National Institute for Health and Care Excellence

FINAL

Depression in adults

[F] Depression with coexisting personality disorder

NICE guideline NG222

Evidence review underpinning recommendations 1.11.1 to 1.11.4 in the NICE guideline

June 2022

Final

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Review question

For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Introduction

The interrelationship between depression and personality disorder (PD) poses clinical problems, since both depression and some types of personality disorder may be viewed as emotion regulation disorders and either may present with irritability, distress or depression at any one time-point. Therefore a careful clinical assessment, including longitudinal assessment of mood, may be needed to make a reliable diagnosis. Additionally, since both depression and PD may share important antecedents, including early trauma, and they frequently co-occur, final diagnosis may conclude an individual has both depression and PD. While clinical services for depression and PD may exist separately and NICE guidance is available for PD, there are associated clinical risks of under-treating, or incorrectly treating, either the PD or the depression, although the symptoms of PD may improve on recovery from depression. The situation is further complicated by the fact that PD is not a single disease, and there are a number of different types of PD with different presentations that may respond differently to treatment.

In reviewing the evidence for further-line treatment (see Evidence review D), the committee agreed that it was not meaningful to separate out subgroups with coexisting personality disorders, psychotic depression, and chronic depression. Therefore, a single category was formed 'further-line treatment' which combined all these groups where participants are randomised at the point of non-response and treatment strategies include increasing dose, augmenting or switching. However, the committee were also aware that there are people with depression and a coexisting PD who have not received treatment for the current episode, or who have recovered following initial treatment, and that it was not appropriate to combine these groups with those who have shown an inadequate response to initial treatment. The committee therefore agreed to review the evidence for first-line treatment and relapse prevention of depression with a coexisting PD in the current evidence report, and the evidence for further-line treatment of depression with a coexisting PD is considered in the context of a broader evidence base in Evidence review D.

The aim of this review is to identify the most effective first-line or relapse prevention treatment strategy for the co-occurrence of depression and PD and to give guidance on the available management choices.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with depression and a coexisting personality disorder
Intervention	Psychological interventions: • Behavioural therapies • Cognitive and cognitive behavioural therapies

	• Counselling • Family interventions/couples therapy • Psychodynamic psychotherapies • Self-help with or without support • Art therapy • Music therapy • Eye movement desensitization and reprocessing (EMDR) (for depression, not PTSD) Psychosocial interventions: • Peer support (including befriending, mentoring, and community navigators) • Mindfulness, meditation or relaxation Pharmacological interventions: • SSRIs • TCAs • SNRIs • Other antidepressant drugs (including mirtazapine and trazodone) • Antipsychotics • Lithium • Omega-3 fatty acids Physical interventions: • Acupuncture • ECT • Exercise • Yoga • Light therapy (for depression, not SAD)
Comparison	• Treatment as usual • Waitlist • No treatment • Placebo • Other active intervention (must also meet inclusion criteria above)
Outcomes	**Critical:** • Depression symptomatology • Remission • Response • Relapse (for relapse prevention strategies) • Discontinuation due to any reason • Discontinuation due to side effects (for pharmacological trials) **Important:** • Quality of life • Personal, social, and occupational functioning

ECT: electroconvulsive therapy; PTSD: post-traumatic stress disorder; SAD: seasonal affective disorder; SNRI: serotonin-noradrenaline reuptake inhibitors; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

For further details, see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Ten RCTs were included in this review. Due to one study reporting on a 4 arm trial (Shea 1990), there were 13 different comparisons. Of the 10 RCTs, 3 included only those with depression and coexisting PD, and so all reported data could be used. The remaining 7 RCTs included people with depression with and without a coexisting PD but analysed those with a coexisting PD as a subgroup, for these studies only the subgroup data was extracted and used.

All the RCTs included examined first-line treatment of depression and coexisting PD, and no studies were identified for relapse prevention strategies for depression with coexisting PD.

The included studies are summarised in Table 2 to Table 14.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

See appendix K for studies not included in this review with reasons for their exclusion.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2 to Table 14.

