID, there is no consensus based, internationally accepted threshold. However, it was reported that MCID estimates of ≥28.5% ± 28.7% change [122].
Beck Depression Inventory (BDI) [135]	A self-reported 21-question multiple-choice inventory for measuring the severity of depression. Higher total scores indicate more severe depressive symptoms. Regarding MCID, there is no consensus based, internationally accepted threshold. However change of at least 5 points after treatment has been reported [136].

Name of measurement instrument	Description
Schizophrenia	
Symptom outcomes	
Positive and Negative Syndrome Scale (PANSS) [137] [76]	A clinician-administered 30-item rating scale including three subscales for measuring the severity of positive symptoms, negative symptoms, and general psychopathology. Each item is rated on a 7-point scale. The possible scores range from 30 to 210, with higher scores indicating a worse outcome. Regarding MCID, there is no consensus based, internationally accepted threshold. However, in one study, it was reported that the MCID calculated varied from 14.02 to 31.50 for PANSS, 15.14 to 42.79% for PANSS reduction rate [97].
Scale for the Assessment of Positive Symptoms (SAPS) [76, 137]	A clinician-administered instrument to assess the positive symptoms of schizophrenia. Each item is based on a 6-point scale. Higher scores indicate more severe symptoms.
Scale for the Assessment of Negative Symptoms (SANS) [76, 137]	A clinician-administered instrument to assess the negative symptoms of schizophrenia. Each item is based on a 6-point scale. Higher scores indicate more severe symptoms.
Brief Psychiatric Rating Scale (BPRS) [138]	A clinician-administered 18-item rating scale measuring the positive, negative, and affective symptoms of individuals who have psychotic disorders. The possible scores range from 18 to 126, with high scores indicating more severe symptoms. Regarding MCID, there is no consensus based, internationally accepted threshold. However, BPRS reduction of 24% at week 1, 27% at week 2, and 30% at week 4 is considered minimal improvement [122].

Abbreviations: MCID – minimally clinically important difference.

Literature search strategies

Search strategy for Systematic reviews

Search strategy for Medline via Ovid for Depression 2017-2023

Database: Ovid MEDLINE(R) ALL <1946 to January 23, 2024>		
Search name: ECT for Depression SRs (2017-2023)		
ID	Query	Results
#1	exp Electroconvulsive Therapy	14,387
#2	electro?convuls*.mp.	18,652
#3	electro-convuls*.mp.	327
#4	(convulsi* adj5 electr*).mp.	1,960
#5	exp Electroshock/	32,460
#6	electro?shock*.mp.	15,391
#7	electro-shock*.mp.	158
#8	(electr* adj shock*).mp.	6,728
#9	ECT.ti,ab.	10,808
#10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	45,022
#11	exp Depression/	154,903
#12	exp Depressive Disorder/	123,673
#13	depress*.mp.	667,415
#14	exp Depressive Disorder, Treatment-Resistant/	2,246
#15	treatment-resistant.mp.	13,440
#16	11 or 13	667,415
#17	15 and 16	6,242
#18	14 or 17	6,242
#19	10 and 18	942
#20	limit 19 to (meta analysis or "systematic review")	52
#21	limit 20 to yr="2017 – 2023"	32
#22	limit 21 to (english or german)	31

Search strategy for primary studies

Cochrane Database

Search Name: ECT for Depression and Schizophrenia	
Search date: 22/12/2023	
ID	Search
#1	MeSH descriptor: [Electroconvulsive Therapy] explode all trees
#2	(electro*convuls*) (Word variations have been searched)
#3	electro-convuls* (Word variations have been searched)
#4	(convulsi* NEAR electr*):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Electroshock] explode all trees
#6	(electro*shock*) (Word variations have been searched)
#7	(electro-shock*) (Word variations have been searched)
#8	(electr* NEAR shock*):ti,ab,kw (Word variations have been searched)

