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Effectiveness of pharmacological and non-pharmacological interventions for treatment-resistant depression in older patients: a systematic review and meta-analysis

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ABSTRACT

Background Depression in older adults is often undertreated. A 2011 systematic review of treatments for treatment-resistant depression (TRD) in older adults identified one placebo-controlled randomised controlled trial (RCT). We aimed to update this review, synthesising evidence for the effectiveness of treatments for TRD in older people.

Methods We systematically searched electronic databases (PubMed, Cochrane, Web of Science) from 9 January 2011 through 10 December 2023 (updating our search on 7 January 2024 for RCTs investigating TRD therapies in adults aged ≥55 years, defining treatment resistance as ≥1 unsuccessful treatment. We assessed bias with the Cochrane Risk of Bias (RoB) 2 tool, meta-analysed remission rates and evaluated evidence using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria.

Results 14 studies (11 newly identified, 3 from previous review) involving 1196 participants (mean age 65.0, male/female 548/648) met the inclusion criteria; 10 were placebo controlled and 4 were rated as low RoB. The pooled proportion of participants in intervention arms remitting was 0.35 (17 arms; 95% CI=0.26; 0.45). Relative to placebo, intervention participants were more likely to remit (9 studies; OR 2.42 (95% CI=1.49; 3.92)). Relative to controls, remission rates favoured ketamine (n=3; OR 2.91 (1.11; 7.65)), with a trend towards transcranial magnetic stimulation (TMS) (n=3; 1.99 (0.71; 5.61)), and in single placebo-controlled studies, selegiline, aripiprazole augmentation, pharmacogenetic-guided prescribing (PGP) and cognitive remediation favoured interventions.

Conclusions We identified weak evidence that ketamine therapy and aripiprazole augmentation, and very weak evidence that TMS, PGP and cognitive remediation increased remission. Lack of evidence regarding routinely prescribed antidepressants and psychosocial treatments is problematic, requiring clinicians to extend evidence from younger populations.

PROSPERO registration number CRD42023494513.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The 2011 World Federation of Societies of Biological Psychiatry (WFSBP) systematic review of treatments for treatment-resistant depression (TRD) in older adults identified only one placebo-controlled randomised controlled trial (RCT).

WHAT THIS STUDY ADDS

⇒ Over a third of older adults with TRD responded to experimental treatments.
⇒ We identified, respectively, weak and very weak quality evidence from meta-analyses that ketamine therapy and transcranial magnetic stimulation (TMS) increased remission of depressive illness, in short term.
⇒ From individual studies, we found weak quality evidence that aripiprazole augmentation increased remission, and very weak quality evidence that cognitive remediation and pharmacogenetic testing-guided prescribing increased remission.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research to explore the longer-term outcomes and safety of ketamine and TMS in older populations is needed.
⇒ Aripiprazole augmentation and computerised cognitive remediation also warrant investigation.
⇒ Large-scale studies reporting outcomes for routinely available treatments for TRD in older adults could support evidence-based care.

INTRODUCTION

Depression is the leading global cause of disability, affecting around 13% of older people,[1] of whom a third meet the criteria for treatment resistance.[2] Mental disorders (most commonly depression and anxiety) account for 10.6% of disability-adjusted life years among older adults. Antidepressant use by older people with depression is increasing,[3] but the condition remains under-recognised and under-treated,[4] and is more commonly resistant to treatment in this age group.[5] Globally, around a quarter of deaths from suicide (27.2%) are among people aged 60 years or over.[6] Depression may increase the risk of developing dementia.[7]

The Food and Drugs Association defines treatment-resistant depression (TRD) as 'inadequate response to at least two antidepressants,

where there was an acceptable treatment trial and adherence'. This definition does not account for psychological treatment, effective at treating late life depression.[8] Lifestyle, such as dietary changes, can also be useful adjuncts to therapy.[2] People with TRD have lower quality of life, activity impairment and use more healthcare resources than people with non-resistant depression and the general population.[9]

The National Institute for Health and Care Excellence (NICE) therapeutic guidelines for depression (NG222)[10] unresponsive to initial treatment recommend increasing the dose, switching agents, adding psychological therapies or augmenting treatment with antidepressant medication, second-generation antipsychotics, lithium, electroconvulsive therapy, lamotrigine or triiodothyronine (liothyronine). Nuñez *et al*[11] compared the efficacy of augmentation agents in TRD, finding the strongest evidence for atypical antipsychotics, thyroid hormones, dopamine compounds and lithium. Additional NICE guidelines support the use of repetitive transcranial magnetic stimulation (rTMS) for depression.[12]

Most evidence underpinning TRD therapeutic guidelines derives from research with younger adults, but optimal treatment of depression in older and younger populations may differ. Higher rates of physical and cognitive comorbidity, greater likelihood of polypharmacy and age-related pharmacodynamic and pharmacokinetic changes that increase susceptibility to side effects mean that specific guidelines for clinicians treating older adults with TRD are of value.

