Treatments for partial remission of major depressive disorder: a systematic review and meta-analysis

Joost Gülpen,1,2 Marlies E Brouwer,1,2 Gert J Geurtsen,3,4 Eva A M van Dis,1 Damiaan A J P Denys,1,4 Claudi L Bockting1,2

ABSTRACT

Question Partial remission of major depressive disorder (MDD) is a debilitating and distressing clinical state related to chronicity, morbidity and relapse. Although one-third of patients remit partially, evidence for treatment efficacy is unclear. We provide an overview of treatment options and their efficacy.

Study selection and analysis Embase, PsycINFO, Medline and SCOPUS were systematically searched through February 2023. Included were randomised controlled trials (RCTs) examining any treatment in patients with partially remitted MDD aged 13–65 years, reporting data on severity, remission or relapse.

Findings Seven RCTs examining psychotherapy including 1024 patients were eligible. There were not enough RCTs to examine effects of pharmacotherapy. Psychotherapy was associated with lower depressive symptom severity at post-treatment (Hedges’ g = 0.50; 95% CI 0.23 to 0.76), but not at follow-up up to 1 year (Hedges’ g = 0.36; 95% CI −0.30 to 1.02) or longer (Hedges’ g = 0.02; 95% CI −0.09 to 0.12). Psychotherapy was associated with superior remission rates at post-treatment (OR 2.57; 95% CI 1.71 to 3.87) and follow-up 6 months or longer (OR 1.75; 95% CI 1.21 to 2.53), although not with improved relapse rates at post-treatment (OR 0.17; 95% CI 0.01 to 4.83) or follow-up 6 months or longer (OR 0.46; 95% CI 0.21 to 1.03). Overall methodological quality was poor.

Conclusions Psychotherapy targeting partial remission may be effective in lowering depressive symptom severity and patients may potentially achieve full remission twice as likely. Yet, long-term and prophylactic effects are lacking. Given the risk of chronicity, more high-quality RCTs are needed.

PROSPERO registration number CRD42020188451.

BACKGROUND

Major depressive disorder (MDD) is highly prevalent and one of the leading causes of disease burden worldwide.1-3 Unfortunately, approximately one-third of patients treated with pharmacotherapy and/or psychotherapy continue to experience considerable symptoms and only reach partial remission of MDD.4-7 Surprisingly, while a myriad of reviews and randomised clinical trials (RCTs) have examined treatment effects for acute MDD or relapse prevention,8-10 partial remission has been a neglected research area. Therefore, an overview of the evidence for treatment targeting partial remission is highly needed.

In general, partial remission of MDD, also referred to as residual symptoms, is defined as a period of improvement in which patients no longer meet the full syndromal criteria for MDD, but continue to experience substantial symptoms. Patients experience considerable morbidity between episodes,11 including a lower quality of life,12 cognitive deficits,13 almost threefold higher suicide risk14 and psychosocial impairments.11,14 In addition, partial remission is a robust and strong predictor of low-grade chronic depression and early relapse.15-19 Patients in partial remission show relapse rates of approximately 70%,3,5 and relapse three times faster than those fully recovered, even while continuing...
pharmacotherapy. Patients moreover spend considerable time in partial remission and often spend more time in this phase of illness than the acute episode itself. Therefore, partial remission comes at great societal cost, as those with residual symptoms access health services more often and have lower work productivity than those in full recovery. In sum, partial remission of MDD is a debilitating and distressing clinical phase, predicting future relapse, chronicity and morbidity.

This shows the need for adequate treatment. Current treatment guidelines advice to prolong pharmacotherapy or psychotherapy, or to switch, combine or augment current treatment. However, recommendations for partial remission are non-specific and clinical efficacy is unclear. While previous studies found promising effects in this at-risk group, meta-analytic evidence is missing. To our knowledge, this is the first systematic study that examines the robust clinical efficacy of treatment options specifically targeting partial remission in MDD. The aim of this study is to provide a comprehensive overview of treatment options for partial remission and an estimate of their efficacy, to determine whether the evidence of treatment efficacy is convincing enough to guide clinical practice.