#9	(ECT):ti,ab,kw
#10	MeSH descriptor: [Transcranial Magnetic Stimulation] explode all trees
#11	(((repetiti* OR repeat*) NEAR (transcrani* OR magnet*)) AND stimul*):ti,ab,kw (Word variations have been searched)
#12	rTMS:ti,ab,kw
#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] explode all trees
#15	MeSH descriptor: [Depressive Disorder, Major] explode all trees
#16	MeSH descriptor: [Depression] explode all trees
#17	MeSH descriptor: [Depressive Disorder] explode all trees
#18	(depress*) (Word variations have been searched)
#19	#16 OR #17 OR #18
#20	(treatment-resist*) (Word variations have been searched)
#21	(major)
#22	#20 OR #21
#23	#19 AND #22
#24	((major OR severe OR treatment-resist* OR bipolar) NEAR depress*):ti,ab,kw (Word variations have been searched)
#25	(TRD):ti,ab,kw
#26	MeSH descriptor: [Schizophrenia, Treatment-Resistant] explode all trees
#27	(schizophreni*) (Word variations have been searched)
#28	treatment-resist* (Word variations have been searched)
#29	#27 AND #28
#30	(treatment-resist* NEAR schizophreni*):ti,ab,kw (Word variations have been searched)
#31	(TRS):ti,ab,kw (Word variations have been searched)
#32	#14 OR #15 OR #23 OR #24 OR #25 OR #26 OR #29 OR #30 OR #31
#33	#13 AND #32
#34	#13 AND #32 with Publication Year from 2017 to 2023, in Trials
#35	#13 AND #32 with Cochrane Library publication date Between Dec 2016 and Dec 2023
#36	#34 OR #35
#37	English:la
#38	German:la
#39	#37 OR #38
#40	#36 AND #39
#41	(conference proceeding):pt
#42	(abstract):so
#43	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#44	#41 OR #42 OR #43
#45	#40 NOT #44
Total hits: 731	

Embase

Search Name: ECT for Depression and Schizophrenia		
Search date: 22.12.2023		
ID	Query	Results
#41	#39 NOT #40	889
#40	#39 AND 'Conference Abstract'/it	486
#39	#38 AND ([english]/lim OR [german]/lim)	1,375
#38	#37 AND [30-12-2016]/sd NOT [23-12-2023]/sd	1,392
#37	#33 OR #35 OR #36	2,468
#36	#32 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	884
#35	#32 AND #34	1,257
#34	((double NEXT/1 blind*):de,ab,ti) OR placebo*:ab,ti OR blind*:ab,ti	742,402
#33	#13 AND #31 AND [randomized controlled trial]/lim	1,166
#32	#13 AND #31	12,495
#31	#14 OR #15 OR #22 OR #23 OR #24 OR #25 OR #28 OR #29 OR #30	414,064
#30	trs:ti,ab,kw	5,371
#29	'treatment resist*' NEAR/2 schizophreni*	2,834
#28	#26 AND #27	4,551
#27	'treatment-resist*'	31,073
#26	schizophreni*	260,726
#25	'treatment-resistant schizophrenia'/exp	1,274
#24	trd:ti,ab,kw	4,026
#23	(major OR severe OR 'treatment resist*' OR bipolar) NEAR/2 depress*	135,472
#22	#18 AND #21	392,221
#21	#19 OR #20	7,146,307
#20	major	7,126,634
#19	'treatment-resist*'	31,073
#18	#16 OR #17	1,057,906
#17	depress*	1,009,575
#16	'depression'/exp	660,833
#15	'major depression'/exp	85,237
#14	'treatment resistant depression'/exp	5,452
#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	91,415
#12	rtms:ti,ab,kw	10,123
#11	(repetiti* OR repeat*) NEAR/1 (transcrani* OR magnet* OR stimul*)	19,937
#10	'transcranial magnetic stimulation'/exp	32,491
#9	ect:ti,ab,kw	15,992
#8	electr* NEAR/1 shock*	18,361
#7	'electro-shock*'	190
#6	electro*shock*	5,691
#5	'electric shock'/exp	13,797
#4	convulsi* NEAR/4 electr*	2,266
#3	'electro-convuls*'	525
#2	electro*convuls*	27,056
#1	'electroconvulsive therapy'/exp	24,245