In 2011, the Old Age Task Force of the World Federation of Biological Psychiatry systematically reviewed studies investigating the efficacy of treatment for TRD in older adults, defining TRD as failure to respond to at least one course of treatment for depression during the current illness episode. This definition, more inclusive than those described above, was selected to ensure all relevant evidence was considered. Of the 14 studies included, 3 were RCTs and 1 was placebo-controlled.[13] This 2011 review informed national guidelines in the UK,[14] Japan[15] and Canada.[16]

A decade later, with the advent of new treatments for depression, including rTMS and ketamine, our objective was to update this systematic review, to identify the best current evidence for the effectiveness of pharmacological or psychological treatments for TRD in older people.

METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42023494513). No ethics approval was required. We followed the published protocol, with the following changes: we substituted the Cochrane risk of bias-2 tool as the validity rating method, included the RCTs identified in the previous review (these changes on the advice of journal reviewers) and did not include global change as an outcome because few studies used it, while all measured depressive symptoms.

Search strategy

We searched three databases (PubMed, Cochrane Database of Systematic Reviews and Web of Science) from 8 January 2010 to 10 December 2023 using the keywords: (resist* OR refractory OR inadequate response OR partial response) AND (depress*) AND (elderly OR old* OR geriatric) AND (treatment OR trial). We repeated the searches of all databases on 14 July 2024 and found no further eligible studies. We imported results to 'Covidence' software. Two authors independently screened titles and abstracts, identifying all studies of potential relevance for full-text review. Any conflicts were resolved by discussion with a third author. We screened reference lists of studies identified for full-text review and relevant reviews. Full strategies for each database are in online supplemental material appendix 1.

Selection criteria

We drew on the 2011 systematic review methods,[13] additionally restricting evidence to RCTs. We included primary research studies describing RCTs that compared an intervention intended as a treatment for depression against placebo or another active treatment; where all participants, or a separately analysed subgroup were, on average, aged >55 years, had a clinical diagnosis of depressive disorder and were classified as treatment resistant at baseline. For this, the same, inclusive definition as the 2011 review: failure to respond to at least one adequate treatment (pharmacological or psychological; acceptable treatment trial and adherence) was used.[13]

Data extraction

Two authors extracted information from each included study (online supplemental table 1 shows data extracted). They worked independently then compared the results to identify discrepancies. We extracted outcomes that measured intervention efficacy, including the proportion achieving response or remission, and changes in depression scores from before to after interventions. Both response and remission could be categorised by reaching a certain level on a depression rating scale or change from baseline. Each study used their own definition, as reported in online supplemental table 1. Where more than one outcome point was reported, we prioritised the primary outcome. We contacted authors where data were not available from papers.

Risk of bias assessment

We used the Cochrane Risk of Bias-2 tool. Two authors independently rated each study. Any conflicts within the scoring were discussed to reach consensus.

GRADE (Grading of Recommendations Assessment, Development and Evaluation)

For each meta-analysis and placebo-controlled trial,[18] two authors independently determined evidence GRADE, before discussing with all authors to reach consensus regarding evidence certainty for interventions.[19]

Data analysis

We used the statistical software 'R' (V.4.2.2) for meta-analyses with full codes presented in online supplemental appendix 2. We used the 'meta' package for analysis of the proportion of participants and funnel plot for figures 1 and 2. We used the 'metafor' and 'readxl' packages for analysis of odds of remission for figures 3 and 4. We conducted two preplanned meta-analyses with random effect models. First, we calculated the pooled proportion of participants attaining remission across all active treatments; second, the odds of remission in intervention compared with placebo control conditions. We also conducted subgroup analyses of studies investigating comparable interventions. P values were calculated via Wald-type tests, with values <0.05 indicating significance. For any meta-analyses, the I^2 statistic was calculated. This is a measure of heterogeneity estimating the percentage of variance not due to chance. A low