**STUDY SELECTION AND ANALYSIS**

**Search strategy and selection criteria**

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (online supplemental appendix 1), and followed the Cochrane recommendations. The protocol was preregistered on PROSPERO (CRD42020188451). Embase, APA PsycINFO, Medline and SCOPUS were searched for articles published from their origin through 27 February 2023, using search strings targeting: (1) MDD; (2) partial remission; (3) treatment and (4) RCTs (online supplemental appendix 2). References of included studies and reviews were screened to maximise finding of eligible articles.

Included were RCTs testing the efficacy of any treatment compared with any treatment or control group, where patients aged 13–65 years with partial remission of MDD were randomised during this clinical stage. To be eligible for inclusion in our meta-analysis, RCTs needed to include a depressive symptomatology measure at post-treatment and/or follow-up, and report sufficient statistics or information to calculate effect sizes or provide these on request. We operationalised partial remission of MDD in accordance with previous research and the definition offered by Frank et al: (1) a previous MDD, yet no current major depressive episode (MDE) based on a clinical interview or clinician-confirmed assessment; (2) in partial remission, with residual symptoms from an MDE remaining, as determined by a depression severity scale, clinical interview or clinician-based assessment and (3) at least considerable residual symptomatology, stating a lower boundary close to 8 on the 17-item Hamilton Depression Rating Scale (HDRS-17). Other symptom-level scores were transformed to HDRS-17 scores to compare inclusion criteria (online supplemental methods).

No limitations were used for treatment or publication year. All types of control groups were included and classified as (1) treatment as usual (TAU), in which participants received the same care as they could normally receive outside trial context, which could include pharmacotherapy or (2) antidepressant medication continuation (ADMc). Primary outcome was treatment efficiency measured as the mean difference in depressive symptomatology scores between treatment and control groups at post-treatment. Secondary outcome measures were mean differences in depressive symptomatology at follow-up, and remission, and relapse rates across groups at post-treatment and follow-up 6 months or more, as well as time to relapse. Definitions for ‘remission’ and ‘relapse’ in the included trials were followed (online supplemental table 1). Exclusion criteria were a primary diagnosis of other psychiatric or somatic disorders.

**Screening process and data extraction**

After duplicate removal, four screeners independently screened titles and abstracts and selected studies for potential inclusion. Subsequently, full-text articles of selected studies were independently reviewed, and disagreements were resolved through consensus or consulting senior authors. Two reviewers independently extracted the data, with conflicts resolved through consensus or consultation. Extracted data were patient characteristics; diagnostic instrument(s); criteria to determine partial remission, remission and relapse of MDD; treatment and control characteristics; depressive symptomatology (M and SD) measured at baseline, post-treatment and follow-up; follow-up time; remission and relapse rates and study quality. When articles reported on the same data, the most recent or comprehensive article was included. If relevant data or information was missing, authors were contacted and reminded twice. Eight authors were contacted and three provided additional data.

**Quality assessment**

Two reviewers independently rated the risk of bias using the Cochrane Risk-of-Bias 2 (RoB-2) tool across five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. Each domain was assessed as a low risk of bias, some concerns or a high risk of bias, leading to an overall judgement following the RoB-2 algorithm. Assessment was piloted, justifications were registered (online supplemental appendix 4) and disagreements between authors were resolved via consensus meetings or consulting senior authors. Initial inter-rater agreement was 0.83. Certainty of the evidence for each outcome was evaluated using the criteria proposed by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.