Search strategy for Medline via Ovid

Datababse: Ovid MEDLINE(R) ALL <1946 to December 21, 2023>		
Search name: ECT for Depression and Schizophrenia		
ID	Query	Results
#1	exp Electroconvulsive Therapy	14,373
#2	electro?convuls*.mp.	18,618
#3	electro-convuls*.mp.	326
#4	(convulsi* adj5 electr*).mp.	1,957
#5	exp Electroshock/	32,384
#6	electro?shock*.mp.	15,387
#7	electro-shock*.mp.	158
#8	(electr* adj shock*).mp.	6,721
#9	ECT.ti,ab.	10,748
#10	exp Transcranial Magnetic Stimulation/	15,265
#11	((repetiti* or repeat*) adj3 (Transcrani* adj3 Magnet* Stimul*)).mp.	6,562
#12	rTMS.ti,ab.	6,222
#13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	61,097
#14	exp Depressive Disorder, Treatment-Resistant/	2,226
#15	exp Depressive Disorder, Major/	39,439
#16	exp Depression/	154,134
#17	exp Depressive Disorder/	123,334
#18	depress*.mp.	664,495
#19	16 or 17 or 18	665,269
#20	treatment-resist*.mp.	1,8805
#21	major.mp.	1,737,343
#22	20 or 21	1,751,812
#23	19 and 22	102,083
#24	((major or severe or treatment-resist* or bipolar) adj3 depress*).mp.	89,667
#25	TRD.ti,ab.	2,486
#26	exp Schizophrenia, Treatment-Resistant/	144
#27	schizophreni*.mp.	168,380
#28	20 and 27	2,525
#29	(treatment-resist* adj3 schizophreni*).mp.	1,792
#30	TRS.ti,ab.	3,900
#31	14 or 15 or 23 or 24 or 25 or 26 or 28 or 29 or 30	122,893
#32	13 and 31	6,046
#33	limit 32 to randomized controlled trial	641
#34	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1,490,566
#35	32 and 34	1,315
#36	limit 32 to (meta analysis or "systematic review")	304
#37	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.	737,630
#38	32 and 37	649
#39	33 or 35 or 36 or 38	1,701

#40	limit 39 to dt=20161230-20231220	830
#41	limit 39 to ed=20161230-2023122	739
#42	40 or 41	888
#43	limit 42 to (english or german)	873
#44	remove duplicates from 43	870

Search strategy for HTA-INATHTA

Search Name: ECT for Depression and Schizophrenia	
Search date: 22/12/2023	
ID	Search
43	(((((TRS) OR (("treatment-resistant") AND (schizophreni*)) OR (("treatment-resistant") AND (schizophreni*)) OR ("Schizophrenia Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]))) FROM 2016 TO 2023) AND (English OR German)[Language]) OR (((((TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe]))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]))) FROM 2016 TO 2023) AND (English OR German)[Language]),"18","2023-12-21T17:07:49.000000Z"
42	((((TRS) OR (("treatment-resistant") AND (schizophreni*)) OR (("treatment-resistant") AND (schizophreni*)) OR ("Schizophrenia Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]))) FROM 2016 TO 2023) AND (English OR German)[Language],"1","2023-12-21T16:05:50.000000Z"
41	(((TRS) OR (("treatment-resistant") AND (schizophreni*)) OR (("treatment-resistant") AND (schizophreni*)) OR ("Schizophrenia Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]))) FROM 2016 TO 2023,"1","2023-12-21T16:05:16.000000Z"
40	((TRS) OR (("treatment-resistant") AND (schizophreni*)) OR (("treatment-resistant") AND (schizophreni*)) OR ("Schizophrenia Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe])),"2","2023-12-21T16:04:43.000000Z"
39	((TRS) OR (("treatment-resistant") AND (schizophreni*)) OR (("treatment-resistant") AND (schizophreni*)) OR ("Schizophrenia Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe])),"2","2023-12-21T16:04:25.000000Z"
38	((TRS) OR (("treatment-resistant") AND (schizophreni*)) OR (("treatment-resistant") AND (schizophreni*)) OR ("Schizophrenia Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe])),"2","2023-12-21T16:03:40.000000Z"
37	(TRS) OR (("treatment-resistant") AND (schizophreni*)) OR (("treatment-resistant") AND (schizophreni*)) OR ("Schizophrenia Treatment-Resistant"[mhe]),"10","2023-12-21T16:02:58.000000Z"
36	TRS,"2","2023-12-21T16:02:20.000000Z"
35	("treatment-resistant") AND (schizophreni*),"9","2023-12-21T16:01:58.000000Z"
34	("treatment-resistant") AND (schizophreni*),"9","2023-12-21T16:01:15.000000Z"
33	"treatment-resistant","68","2023-12-21T16:01:06.000000Z"
32	schizophreni*,"116","2023-12-21T16:00:40.000000Z"
31	"Schizophrenia Treatment-Resistant"[mhe],"0","2023-12-21T16:00:17.000000Z"