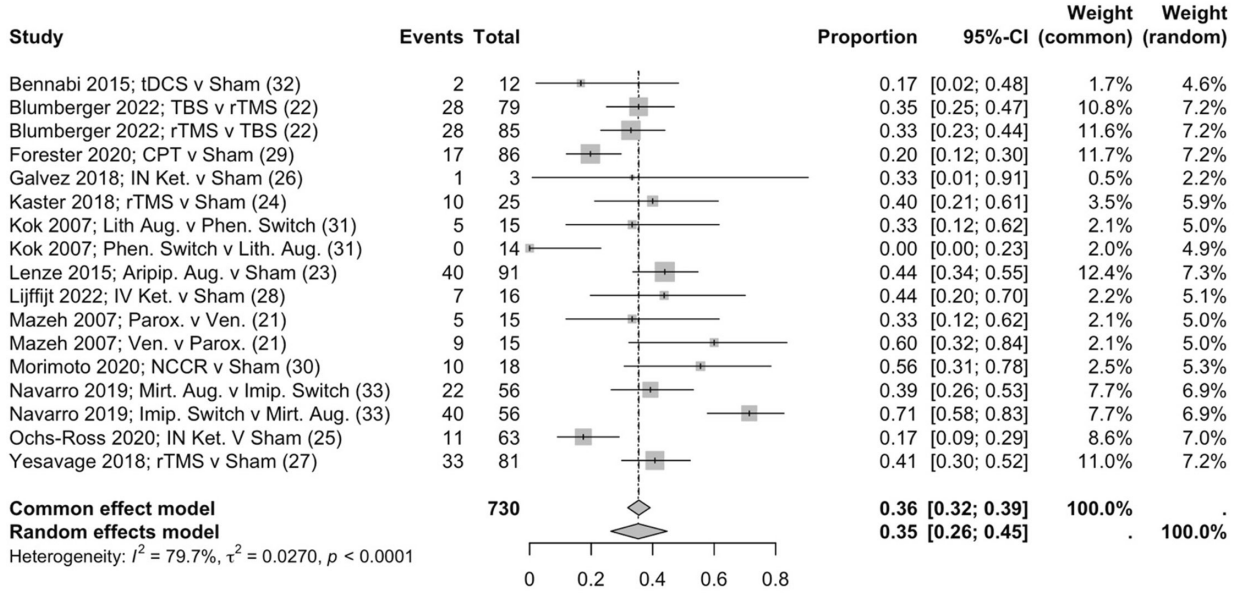


Figure 1 Showing the proportion of participants achieving remission with intervention.[a] [a]Pooled proportion meta-analysis for 17 interventions. Interventions by Sunderland *et al*[20] could not be included due to no reporting of the number remitting. Aripip., aripiprazole; Aug., augmentation; CPT, combinatorial pharmacogenetic testing; Events, number who remitted; Imip., imipramine; IN, intranasal; IV, intravenous; Ket., ketamine; Lith., lithium; Mirt., mirtazapine augmentation; NCCR, neuroplasticity-based computerised cognitive remediation; Parox., paroxetine; Phen., phenelzine; rTMS, repetitive transcranial magnetic stimulation; TBS, theta-burst stimulation; tDCS, transcranial direct current stimulation; Total, number in the intervention group; Ven., venlafaxine.

percentage indicates limited heterogeneity. Publication bias was assessed using visual examination of funnel plots for asymmetry, where there were 10 or more data points. We used a restricted maximum likelihood approach which provides an estimate of tau^2. We did not use a Hartung-Knapp adjustment.

RESULTS

Search results

Figure 5 describes the results of our search. We included 14 studies: 11 studies identified in our updated search and 3 from the previous review[20–22] (online supplemental table 1). Four studies were rated as low risk of bias,[23–26] one as high risk of bias[27]; the remaining nine were rated in the intermediate category of 'some concerns' (online supplemental table 1).

Study description

Seven of the identified studies were conducted in the USA, two in Canada and one each in Australia, France, Israel, The Netherlands and Spain. Participants were mostly recruited via convenience sampling from psychiatric clinics. The mean age of all participants with outcome data available was 65.0 and ranged from 55.2[28] to 75.9.[22] Nine studies specified a minimum age as an inclusion criterion.[22–26 29–32] The remaining five included all adults.[20 27 28 33 34] Overall, 648 out 1168 (55.5%) of participants were female. No study reported the effect of age or gender on treatment.

Eight studies excluded patients with suspected or confirmed dementia.[22–25 28 30–32] Among those that did not, three included cognition as an outcome[26 27 33] and two did not.[29 34] Six studies excluded anyone expressing acute suicidal intent,[23 25–28 30] and three measured suicidal ideation as a secondary outcome.[24 28 29] Most studies excluded uncontrolled acute but accepted stable medical conditions. Nine studies excluded anyone with a current or previous psychotic episode or prescribed antipsychotic medication.[20 24–26 29–33] Others included people taking antipsychotic medication.[23 27] Navarro *et al* included people with psychotic depression, with 13% of participants prescribed antipsychotic medication at baseline.[34] Yesavage *et al* investigated US veterans with comorbid post-traumatic stress disorder and allowed any concomitant psychiatric medications.[28]