Table 2: Summary of included studies. Comparison 1. Behavioural therapy versus short-term psychodynamic psychotherapy

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Liberman 1981 RCT US	N=28 Mean age (years): 29.7 Gender (% female): 67 Ethnicity (% BME): NR	Behaviour therapy + TAU Intensity: 4-hours of therapy a day over 8-day period (32 hours in total)	Insight-oriented therapy + TAU Intensity: 4-hours of therapy a day over 8-day period (32 hours in total)	Primary RCT (inclusion criteria do not include diagnosis of depression or personality disorder but all participants would meet DSM-III	Treatment length (weeks): 1 Outcomes: • Depression symptomatology at endpoint • Depression symptomatology at 1-month follow-up

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	Baseline severity: BDI 25.5 (more severe) Type of personality disorder: NR (most patients would meet DSM-III criteria for an axis 2 disorder)			criteria for MDE, dysthymic disorder, or adjustment disorder with depression, and most patients would meet DSM-III criteria for an axis 2 disorder)	• Depression symptomatology at 3-month follow-up • Depression symptomatology at 6-month follow-up • Depression symptomatology at 8-month follow-up

BDI: Beck depression inventory; BME: black and minority ethnic; DSM: diagnostic statistical manual; MDE: major depressive episode; NR: not reported; RCT: randomised controlled trial; TAU: treatment as usual

Table 3: Summary of included studies. Comparison 2. Cognitive behavioural therapy versus counselling

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Erkens 2018 RCT Germany	N=103 Mean age (years): 45.4 Gender (% female): 64 Ethnicity (% BME): NR Baseline severity: HAMD 25.32 (more severe) Type of personality disorder: Subgroup analysis of those with a personality disorder diagnosis (not antisocial, schizotypal, or borderline	Cognitive Behavioural Analysis System of Psychotherapy (CBASP) Intensity: 20x weekly or twice-weekly sessions (+ 8 monthly post-acute-treatment booster sessions)	Non-specific supportive psychotherapy (SP) Intensity: 20x weekly or twice-weekly sessions (+ 8 monthly post-acute-treatment booster sessions)	Subgroup analysis	Treatment length (weeks): 20 Outcome: • Depression symptomatology at endpoint

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	personality disorder, which were exclusion criteria for the trial). Of those included in the subgroup analysis, 84% had ≥1 cluster C PD, mostly anxious avoidant (62%) or obsessive-compulsive (39%)				

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; PD: personality disorder; RCT: randomised controlled trial

Table 4: Summary of included studies. Comparison 3. Cognitive behavioural therapy versus interpersonal therapy

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Shea 1990 RCT US	N=86 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR Type of personality disorder[a]: Subgroup analysis of those with any personality disorder (except antisocial personality	CBT individual Intensity: 16-20x weekly 50-min sessions	IPT Intensity: 16-20x weekly 50-min sessions	Subgroup analysis	Treatment length (weeks): 16 Outcome: • Depression symptomatology at endpoint

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	disorder, which was an exclusion criterion for the trial), assessed using clinical cut-offs on the Personality Assessment Form. 87% scored above clinical cut-off for anxious-fearful axis II cluster, 26% odd-eccentric cluster, and 22% dramatic-erratic cluster (do not sum to 100% as 30% scored above clinical cut-off for >1 PD)				
van Bronswijk 2018 RCT Netherlands	N=49 Mean age (years): 41.1 Gender (% female): 63 Ethnicity (% BME): NR Baseline severity: BDI-II 32.16 (more severe) Type of personality disorder: Subgroup analysis of those with one or more DSM-IV Axis II disorder: 46% had avoidant PD; 32% had	Cognitive therapy Intensity: 16-20 x 45-min sessions	IPT Intensity: 16-20 x 45-min sessions	Subgroup analysis	Treatment length (weeks): 30 Outcomes: • Depression symptomatology at 5-month follow-up • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	obsessive-compulsive PD; 6% paranoid PD; 6% borderline PD; 3% dependent PD; 3% schizotypal PD; 2% schizoid PD; 2% PD not otherwise specified.				