**Data analysis**

R (V4.2.0) was used to calculate pooled effect sizes (Hedges’ g), ORs, 95% CIs, forest plots, heterogeneity and funnel plots, according to our preregistration (CRD42020188451). Pooled effect sizes were calculated with random effects analyses, with positive effect sizes indicating treatment superiority. If trials included several measures, clinician-rated depression severity was considered more reliable and included in the main effect. Hedges’ g effect sizes were interpreted as small (0.2–0.49), moderate (0.5–0.79) or large (≥0.8). Heterogeneity was assessed using I² statistics and prediction intervals (PI), to show effect ranges where future trials may fall. Heterogeneity using I² was considered absent (0%–24%), low (25%–49%), moderate (50%–74%) or high (75%–100%) if the 95% CIs around I² were calculated using the non-central χ²-based approach. In line with previous research, we pooled all forms of psychotherapy in any delivery format. Small-study effects bias was investigated visually using funnel plots, and—if possible—tested and adjusted using Egger’s test of the intercept, and trim and fill procedure by Duval and Tweedie. Prespecified meta-regression and subgroup analyses using mixed-effect models (random within and fixed across subgroups) were planned, including on...
treatment and control types, and risk of bias. Sensitivity analyses were conducted by excluding outlier trials with a 95% CI showing no overlap with the pooled effect CI, a high risk of bias or small samples (n<10 patients per group).

**FINDINGS**

**Selection and characteristics of included studies**

After removal of duplicates, 5450 records were identified and screened. Out of 118 full-text articles, 17 articles reporting on 10 unique RCTs were included (figure 1 and online supplemental appendix 3). Table 1 summarises the characteristics of included studies. Due to considerable methodological differences, the three RCTs examining pharmacotherapy for partial remission could not be meta-analysed and were included only in the qualitative review (table 1 and online supplemental table 2). One study compared cognitive therapy (CT) augmentation with lithium augmentation while antidepressant medication (ADM) was continued. Another RCT examined oestrogen augmentation to ADM in women with perimenopausal depression experiencing partial remission after ADM. Lastly, one trial investigated the efficacy of iloperidone augmentation of ADM. This resulted in a final set of 7 included RCTs in the quantitative analysis, including 1024 patients who received psychotherapy (n=517) or a control intervention (n=507). All RCTs examined a cognitive behavioural therapy (CBT)-derived psychotherapy strategy: CT (k=1), guided self-help CBT (k=2), rumination-focused CBT (k=2), group-based mindfulness-based cognitive therapy (MBCT; k=1) and MBCT-based guided self-help (k=1). Three studies (n=290) examined psychotherapy as add-on to ADM and four studies (n=734) examined psychotherapy as an add-on to TAU compared with TAU only. Treatment length ranged from 6 to 20 weeks. The weighted mean age of participants was 46.56 years with all studies only including patients aged 18 years or older, and the majority were female (71.23%). Publication dates ranged from 1999 to 2020. All studies determined the presence of partial remission of MDD on a symptom-level cut-off with a clinical interview. Time to relapse was only examined in one study. Study duration (ie, treatment and follow-up) ranged from 1.5 to 72 months, with a median follow-up of 13.5 months.