30	((((TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe]))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]))) FROM 2016 TO 2023) AND (English OR German)[Language],"18","2023-12-21T15:50:40.000000Z"
29	(((TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe]))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]))) FROM 2016 TO 2023,"21","2023-12-21T15:50:15.000000Z"
28	((TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe]))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe])),"35","2023-12-21T15:50:00.000000Z"
27	((TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe]))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe])) AND ((rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe])),"35","2023-12-21T15:49:18.000000Z"
26	(TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe]))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe]),"182","2023-12-21T15:49:00.000000Z"
25	TRD,"12","2023-12-21T15:47:58.000000Z"
24	(major OR severe OR "treatment-resistant") AND (depress*),"168","2023-12-21T15:47:38.000000Z"
23	((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe])),"123","2023-12-21T15:46:28.000000Z"
22	(major) OR ("treatment-resistant"),"817","2023-12-21T15:46:12.000000Z"
21	major,"772","2023-12-21T15:46:02.000000Z"
20	"treatment-resistant","68","2023-12-21T15:44:38.000000Z"
19	(depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe]),"483","2023-12-21T15:43:47.000000Z"
18	depress*,"458","2023-12-21T15:43:36.000000Z"
17	"Depressive Disorder"[mhe],"173","2023-12-21T15:43:19.000000Z"
16	"Depression"[mhe],"167","2023-12-21T15:42:54.000000Z"
15	"Depressive Disorder Major"[mhe],"59","2023-12-21T15:42:30.000000Z"
14	"Depressive Disorder Treatment-Resistant"[mhe],"33","2023-12-21T15:41:44.000000Z"
13	(rTMS) OR ((repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*)) OR ("Transcranial Magnetic Stimulation"[mhe]) OR (ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]),"98","2023-12-21T15:41:08.000000Z"
12	rTMS,"25","2023-12-21T15:39:45.000000Z"
11	(repetiti* OR repeat*) AND (transcrani* OR magnet* OR stimul*),"43","2023-12-21T15:39:21.000000Z"
10	"Transcranial Magnetic Stimulation"[mhe],"48","2023-12-21T15:38:19.000000Z"
9	ECT,"23","2023-12-21T15:36:25.000000Z"
8	(electr*) AND (shock*),"12","2023-12-21T15:36:01.000000Z"
7	electro-shock*,"0","2023-12-21T15:35:22.000000Z"
6	electroshock*,"0","2023-12-21T15:35:09.000000Z"
5	"Electroshock"[mhe],"13","2023-12-21T15:34:45.000000Z"
4	(convulsi*) AND (electr*),"6","2023-12-21T15:34:19.000000Z"
3	electro-convuls*,"0","2023-12-21T15:33:42.000000Z"
2	electroconvuls*,"20","2023-12-21T15:32:24.000000Z"
1	"Electroconvulsive Therapy"[mhe],"10","2023-12-21T15:31:30.000000Z"
Total hits: 18	