[a]*Personality disorder percentages based on the whole 4-armed trial and not only the 2 arms included here*
BDI-II: Beck depression inventory; BME: black and minority ethnic; CBT: cognitive behavioural therapy; DSM: diagnostic statistical manual; IPT: interpersonal therapy; NR: not reported; PD: personality disorder; RCT: randomised controlled trial

Table 5: Summary of included studies. Comparison 4. Cognitive behavioural therapy versus short-term psychodynamic psychotherapy

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Hardy 1995 RCT UK	N=27 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: BDI 25.05 (more severe) Type of personality disorder: Subgroup analysis of those with a DSM-III-R diagnosis of ≥1 cluster C personality disorder (33%	CBT individual Intensity: 8 or 16 sessions weekly (2 arms combined)	Psychodynamic-interpersonal psychotherapy Intensity: 8 or 16 sessions weekly (2 arms combined)	Subgroup analysis	Treatment length (weeks): 8 or 16 weeks (2 arms combined) Outcomes: • Depression symptomatology at endpoint • Depression symptomatology at 3-month follow-up • Depression symptomatology at 12-month follow-up • Interpersonal problems at endpoint • Interpersonal problems at 3-month follow-up • Interpersonal problems at

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	had 2 PD diagnoses): 11% avoidant disorder and obsessive-compulsive disorder; 19% avoidant and dependent; 4% obsessive-compulsive and dependent; 19% avoidant only; 37% obsessive-compulsive only; 11% dependent only.				12-month follow-up

BDI: Beck depression inventory; BME: black and minority ethnic; DSM: diagnostic statistical manual; NR: not reported; PD: personality disorder; RCT: randomised controlled trial

Table 6: Summary of included studies. Comparison 5. Cognitive behavioural therapy versus pill placebo

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Shea 1990[a] RCT US	N=93 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR Type of personality disorder[a]: Subgroup analysis of those with any personality disorder	CBT individual Intensity: 16-20x 50-min sessions	Pill placebo Intensity: NR	Subgroup analysis	Treatment length (weeks): 16 Outcome: • Depression symptomatology at endpoint

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	(except antisocial personality disorder, which was an exclusion criterion for the trial), assessed using clinical cut-offs on the Personality Assessment Form. 87% scored above clinical cut-off for anxious-fearful axis II cluster, 26% odd-eccentric cluster, and 22% dramatic-erratic cluster (do not sum to 100% as 30% scored above clinical cut-off for >1 PD)				

[a]*Personality disorder percentages based on the whole 4-armed trial and not only the 2 arms included here*
BME: black and minority ethnic; NR: not reported; RCT: randomised controlled trial

Table 7: Summary of included studies. Comparison 6. Cognitive behavioural therapy versus antidepressant

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Fournier 2008 RCT US	N=86 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR Type of personality disorder:	Cognitive therapy Intensity: 20-28 x 50-minute weekly or twice-weekly sessions	Paroxetine Intensity: NR	Subgroup analysis	Treatment length (weeks): 16 Outcomes: • Remission • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	Subgroup analysis of those with a DSM-III-R diagnosis of personality disorder (not antisocial, borderline, or schizotypal PDs which were excluded from the trial), proportions with cluster C (avoidant, dependent, obsessive-compulsive), cluster A (paranoid, schizoid), and cluster B (histrionic, narcissistic) NR for subgroup analysis.				
Shea 1990 RCT US	N=89 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR Type of personality disorder[a]: Subgroup analysis of those with any personality disorder (except antisocial personality disorder, which was an	CBT individual Intensity: 16-20x 50-min sessions	Imipramine Intensity: NR	Subgroup analysis	Treatment length (weeks): 16 Outcome: • Depression symptomatology at endpoint

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	exclusion criterion for the trial), assessed using clinical cut-offs on the Personality Assessment Form. 87% scored above clinical cut-off for anxious-fearful axis II cluster, 26% odd-eccentric cluster, and 22% dramatic-erratic cluster (do not sum to 100% as 30% scored above clinical cut-off for >1 PD)				

[a]*Personality disorder percentages based on the whole 4-armed trial and not only the 2 arms included here*
BME: black and minority ethnic; DSM: diagnostic statistical manual; NR: not reported; PD: personality disorder; RCT: randomised controlled trial

Table 8: Summary of included studies. Comparison 7. CBT + fluoxetine versus IPT + fluoxetine

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Bellino 2007 RCT Italy	N=32 Mean age (years): 30.6 Gender (% female): 73 Ethnicity (% BME): NR Baseline severity: HAMD 19.7 (more severe) Type of personality disorder:	Cognitive therapy + fluoxetine Intensity: 24 x 1-hour weekly sessions + fluoxetine 20-40mg/day	IPT + fluoxetine Intensity: 24 x 1-hour weekly sessions + fluoxetine 20-40mg/day	Primary RCT (all participants met DSM-IV-TR criteria for borderline personality disorder and MDE)	Treatment length (weeks): 24 Outcomes: • Depression symptomatology at endpoint • Remission • Discontinuation due to any reason • Global functioning at endpoint