**Treatment efficacy: depressive symptom severity**

Overall, psychotherapy was associated with superior outcomes on depression severity immediately post-treatment (Hedges’ g=0.50; 95% CI 0.23 to 0.76; k=7), compared with control conditions (figure 2 and table 2). Heterogeneity was moderate (I²=51%; 95% CI 0% to 79%). A wide PI was observed, indicating that future studies might find no or small effects (95% PI −0.06 to 1.05). Separating this effect for different informants, psychotherapy was not associated with better outcomes.
<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of partial remission of MDD</th>
<th>Mean baseline severity</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Final FU (mo)</th>
<th>Outcome instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paykel et al</td>
<td>MDD (DSM-III-R) in last 18 mo, but not in last 2 mo (SADS); residual symptoms of ≥8 on HDRS-17 and ≥9 on BDI, for ≥2–18 mo</td>
<td>HDRS-17: 12.1</td>
<td>CT: 16 individual sessions for 20 wk plus 2 booster sessions, 6 and 14 wk later.</td>
<td>ADM only: every 4 wk during treatment and every 8 wk during FU, with CM sessions 30 min each. CT or formal PT techniques prohibited. ADM usage: 100% Additional PT: 0%</td>
<td>72</td>
<td>BDI; CID; SADS; HDRS-17</td>
</tr>
<tr>
<td>Kennedy et al</td>
<td>Showing partial response (HDRS-17 score 8–15) to 8–14 wk of open-label ADM; initially met DSM-IV criteria for MDE (SAD)</td>
<td>HDRS-17: 11.9 Previous MDE: 2.2</td>
<td>LA: lithium carbonate augmentation of ADM for 8 wk, 600 mg/day prescribed, with clinicians permitted to increase dosing by 300 mg/day after 2–4 wk based on clinical response, tolerability and serum levels. Seen every 2 wk for CM. ADM usage: 100%</td>
<td></td>
<td>3</td>
<td>BDI; HDRS-17</td>
</tr>
<tr>
<td>Morgan et al</td>
<td>MDD in partial remission (SCID); residual symptoms of 8–14 on HDRS-17; taking ADM for ≥8 wk</td>
<td>HDRS-17: 11.1</td>
<td>Oestradiol: conjugated oestradiol 0.625 mg/day for 6 wk. New supply of medication at 2 wk intervals. ADM continued, prescribed by their primary treating physician. ADM usage: 100%</td>
<td>Placebo: placebo for 6 wk. New supply of medication at 2 wk intervals. ADM continued, prescribed by their primary treating physician. ADM usage: 100%</td>
<td>24</td>
<td>BDI-II; MADRS-S; SCID-I</td>
</tr>
<tr>
<td>Holländer et al</td>
<td>≥1 MDE in last 5 yrs, no current MDE (SCID); residual symptoms of ≥7–19 on MADRS-5, ≥1 on BDI-II</td>
<td>HDRS-17: 10.76 Previous MDE: 5.96</td>
<td>Internet-based CBT: 16 modules over 10 wk guided self-help. CBT: Unrestricted email communication with a personal therapist. ADM usage: 43% Additional PT: 0%</td>
<td></td>
<td>24</td>
<td>BDI-II; HDRS-17; SCID-I</td>
</tr>
<tr>
<td>Watkins et al</td>
<td>MDD (DSM-IV) in past 18 mo, but not in last 2 mo (SCID); residual symptoms of ≥8 on HDRS-17 and ≥9 on BDI-II; taking ADM for at least 8 wk continuously during the MDE and within the past 2 mo</td>
<td>HDRS-17: 12.74 Previous MDE: 5.14</td>
<td>RF-CBT: 12 weekly/fortnightly individual sessions of manualised PT, for 60 min each. Helps individuals shift to constructive rumination, through functional analysis, experiential/imagery exercises and behavioural experiments. ADM+C-PT: ADM and outpatient CM, for 12 wk. Referred to as TAU. ADM usage: 100% Additional PT: 33%</td>
<td></td>
<td>12</td>
<td>HDRS-17; IDS; SCID-I</td>
</tr>
<tr>
<td>Geschwind et al</td>
<td>≥1 previous MDE, but no current MDD (SCID); residual symptoms of HDRS-17 ≥7</td>
<td>HDRS-17: 10.25</td>
<td>MBCT: 7 weekly group sessions for 2.5 hours, with meditation, experiential exercises and discussions. Digital guided exercises and homework (30–60 min/day). TAU: usual treatment, if any, or waiting list, for 8 wk. ADM usage: 32% Additional PT: 12%</td>
<td></td>
<td>12</td>
<td>HDRS-17; IDS; SCID-I</td>
</tr>
<tr>
<td>Schößwohler et al</td>
<td>MDD in partial remission (DSM-IV-TR), based on the MINI; treated with adequate doses of ≥1 ADM before trial residual symptoms of HDRS-17 10–19</td>
<td>HDRS-17: 12.55</td>
<td>Cognitive behavioural guided self-help: self-help book for depressive disorders, over 6 wk, guided by psychotherapist (2 sessions, 45 min each). ADM+C: pharmacotherapy and CM by psychiatrist, over 6 wk. ADM usage: 100% Additional PT: 0%</td>
<td></td>
<td>24</td>
<td>BDI-II; HDRS-17</td>
</tr>
<tr>
<td>Teismann et al</td>
<td>(Recruited) partially remitted MDD (DSM-IV), based on the SCID; residual symptoms of BDI-II ≥9</td>
<td>HDRS-17: 15.39 Previous MDE: 4.1</td>
<td>RF-CBT: cognitive-behavioural small-group treatment for depressive rumination, in 11 weekly sessions for 90 min each. ADM usage: 38% Additional PT: 0%</td>
<td></td>
<td>12</td>
<td>BDI-II</td>
</tr>
</tbody>
</table>