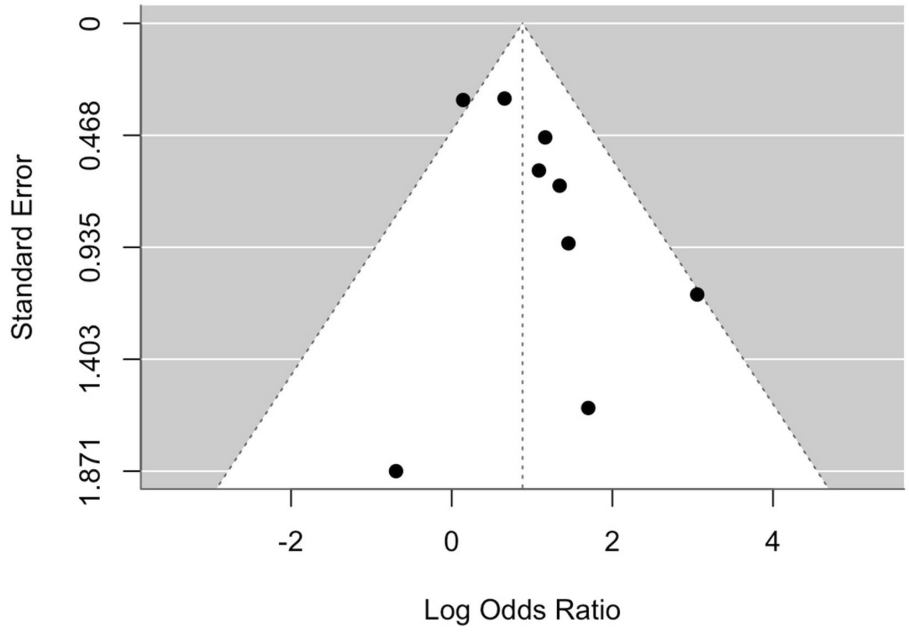
In addition to requiring evidence of at least one previous treatment failure, three studies confirmed treatment resistance prior to randomisation by conducting a 10–12 week trial of venlafaxine[24 34] or an 8-week trial of a selective serotonin receptor inhibitor followed by an 8-week trial of an additional antidepressant.[22] Another study prospectively assessed adherence to pre-study antidepressant medication regimen for 4 weeks.[26]

Overall treatment efficacy

We first investigated the likelihood of achieving remission across all the studies. In our pooled meta-analysis of the proportion of participants in active intervention groups achieving remission, we included 17 active interventions, as four studies compared active treatments.[22 30 32 34] We were unable to include one study that did not report remission rates.[20] Over study periods of 1–12 weeks, the overall odds of remission was 0.35 (n=17; 95% CI=0.26; 0.45). There was considerable heterogeneity between groups (I^2=79.7% (95% CI=66.6%; 88.0%)).

We then compared the odds of achieving remission in active intervention relative to placebo arms. We could not include the four studies that did not have a placebo-control arm,[22 23 32 34] nor one placebo-controlled trial as required data were unavailable.[20] In our random effects model, the overall OR of 2.42 (n=9; 95% CI=1.49; 3.92) favoured the intervention arms. The funnel plot displayed reasonable symmetry, indicating that there was no significant publication bias and we did not find evidence of heterogeneity (I^2 statistic=28.6%).

Only two interventions were studied in more than one RCT: ketamine and interventions involving transcranial magnetic stimulation (TMS). Subgroup analysis findings are discussed below.



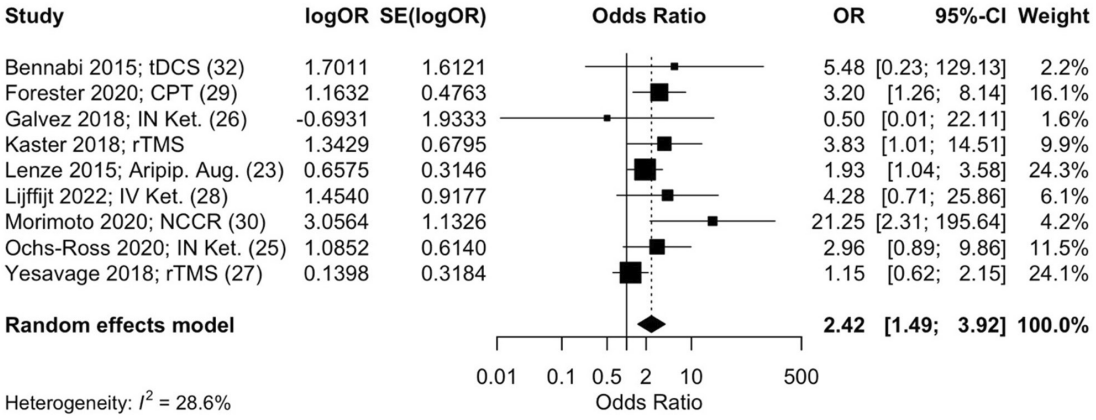


Figure 2 Above: Funnel plot demonstrating publication bias in placebo-controlled studies.[a] Below: Figure showing likelihood of remission with intervention compared with control.[ba]Shows no significant asymmetry between studies, with dotted lines representing a symmetrical distribution. [b]Shows the meta-analysis for all placebo-controlled studies with the plot showing the odds of remission with intervention compared with control. Diamond shows the overall effect of intervention. Aripip., aripiprazole; Aug., augmentation; CPT, combinatorial pharmacogenetic testing; IN, intranasal; IV, intravenous; Ket., ketamine; NCCR, neuroplasticity-based computerised cognitive remediation; RE, random effects; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

Ketamine therapy

Three studies investigated the effects of ketamine therapy on TRD.[26 27 29] All defined remission using the Montgomery-Asperg Depression Rating Scale (MADRS) (online supplemental table 1). Gálvez *et al*[27] and Ochs-Ross *et al*[26] administered eight treatments of intranasal (IN) esketamine over 4 weeks, with the control group receiving IN midazolam. Gálvez *et al*[27] used a fixed dose of 100 mg esketamine in a small pilot RCT, for which the primary aim was to evaluate safety and feasibility. Ochs-Ross *et al*[26] used flexible dosing, starting at 28 mg, then increasing to 56 or 84 mg at clinician discretion; for the primary endpoint of MADRS scores, the estimate of the treatment difference (−3.6, 95% CI (−7.20, 0.07)) did not attain significance (figure 3).