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	Borderline personality disorder				

BME: black and minority ethnic; CBT: cognitive behavioural therapy; DSM: diagnostic statistical manual; HAMD: Hamilton depression scale; IPT: interpersonal therapy; MDE: major depressive episode; NR: not reported; RCT: randomised controlled trial

Table 9: Summary of included studies. Comparison 8. IPT versus pill placebo

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Shea 1990 RCT US	N=89 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR Type of personality disorder[a]: Subgroup analysis of those with any personality disorder (except antisocial personality disorder, which was an exclusion criterion for the trial), assessed using clinical cut-offs on the Personality Assessment Form. 87% scored above clinical cut-off for anxious-fearful axis II cluster, 26% odd-eccentric	IPT Intensity: 16-20x 50-min sessions	Pill placebo Intensity: NR	Subgroup analysis	Treatment length (weeks): 16 Outcome: • Depression symptomatology at endpoint

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	cluster, and 22% dramatic-erratic cluster (do not sum to 100% as 30% scored above clinical cut-off for >1 PD)				

[a]*Personality disorder percentages based on the whole 4-armed trial and not only the 2 arms included here*
BME: black and minority ethnic; IPT: interpersonal therapy; NR: not reported; PD: personality disorder; RCT: randomised controlled trial

Table 10: Summary of included studies. Comparison 9. IPT versus imipramine

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Shea 1990 RCT US	N=85 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR Type of personality disorder[a]: Subgroup analysis of those with any personality disorder (except antisocial personality disorder, which was an exclusion criterion for the trial), assessed using clinical cut-offs on the Personality Assessment Form. 87% scored above	IPT Intensity: 16-20x 50-min sessions	Imipramine Intensity: NR	Subgroup analysis	Treatment length (weeks): 16 Outcome: • Depression symptomatology at endpoint

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	clinical cut-off for anxious-fearful axis II cluster, 26% odd-eccentric cluster, and 22% dramatic-erratic cluster (do not sum to 100% as 30% scored above clinical cut-off for >1 PD)				

[a]*Personality disorder percentages based on the whole 4-armed trial and not only the 2 arms included here*
BME: black and minority ethnic; IPT: interpersonal therapy; NR: not reported; RCT: randomised controlled trial

Table 11: Summary of included studies. Comparison 10. IPT + fluoxetine versus fluoxetine

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Bellino 2006 RCT Italy	N=39 Mean age (years): 26.4 Gender (% female): 63 Ethnicity (% BME): NR Baseline severity: HAMD 19.1 (more severe) Type of personality disorder: Borderline personality disorder	IPT + fluoxetine Intensity: 24 x weekly 1-hour sessions + fluoxetine 20-40mg/day	Fluoxetine Intensity: 20-40mg/day	Primary RCT (all participants met DSM-IV-TR criteria for borderline personality disorder and MDE)	Treatment length (weeks): 24 Outcomes: • Depression symptomatology at endpoint • Remission • Discontinuation due to any reason

BME: black and minority ethnic; CBT: cognitive behavioural therapy; DSM: diagnostic statistical manual; HAMD: Hamilton depression scale; IPT: interpersonal therapy; MDE: major depressive episode; NR: not reported; RCT: randomised controlled trial

Table 12: Summary of included studies. Comparison 11. Short-term psychodynamic psychotherapy + any antidepressant versus any antidepressant

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Kool 2003 RCT Netherlands	N=85 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: HAMD 20.39 (more severe) Type of personality disorder: Subgroup analysis of those with DSM-III-R PD. Proportions NR for subgroup analysis but most common types of PD were paranoid, avoidant, dependent, and borderline	Short-term psychodynamic supportive psychotherapy + any antidepressant (based on algorithm) Intensity: 16 x weekly or fortnightly 45-min sessions + antidepressant (fluoxetine 20 mg/day; amitriptyline 100-150mg/day; moclobemide 300-600mg/day)	Any antidepressant (based on algorithm) Intensity: Fluoxetine 20 mg/day; amitriptyline 100-150mg/day; moclobemide 300-600mg/day	Subgroup analysis	Treatment length (weeks): 24 Outcomes: • Depression symptomatology at endpoint • Remission • Quality of life

BME: black and minority ethnic; DSM: diagnostic statistical manual; HAMD: Hamilton depression scale; NR: not reported; PD: personality disorder; RCT: randomised controlled trial