Continued
### Table 1 Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of partial remission of MDD</th>
<th>Mean baseline severity</th>
<th>Final FU (mo)</th>
<th>Placebo/Iloperidone order</th>
<th>Treatment received</th>
<th>Sample (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionescu et al (2023)</td>
<td>HDRS-28: 20.2†</td>
<td>HDRS-28: 28</td>
<td>38*</td>
<td>MDD in partial remission (SCID); ≥8 on HDRS-28: 20.2†</td>
<td>Placebo/Iloperidone order</td>
<td>28</td>
</tr>
<tr>
<td>Segal et al (2023)</td>
<td>HDRS-28: 28</td>
<td>HDRS-28: 28</td>
<td>9</td>
<td>MDD in partial remission (SCID); ≥8 on HDRS-28: 28</td>
<td>Iloperidone/Placebo order</td>
<td>230</td>
</tr>
</tbody>
</table>

*Only included in qualitative review and meta-analysed.

**Additional PT:**
- CBT: cognitive-behavioural therapy.
- MBCT: mindfulness-based cognitive therapy.
- CBT-I: cognitive therapy.
- DRT: diet and relaxation therapy.
- TAU: treatment as usual.
- placebo: could include ADM, individual or group psychotherapy, or both, for period of 12 wk.

### Treatment efficacy: remission and relapse rates

Patients receiving psychotherapy were about two-and-a-half times more likely to achieve full remission post-treatment, compared with control conditions (OR 2.57; 95% CI 1.71 to 3.87; $\Gamma=0.0%$; 95% CI 0% to 79%; $k=5$). At follow-up 6 months or longer, patients receiving treatment were almost twice as likely to be in full remission (OR 1.75; 95% CI 1.21 to 2.53; $\Gamma=0.0%$; 95% CI 0% to 90%; $k=3$), indicating that treatment was superior to control conditions in attaining full remission. These results are presented in table 2. Pooled remission rates immediately post-treatment were estimated at 44.0% for the treatment group (95% CI 27.1% to 62.3%) and 20.6% for the control conditions (95% CI 10.4% to 36.7%). Remission rates were higher at follow-up 6 months or longer in both treatment (53.7%; 95% CI 34.4% to 72.0%) and control conditions (37.0%; 95% CI 15.6% to 65.1%).

Immediately post-treatment, psychotherapy was not significantly associated with differences in the odds of relapse, compared with those in the control conditions (OR 0.17; 95% CI 0.01 to 4.83; $\Gamma=63.6%$; 95% CI 0% to 89%; $k=3$). Similarly, as can be seen in table 2, after follow-up 6 months or more, no significant associations were found (OR 0.46; 95% CI 0.21 to 1.03, $\Gamma=0.0%$; 95% CI 0% to 90%; $k=3$). Pooled relapse rates immediately post-treatment were 5.7% for the treatment group (95% CI 0.4% to 48.3%) and 29.0% for the control conditions (95% CI 7.2% to 68.4%). These were somewhat higher at follow-up 6 months or longer, with 15.6% (95% CI 6.6% to 32.8%) experiencing a relapse after treatment compared with 30.6% (95% CI 14.5% to 53.3%) in the control conditions.