Cochrane Database

Search Name: ECT for Depression (2014-2016)	
Search date: 08/01/2024	
ID	Search
#1	MeSH descriptor: [Electroconvulsive Therapy] explode all trees
#2	(electro*convuls*) (Word variations have been searched)
#3	electro-convuls* (Word variations have been searched)
#4	(convulsi* NEAR electr*):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Electroshock] explode all trees
#6	(electro*shock*) (Word variations have been searched)
#7	(electro-shock*) (Word variations have been searched)
#8	(electr* NEAR shock*):ti,ab,kw (Word variations have been searched)
#9	(ECT):ti,ab,kw
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] explode all trees
#12	MeSH descriptor: [Depressive Disorder, Major] explode all trees
#13	MeSH descriptor: [Depression] explode all trees
#14	MeSH descriptor: [Depressive Disorder] explode all trees
#15	(depress*) (Word variations have been searched)
#16	#13 OR #14 OR #15
#17	(treatment-resist*) (Word variations have been searched)
#18	(major)
#19	#17 OR #18
#20	#16 AND #19
#21	((major OR severe OR treatment-resist* OR bipolar) NEAR depress*):ti,ab,kw (Word variations have been searched)
#22	(TRD):ti,ab,kw
#23	#11 OR #12 OR #20 OR #21 OR #22
#24	#10 AND #23
#25	#10 AND #23 with Publication Year from 2014 to 2016, in Trials
#26	#10 AND #23 with Cochrane Library publication date Between Nov 2014 and Dec 2016
#27	#25 OR #26
#28	English:la
#29	German:la
#30	#28 OR #29
#31	#27 AND #30
#32	(conference proceeding):pt
#33	(abstract):so
#34	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#35	#32 OR #33 OR #34
#36	#31 NOT #35
Total hits: 91	

Embase

Search Name: ECT for Depression (2014-2016)		
Search date: 08.01.2024		
ID	Query	Results
#32	#30 NOT #31	56
#31	#30 AND 'Conference Abstract'/it	19
#30	#29 AND ([english]/lim OR [german]/lim)	75
#29	#28 AND [21-11-2014]/sd NOT [31-12-2016]/sd	75
#28	#24 OR #26 OR #27	1,325
#27	#23 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	538
#26	#23 AND #25	649
#25	((double NEXT/1 blind*):de,ab,ti) OR placebo*:ab,ti OR blind*:ab,ti	743,504
#24	t #10 AND #22 AND [randomized controlled trial]/lim	527
#23	#10 AND #22	8,719
#22	#11 OR #12 OR #19 OR #20 OR #21	406,859
#21	trd:ti,ab,kw	4,042
#20	(major OR severe OR 'treatment resist*' OR bipolar) NEAR/2 depress*	135,740
#19	#15 AND #18	393,095
#18	#16 OR #17	7,160,657
#17	major	7,140,925
#16	'treatment-resist*'	31,178
#15	#13 OR #14	1,059,992
#14	depress*	1,011,553
#13	'depression'/exp	662,412
#12	'major depression'/exp	85,429
#11	'treatment resistant depression'/exp)	5,477
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	51,010
#9	ect:ti,ab,kw	16,017
#8	electr* NEAR/1 shock*	18,373
#7	'electro-shock*'	190
#6	electro*shock*	5,694
#5	'electric shock'/exp	13,806
#4	convulsi* NEAR/4 electr*	2,269
#3	'electro-convuls*'	526
#2	electro*convuls*	27,089
#1	'electroconvulsive therapy'/exp	24,276

Search strategy for Medline via Ovid

Databse: Ovid MEDLINE(R) ALL <1946 to January 05, 2024>		
Search Name: ECT for Depression (2014-2016)		
ID	Query	Results
#1	exp Electroconvulsive Therapy/	14,373
#2	electro?convuls*.mp.	18,631
#3	electro-convuls*.mp.	326
#4	(convulsi* adj5 electr*).mp.	1,958
#5	exp Electroshock/	32,414
#6	electro?shock*.mp.	15,389
#7	electro-shock*.mp.	158
#8	(electr* adj shock*).mp.	6,725
#9	ECT.ti,ab.	10,785
#10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	44,953
#11	exp Depressive Disorder, Treatment-Resistant/	2,231
#12	exp Depressive Disorder, Major/	39,517
#13	exp Depression/	154,415
#14	exp Depressive Disorder/	123,444
#15	depress*.mp.	665,788
#16	13 or 14 or 15	666,564
#17	treatment-resist*.mp.	18,891
#18	major.mp.	1,740,456
#19	17 or 18	1,754,997
#20	16 and 19	102,284
#21	((major or severe or treatment-resist* or bipolar) adj3 depress*).mp.	89,864
#22	TRD.ti,ab.	2,499
#23	11 or 12 or 20 or 21 or 22	117,412
#24	10 and 23	4,376
#25	limit 24 to randomized controlled trial	351
#26	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1,493,201
#27	24 and 26	758
#28	limit 24 to (meta analysis or "systematic review")	178
#29	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.	740,862
#30	24 and 29	413
#31	25 or 27 or 28 or 30	1,021
#32	limit 31 to dt=20141121-20161230	95
#33	limit 31 to ed=20141121-20161230	104
#34	32 or 33	138
#35	limit 34 to (english or german)	135