Lijffijt *et al*[29] compared one intravenous ketamine infusion to a midazolam control at 7 days post-infusion, with the aim of comparing three doses: 0.1, 0.25 and 0.5 mg/kg. For the purposes of analysis, 0.25 and 0.5 mg/kg groups were combined. Comparable results for the 0.1 mg/kg intervention group were unavailable for inclusion in the meta-analysis.

In our subgroup meta-analysis, the overall OR on the primary outcomes of remission was 2.91 (n=3; 95% CI=1.11; 7.65), favouring the intervention.

GRADE assessment

Ketamine was evaluated in three RCTs. Due to the high risk of bias exhibited in one study[27] and inconsistency evidenced by the wide CI in the pooled analysis, we downgraded the quality of evidence for the effects of ketamine on remission by two levels to low, concluding that the quality of evidence is weak for ketamine therapy effects on TRD remission in older people.

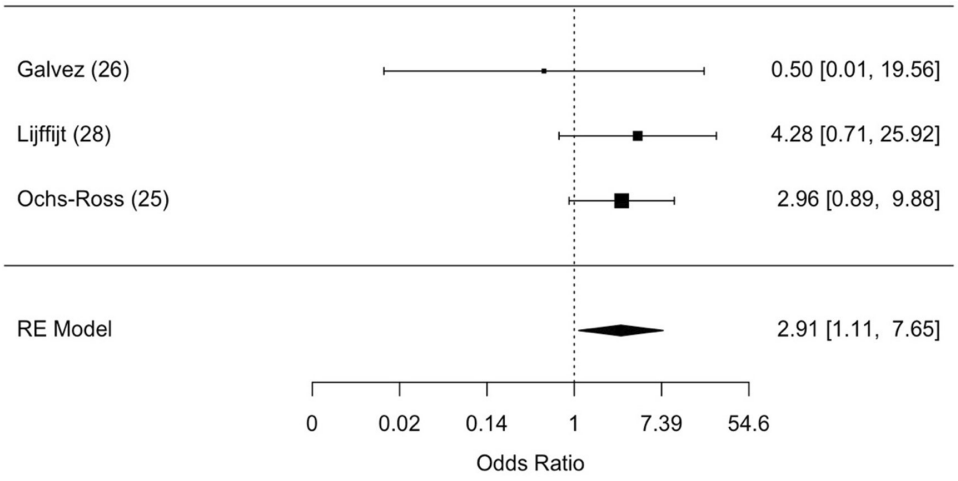


Figure 3 Likelihood of remission with a ketamine-based intervention compared with placebo. Meta-analysis showing odds of remission with ketamine intervention versus placebo. The dotted line shows no difference in odds. The diamond shows overall odds suggested by the model—no interception of line suggests a significant effect. Bracketed numbers alongside intervention are the referenced studies. RE, random effects.

TMS therapies

TMS is a form of non-invasive brain stimulation where a brief magnetic field passes through the scalp and induces an electrical current in the cerebral cortex. Four studies tested interventions involving TMS: transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS) and theta Burst Stimulation (TBS). Bennabi *et al*[33] compared 10 sessions over 5 days of active or sham tDCS applied to the left dorsal left pre-frontal cortex (DLPFC); intervention relative to control group improvements on Hamilton Depression Rating Scale (HDRS) (33% vs 19%; p=0.17) and MADRS scores (27% vs 15%; p=0.35), and a higher level of response (25% vs 9%; p=0.59) and remission (17% vs 0%; p=0.47) did not attain significance (figure 4).

Three studies investigated rTMS.[23 25 28] Two were placebo-controlled trials, both using HDRS as the primary outcome. Kaster *et al*[25] switched from a helmet coil, only stimulating the left DLPFC, to a coil targeting the DLPFC and VLPFC (ventral left pre-frontal cortex) bilaterally, with greater penetration on the left after six patients experienced poor treatment tolerance. Each participant completed 20 sessions over 4 weeks. By contrast, Yesavage *et al*[28] administered five sessions over 12 days, stimulating the DLPFC only. Yesavage *et al*[28] and Kaster *et al*[25] reported suicidality as a secondary outcome, finding a non-significant decrease in the active stimulation groups. Finally, Blumberger *et al*[23] compared two active treatments: rTMS and TBS. Each participant received 20 sessions over 4 weeks. For rTMS, 32.9% achieved remission, and there was an improvement in MADRS and HDRS scores of 32% and 33%, respectively. Results for TBS were similar (35.4% remission; 39% improvement in MADRS; 38% improvement in HDRS).