### Quality assessments

Overall, the risk of bias in the included studies was considerable. Methodological quality was rated as low with a high risk of bias (figure 3 and online supplemental figure 2). Two studies were rated as having ‘some concerns’ and five were rated as having high risk of bias (see justifications in online supplemental appendix 4). The quality of the evidence (GRADE) compared with control conditions for clinician-rated symptom severity (Hedges’ $g=0.37$; 95% CI $-0.04$ to 0.77; $I^2=38\%$; 95% CI 0% to 79%; $k=4$), although such associations were found for self-reported severity (Hedges’ $g=0.48$; 95% CI 0.23 to 0.73; $I^2=46\%$; 95% CI 0% to 77%; $k=7$). At 1–12 months follow-up, the pooled effect size was small but non-significant (Hedges’ $g=0.36$; 95% CI $-0.30$ to 1.02; $k=3$), with moderate heterogeneity ($I^2=67\%$; 95% CI 0% to 91%). Similarly, depression severity pooled effect sizes were small and non-significant after follow-up of 12 months or more (Hedges’ $g=0.02$; 95% CI $-0.09$ to 0.12; $I^2=0\%$; 95% CI 0% to 90%; $k=3$).
was downgraded and judged at very low—low for all pooled outcomes (see online supplemental table 3).

Conclusions and clinical implications
Partial remission of MDD is a debilitating clinical state related to relapse, chronicity, morbidity and dysfunction. As about one-third of patients with MDD achieves only partial remission, 3–7 the best treatment option for partial remission is unclear, objectively synthesising the available evidence becomes imperative. This systematic review and meta-analysis is the first to assess treatment efficacy, specifically focused on partial remission. We identified seven RCTs examining effects of CBT-derived psychotherapy, while, surprisingly, only three pharmacotherapy RCTs were found. This systematic review gives a first indication suggesting that psychotherapy for patients with partial remission of MDD is associated with superior effects on short-term depressive symptom severity and remission rates, compared with control conditions. That is, patients receiving treatment that targets partial remission were almost two-and-a-half times more likely to achieve full remission. While remission rates remained superior at follow-up, the effects on symptomatology wane in the long term after treatment cessation. Moreover, there seems to be a minimal effect of psychotherapy on relapse rates compared with control groups, in this at-risk group.

It is disappointing that treatment gains on depressive symptomatology, while evident for remission status, were not maintained at follow-up. This may likely be explained by the limited studies available at follow-up (k=3). Yet, short-term effects are still of clinical relevance, as partial remission is a robust predictor of chronicity.3, 7, 15–19 Moreover, previous meta-analyses showed that psychotherapy for acute MDD, including CBT, has enduring and prophylactic effects even after treatment termination, comparable to continuing pharmacotherapy after remission.4,5 46 In contrast, preventive effects of ADM disappear when they are discontinued or tapered.47 Another explanation for limited long-term outcomes in our meta-analysis may be that individuals in partial remission of MDD represent a distinct population in which different mechanisms contribute to the maintenance

Figure 2  Forest plot of random effects analysis on depressive symptom severity at post-treatment, comparing treatment with control conditions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges’ g (95% CI)</th>
<th>Hedges’ g</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teismann (2014)</td>
<td>1.10 [0.56; 1.65]</td>
<td>1.10</td>
<td>9.4%</td>
<td></td>
</tr>
<tr>
<td>Watkins (2011)</td>
<td>0.67 [0.05; 1.30]</td>
<td>0.67</td>
<td>7.8%</td>
<td></td>
</tr>
<tr>
<td>Geschwind (2012)</td>
<td>0.59 [0.23; 0.94]</td>
<td>0.59</td>
<td>15.7%</td>
<td></td>
</tr>
<tr>
<td>Segal (2020)</td>
<td>0.55 [0.37; 0.74]</td>
<td>0.55</td>
<td>23.8%</td>
<td></td>
</tr>
<tr>
<td>Holländare (2011)</td>
<td>0.48 [0.05; 0.91]</td>
<td>0.48</td>
<td>12.6%</td>
<td></td>
</tr>
<tr>
<td>Schögelhofer (2014)</td>
<td>0.24 [-0.17; 0.66]</td>
<td>0.24</td>
<td>13.2%</td>
<td></td>
</tr>
<tr>
<td>Paykel (1999)</td>
<td>0.13 [-0.18; 0.44]</td>
<td>0.13</td>
<td>17.5%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Effects for treatment on depressive symptomatology severity, remission and relapse rates