Search strategy for HTA-INATHTA

Search Name: ECT for Depression (2014-2016)	
Search date:08/01/2024	
ID	Search
27	((((TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe])))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe])) AND ((ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]))) FROM 2014 TO 2016) AND (English OR German)[Language],"5","2024-01-08T14:57:59.000000Z"
26	(((TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe])))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe])) AND ((ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]))) FROM 2014 TO 2016,"5","2024-01-08T14:57:26.000000Z"
25	((TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe])))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe])) AND ((ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe])),"22","2024-01-08T14:57:08.000000Z"
24	((TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe])))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe])) AND ((ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe])),"22","2024-01-08T14:56:36.000000Z"
23	(TRD) OR ((major OR severe OR "treatment-resistant") AND (depress*)) OR (((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe])))) OR ("Depressive Disorder Major"[mhe]) OR ("Depressive Disorder Treatment-Resistant"[mhe]),"182","2024-01-08T14:56:04.000000Z"
22	TRD,"12","2024-01-08T14:55:10.000000Z"
21	(major OR severe OR "treatment-resistant") AND (depress*),"168","2024-01-08T14:54:52.000000Z"
20	((major) OR ("treatment-resistant")) AND ((depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe])),"123","2024-01-08T14:54:20.000000Z"
19	(major) OR ("treatment-resistant"),"818","2024-01-08T14:54:07.000000Z"
18	major,"772","2024-01-08T14:53:59.000000Z"
17	"treatment-resistant","69","2024-01-08T14:53:50.000000Z"
16	(depress*) OR ("Depressive Disorder"[mhe]) OR ("Depression"[mhe]),"483","2024-01-08T14:53:34.000000Z"
15	depress*,"458","2024-01-08T14:52:54.000000Z"
14	"Depressive Disorder"[mhe],"173","2024-01-08T14:52:27.000000Z"
13	"Depression"[mhe],"167","2024-01-08T14:52:14.000000Z"
12	"Depressive Disorder Major"[mhe],"59","2024-01-08T14:51:54.000000Z"
11	"Depressive Disorder Treatment-Resistant"[mhe],"33","2024-01-08T14:51:37.000000Z"
10	(ECT) OR ((electr*) AND (shock*)) OR (electro-shock*) OR (electroshock*) OR ("Electroshock"[mhe]) OR ((convulsi*) AND (electr*)) OR (electro-convuls*) OR (electroconvuls*) OR ("Electroconvulsive Therapy"[mhe]),"46","2024-01-08T14:50:44.000000Z"
9	ECT,"24","2024-01-08T14:50:32.000000Z"
8	(electr*) AND (shock*),"12","2024-01-08T14:50:06.000000Z"
7	electro-shock*,"0","2024-01-08T14:49:50.000000Z"
6	electroshock*,"0","2024-01-08T14:49:41.000000Z"
5	"Electroshock"[mhe],"13","2024-01-08T14:49:18.000000Z"
4	(convulsi*) AND (electr*),"6","2024-01-08T14:48:46.000000Z"
3	electro-convuls*,"0","2024-01-08T14:48:24.000000Z"
2	electroconvuls*,"20","2024-01-08T14:48:03.000000Z"
1	"Electroconvulsive Therapy"[mhe],"10","2024-01-08T14:47:17.000000Z"
Total hits: 5	

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