We meta-analysed findings for these studies comparing stimulation to control. The random-effects model OR was 1.99 (n=3; 95% CI=0.71; 5.61). The I^2 statistic indicated a heterogeneity of 44.64%.

GRADE assessment

TMS was evaluated in three RCTs, two rated as having some concerns on risk of bias assessment,[28 33] and there was evidence

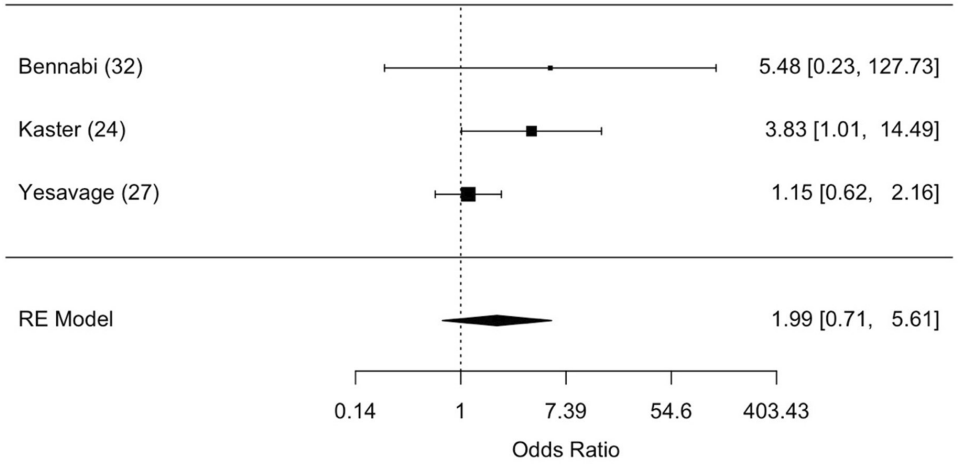


Figure 4 Likelihood of remission with transcranial magnetic stimulation (TMS) compared with control. Meta-analysis showing the odds of remission with TMS compared with control. The dotted line indicates no difference in odds. The diamond shows the overall odds suggested by the model—overlapping the dotted line suggests no significant improvement offered by the intervention. Numbers alongside intervention are the referenced studies. RE, random effect.