<table>
<thead>
<tr>
<th></th>
<th>k</th>
<th>N</th>
<th>Hedges’ g (95% CI)</th>
<th>OR (95% CI)</th>
<th>P value 95% PI</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptomatology</td>
<td>7</td>
<td>1024</td>
<td>0.50 (0.23 to 0.76)</td>
<td>0.004</td>
<td>−0.06 to 1.05</td>
<td>51.1 (0 to 79.2)</td>
</tr>
<tr>
<td>Rater</td>
<td>4</td>
<td>420</td>
<td>0.37 (−0.04 to 0.77)</td>
<td>0.064</td>
<td>−0.55 to 1.28</td>
<td>38.4 (0 to 79.0)</td>
</tr>
<tr>
<td>Self-reported</td>
<td>7</td>
<td>1024</td>
<td>0.48 (0.23 to 0.73)</td>
<td>0.004</td>
<td>0.02 to 0.94</td>
<td>45.5 (0 to 77.0)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3</td>
<td>702</td>
<td>0.36 (−0.30 to 1.02)</td>
<td>0.145</td>
<td>−3.00 to 3.72</td>
<td>66.9 (0 to 90.5)</td>
</tr>
<tr>
<td>≥12 months</td>
<td>3</td>
<td>702</td>
<td>0.02 (−0.09 to 0.12)</td>
<td>0.579</td>
<td>−0.94 to 0.98</td>
<td>0 (0 to 89.6)</td>
</tr>
<tr>
<td>Remission rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-treatment</td>
<td>5</td>
<td>804</td>
<td>2.57 (1.71 to 3.87)</td>
<td>0.003</td>
<td>1.56 to 4.22</td>
<td>0 (0 to 79.2)</td>
</tr>
<tr>
<td>≥6 months follow-up</td>
<td>3</td>
<td>702</td>
<td>1.75 (1.21 to 2.53)</td>
<td>0.023</td>
<td>0.25 to 12.42</td>
<td>0 (0 to 89.6)</td>
</tr>
<tr>
<td>Relapse rates</td>
<td>3</td>
<td>284</td>
<td>0.17 (0.01 to 0.48)</td>
<td>0.150</td>
<td>*</td>
<td>62.7 (0 to 89.3)</td>
</tr>
<tr>
<td>≥6 months follow-up</td>
<td>3</td>
<td>702</td>
<td>0.46 (0.21 to 1.03)</td>
<td>0.053</td>
<td>0.04 to 5.35</td>
<td>0 (0 to 89.6)</td>
</tr>
</tbody>
</table>

*PI is not reported for this outcome, as the estimate is too broad to be useful given the limited number of studies and considerable heterogeneity.

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of symptomatology and relapse. Note that these short-term effects are consistent with those found for subthreshold depression, where psychotherapy had a small-to-moderate effect on symptomatology immediately post-treatment.\textsuperscript{48} Notably, treatment effects were significantly larger in studies using TAU-only control conditions, compared with studies in which all patients were taking ADM. This is unsurprising, as ADM is an established treatment option for MDD and would thus comprise an active control condition, leading to fewer group differences.\textsuperscript{8 10}