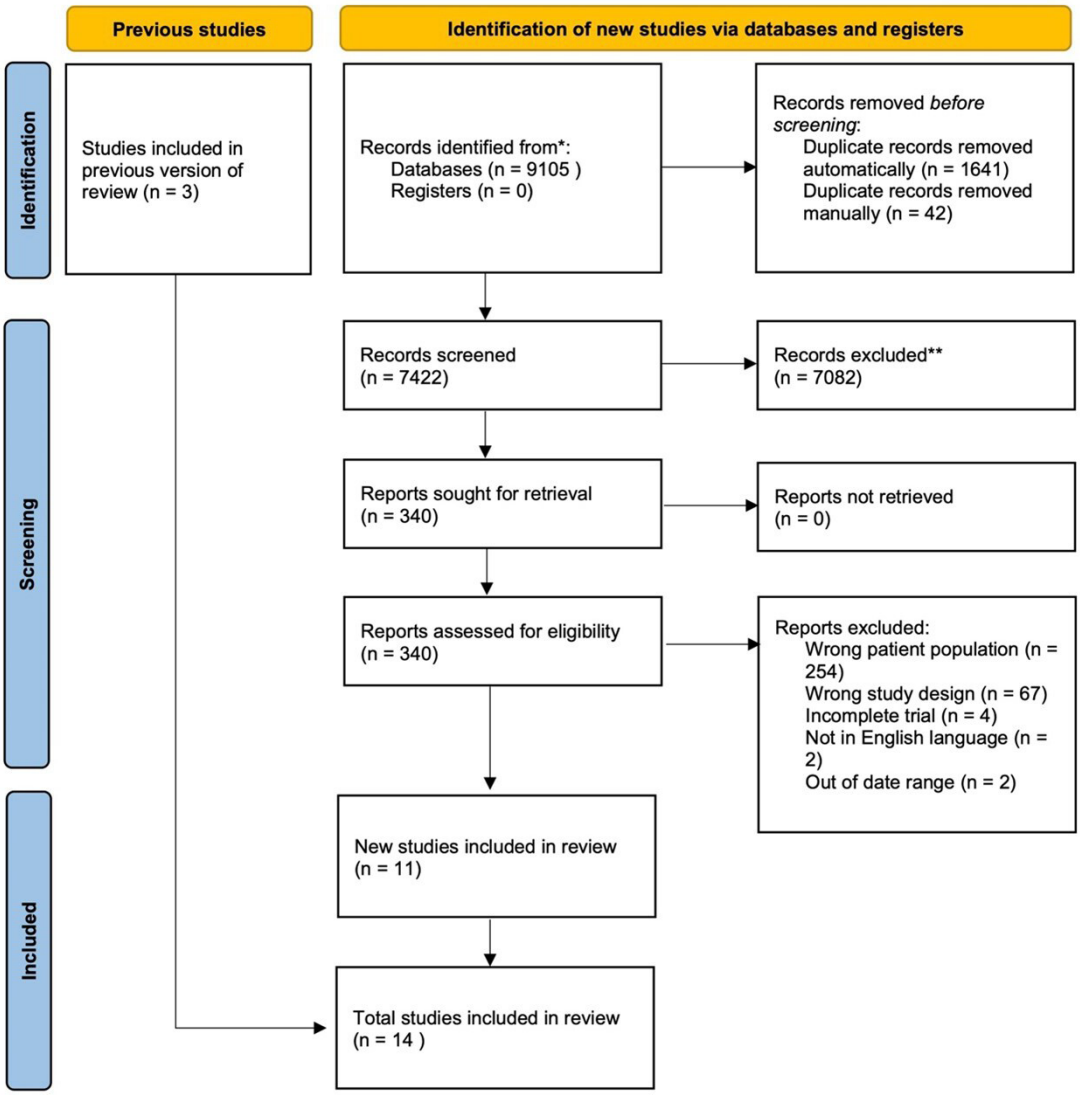


Figure 5 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram illustrating the process of study selection.

of heterogeneity. Risk of bias, inconsistency and imprecision informed our conclusion that the quality of evidence is very weak for TMS effects on TRD remission in older people.

Other pharmacological interventions

Six studies focused on oral pharmacological interventions for TRD.[24 30 34] Lenze *et al*[24] compared 12 weeks of augmentation with aripiprazole to placebo. All patients received venlafaxine extended release, titrated to 300 mg/day. After 12 weeks, those not in remission were randomised to aripiprazole (10–15 mg) or placebo augmentation. On the primary outcome of the MADRS, remission rates were higher in the treatment group (n=181, OR 1.93,1.04–3.58). Lenze *et al*[24] included the Scale of Suicidal Ideation as a secondary outcome; ideation resolved in 22 out of 30 (73.3%) participants presenting with suicidal ideation in the active group at baseline and 11 out of 25 (44%) in the placebo group (p=0.02).

Navarro *et al*[34] compared two active treatments over 10 weeks, with the second group switching their antidepressant rather than adding mirtazapine. Participants who did not remit after 10 weeks of venlafaxine (225–300 mg/day) were randomised to mirtazapine augmentation (30 mg/day) or switch to imipramine (adjusted to plasma levels). 39.28% of those receiving mirtazapine, relative to 71.43% on imipramine, achieved remission (p=0.001).

Forester *et al*[30] evaluated the impact of pharmacogenetic-guided prescribing. Over 24 weeks, clinicians had access to this report for intervention but not control participants. Assessors were only blinded up to week 8, the primary endpoint, where the OR favoured the treatment group (n=184, OR 3.20, 1.26–8.14).

The three RCTs that we included from our previous review were a placebo-controlled trial (evaluating high-dose selegiline)[20] and two studies comparing active treatments (phenelzine and lithium, and venlafaxine and paroxetine, respectively).[22 32] The placebo-controlled trial employed a cross-over method and found that in the objective measures of depression, symptoms significantly improved following active treatment with selegiline 60 mg/day (n=16; 37.4% decrease in HDRS). For the remaining two studies, lithium was found to show a greater rate of remission compared with phenelzine (n=5; 33%, vs n=0; 0%, respectively) as well as a greater rate of response (n=7; 46.7%, vs n=1; 7.1%).[32] Both venlafaxine and paroxetine showed a statistically significant improvement in HAM-D scores, with venlafaxine showing a greater rate of remission (n=9; 60% vs n=5; 33%, respectively).[22]

GRADE assessment

We downgraded evidence for interventions evaluated in single trials, as we could not judge consistency of findings. Low risk of bias informed our conclusion that the quality of evidence is weak for the effect of aripiprazole augmentation on remission of TRD in older people. We concluded that the quality of evidence for pharmacogenetic testing-guided prescribing, evaluated in a trial rated as having 'some concerns' of bias was very weak. The single, placebo-controlled trial of selegiline employed a crossover method alongside a very small sample size; we concluded there was insufficient evidence to make a GRADE assessment.

Psychological interventions

Neuroplasticity-based computerised cognitive remediation (NCCR)[31] involves activities that target the cognitive control deficits thought to influence depression and its poor outcomes in older populations. The authors proposed online activities targeting the processing of sensory stimuli as a depression treatment. In this small, double-blind, randomised trial, the active group was more likely to achieve remission over 4 weeks (n=18; OR 21.25, 2.31–195.64).

GRADE assessment

Risk of bias, inconsistency and imprecision informed our conclusion that the quality of evidence is very weak for the effect of cognitive remediation on TRD remission in older people.

DISCUSSION

A 2011 review of evidence-based interventions for older people with TRD identified only three RCTs, including one placebo-controlled trial, indicating that high-dose selegiline was more effective than placebo. A decade later, we identified, respectively, weak and very weak quality evidence from meta-analyses that ketamine therapy and TMS increased remission of depressive illness, over up to 4 weeks. From individual studies, we found weak quality evidence that aripiprazole augmentation increased remission, and very weak quality evidence that cognitive remediation and pharmacogenetic testing-guided prescribing increased remission.

Ketamine is associated with common adverse effects, including drowsiness, derealisation, tachycardia and hypertension. A need for well-designed, large-scale studies of intravenous ketamine to establish its effectiveness, tolerability and safety in older adults with TRD has been mooted.[35] In 2022, the UK National Institute of Health and Care Excellence (NICE) evaluated esketamine nasal spray for TRD, concluding that there was insufficient cost-effectiveness and long-term safety evidence to support NHS prescribing,[36] although it is licensed by the Medicines and Healthcare Products Regulatory Agency. A recent review of TMS use for TRD in older adults found substantial variability in clinical response (6.7% to 54.3%), concluding that TMS is safe in older adults, although underdosing was common. They proposed a standardised TMS protocol tailored to the TRD in older adults.[37] NICE approved repetitive TMS (rTMS) in 2015, noting a need for further evidence to inform patient selection, treatment protocols and longer-term outcomes.[12]

There is an urgent need for TRD therapies for older adults that preserve cognition and are effective in polypharmacy and physical frailty contexts. While the evidence base remains slender, we think our findings have some implications for clinical practice. Over a third of older adults with TRD responded to experimental treatments in included studies, suggesting that a significant proportion of TRD in older populations could be alleviated by greater implementation of evidence-based treatment. In the included studies, remission among older people with TRD was three times as likely with ketamine therapy or pharmacogenetic-guided prescribing and twice as likely with TMS or aripiprazole augmentation, relative to control conditions. Pharmacological properties of aripiprazole are well characterised,[38] but further research to explore the longer-term outcomes and safety of ketamine and TMS in older populations is needed. Computerised cognitive remediation also warrants further investigation.

Ketamine is among the most studied antidepressant agents.[39] Most antidepressant and psychological therapies routinely prescribed for TRD have no RCT evidence base in older populations, so clinicians are required to extend evidence from younger populations. Large-scale studies reporting outcomes for routinely available treatments for TRD in older adults could greatly increase the evidence base. The growing availability of electronic health record data and novel analytic methods, including trial emulation to exploit these rich databases, is increasing our knowledge of treatment effects to guide antidepressant prescribing.[40] Such studies are warranted for TRD in older populations.

Limitations of this review include the small evidence base identified, despite our inclusive definitions of treatment resistance and 'older' aged (55+). Lack of evidence of efficacy is not evidence of lack of efficacy. Another limitation concerns heterogeneity of populations. Over half of people aged 55–64 years live with a long-term condition.[41] We describe how exclusion criteria, relating to dementia, psychosis and suicidal thoughts defined patient populations. Half of the included studies excluded people with suicidal ideation, but one study found that suicidal ideation reduced with aripiprazole augmentation.[24] Suicidality is an important outcome, especially given its identification as an adverse event associated with antidepressant prescriptions.[42] Study populations were likely to be heterogeneous in terms of cognitive status and symptoms, although we would expect these characteristics to be equally distributed between randomly allocated groups. Socioeconomic (deprivation, gender, ethnicity) and illness factors (severity, comorbidities) may have influenced the likelihood of prospective participants being included. Diversity of depression trial populations has increased recently, with fair representation across genders, although with ongoing concerns about ethnic diversity.[43 44] We assessed publication bias using a funnel plot, a method with limitations where there are fewer than 10 studies. While our search was comprehensive, we did not search trial registries or contact authors regarding forthcoming publications.

We identified weak quality evidence that ketamine therapy and aripiprazole augmentation increased remission, and very weak quality evidence for TMS, cognitive remediation and pharmacogenetic testing- guided prescribing. Lack of evidence regarding routinely prescribed treatments is problematic, requiring clinicians to extend evidence from younger populations. Studies to enhance the evidence base for commonly prescribed treatments in this population have the potential to improve the lives of the many older adults with TRD.

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Contributors AJL and JG drafted the paper, supervised by CC and RIEJ. All authors revised the manuscript critically for intellectual content and approved the final submitted version. CC is the guarantor. AI was used to adapt the presentation of the figures to increase readability inline with reviewer comments only, and not in data analysis. AI was used to adapt the presentation of the figures to increase readability in line with reviewer comments only, and not in data analysis.

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no other conflicts of interest. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. PF is the president of the WFSBP. He was honorary speaker for Janssen-Cilag, AstraZeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth and Essex. During the last 5 years, he was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly and Lundbeck. Presently, he is a member of the advisory boards of Richter Pharma, Abbot and Otsuka.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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