Furthermore, treatment was associated with superior remission rates at both post-treatment (44\%) and follow-up (54\%). In contrast to studies focusing on relapse prevention in remitted MDD, we found no significant effect of psychotherapy on relapse rates. While the overall relapse rate was lower than expected,\textsuperscript{3 5 16 18} there was a pronounced trend at follow-up indicating superior associations with treatment compared with control conditions. It should be noted that the effects may be underestimated due to a lack of statistical power, as well as the time it takes to observe effects on relapse rates. These findings seem to support the distinction between relapse rates as an indication of long-term durability of effects, compared with remission. Longer follow-up times may thus be a more representative exposure to estimate efficacy of relapse prevention.\textsuperscript{69} Contrary to our findings, such preventive effects of psychotherapy have repeatedly been found among patients with remitted MDD.\textsuperscript{9}

Because pharmacological RCTs targeting partial remission are scarce, we could not provide a robust estimate of their effectiveness. Pharmacotherapeutic trials examined different augmentation strategies but yielded conflicting results. Nevertheless, the current study overall provides initial evidence to suggest that offering psychotherapy specifically to patients in partial remission is associated with superior outcomes. These results should still be interpreted with caution, given the limited number of studies, as well as differences in methodological design and treatments. Therefore, importantly, no firm conclusions can be made for some outcomes and treatment modalities, and results are insufficiently robust to definitively guide clinical practice. Nevertheless, findings inform shared decision-making as they suggest that CBT may be at least for the short term an effective treatment for patients in partial remission. Future research should address these issues to optimise depression outcomes in partially remitted patients and reduce their future risk profile.

Our systematic review and meta-analysis has several strengths. To our knowledge, it is the first systematic study to provide an overview of treatment options specifically targeting partial remission in MDD and their efficacy. Additionally, we used a rigorous study protocol with strict inclusion criteria, followed a comprehensive search strategy and, most importantly, stated a clear definition for partial remission of MDD to increase sample homogeneity, in line with previous research.\textsuperscript{7 27 28}

However, several limitations should be noted. Our study was limited by the number of RCTs available, and the relatively small samples in some trials, especially at follow-up. Especially pharmacotherapy RCTs specifically targeting partial remission and trials examining relapse rates were scarce. This may have led to underpowered designs and results should be interpreted with caution. Another source of uncertainty is the considerable heterogeneity and its wide CIs, possibly due to differences in the pooled interventions (eg, treatment length or self-help vs operator-led interventions) or follow-up length. We were unable to adequately examine these differences using extracted study and intervention characteristics by applying subgroup and meta-regression analyses, given the number of studies required to ensure adequate power. Furthermore, the level of evidence was rated as very low or low, due to an overall poor methodological quality of primary studies. While the risk of bias was considerable, our results may still provide valuable input for clinical guidelines. Even more so, it helps setting the agenda for future research by underscoring the importance to conduct high-quality trials with longer follow-ups to examine the efficacy of
treatments that target partial remission. Lastly, this meta-analysis was inherently limited by the availability and usage of aggregate data, and we could not take individual patient profiles, including prognostic or moderating factors, into account. Future research should pool RCT data using an individual patient data meta-analysis approach, offering more power and precision. This might allow for the differentiation of specific patient profiles. Future research on the efficaciousness of treatment for this at-risk population should incorporate such a personalised medicine approach, to improve clinical practice.

Given the chronic trajectory of depression in patients in partial remission, we call for well-designed and adequately powered studies to examine innovative, sequential or combined treatment options to get patients well and facilitate endurance underling mechanisms may help improve outcomes.

CONCLUSIONS

Partial remission of MDD is a debilitating clinical phase associated with a poor prognosis. This meta-analysis suggests that CBTr-derived psychotherapy targeting partial remission may be an effective treatment option. Psychotherapy, relative to control conditions, seems effective in alleviating symptomatology at post-treatment and was associated with increased remission rates, with patients twice as likely to achieve full remission. Long-term and prophylactic effects, including the effects on relapse prevention, were limited, likely due to limited statistical power. Given the lack of pharmacotherapy trials that target partial remission and considerable heterogeneity, more high-quality trials examining long-term effects are warranted, to assess efficacy more accurately in this at-risk population. These novel findings are nevertheless promising and a first indication that psychotherapy has significant relevance for patients with partial remission of MDD.

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