Table 13: Summary of included studies. Comparison 12. Fluoxetine versus nortriptyline

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Joyce 2003 RCT New Zealand	N=83 Mean age (years): 30.4 Gender (% female): 52	Fluoxetine 10-80mg/day	Nortriptyline 50-175mg/day	Subgroup analysis	Treatment length (weeks): 6 Outcomes: • Depression symptomatology endpoint

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	Ethnicity (% BME): NR Baseline severity: MADRS 32.69 (more severe) Type of personality disorder: Subgroup analysis of those with DSM-III-R PD diagnosis: 36% borderline personality disorder; 64% other PD (including 42% avoidant PD)				• Response • Discontinuation due to any reason

BME: black and minority ethnic; DSM: diagnostic statistical manual; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; PD: personality disorder; RCT: randomised controlled trial

Table 14: Summary of included studies. Comparison 13. Imipramine versus pill placebo

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
Shea 1990 RCT US	N=92 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR Type of personality disorder[a]: Subgroup analysis of those with any	Imipramine Intensity: NR	Pill placebo Intensity: NR	Subgroup analysis	Treatment length (weeks): 16 Outcome: • Depression symptomatology endpoint

Study	Population	Intervention	Comparison	Primary RCT or subgroup analysis	Comments
	personality disorder (except antisocial personality disorder, which was an exclusion criterion for the trial), assessed using clinical cut-offs on the Personality Assessment Form. 87% scored above clinical cut-off for anxious-fearful axis II cluster, 26% odd-eccentric cluster, and 22% dramatic-erratic cluster (do not sum to 100% as 30% scored above clinical cut-off for >1 PD)				

[a]*Personality disorder percentages based on the whole 4-armed trial and not only the 2 arms included here*
BME: black and minority ethnic; NR: not reported; RCT: randomised controlled trial

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

A list of excluded economic and utility studies, with reasons for exclusion, is provided in supplement 3 - Health economic included & excluded studies.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Very little meta-analysis was possible for this review, with only one outcome including more than 1 study and even then only 2 studies were included. This was due to variability in the comparisons and outcomes reported, which meant that in the vast majority of instances no 2 studies were reporting on the same outcome for the same comparison.

Comparison 1: Behavioural therapy versus short-term psychodynamic psychotherapy

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=24) shows a clinically important and statistically significant benefit of behavioural therapy, relative to short-term psychodynamic psychotherapy, on depression symptomatology at endpoint for adults with depression and coexisting personality disorder.
- Very low quality evidence from 1 RCT (N=24) shows neither a clinically important nor statistically significant difference between behavioural therapy and short-term psychodynamic psychotherapy on depression symptomatology at 1-month follow-up, for adults with depression and coexisting personality disorder.
- Very low quality evidence from 1 RCT (N=24) shows a clinically important but not statistically significant benefit of behavioural therapy, relative to short-term psychodynamic psychotherapy, on depression symptomatology at 3-month follow-up for adults with depression and coexisting personality disorder.
- Very low quality evidence from 1 RCT (N=24) shows a clinically important and statistically significant benefit of behavioural therapy, relative to short-term psychodynamic psychotherapy, on depression symptomatology at 6-month follow-up for adults with depression and coexisting personality disorder.
- Very low quality evidence from 1 RCT (N=24) shows neither a clinically important nor statistically significant difference between behavioural therapy and short-term psychodynamic psychotherapy on depression symptomatology at 8-month follow-up, for adults with depression and coexisting personality disorder.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 2: Cognitive behavioural therapy versus counselling

Critical outcomes

Depression symptomatology

- Low quality evidence from 1 RCT (N=103) shows neither a clinically important nor statistically significant difference between CBT and counselling on depression symptomatology at endpoint, for adults with depression and coexisting personality disorder.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 3: Cognitive behavioural therapy versus interpersonal therapy

Critical outcomes

Depression symptomatology

- Low quality evidence from 2 RCTs (N=135) shows neither a clinically important nor statistically significant difference between CBT and IPT on depression symptomatology at endpoint, for adults with depression and coexisting personality disorder.

- Very low quality evidence from 1 RCT (N=49) shows neither a clinically important nor statistically significant difference between CBT and IPT on depression symptomatology at 5-month follow-up, for adults with depression and coexisting personality disorder.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=49) shows a higher rate of discontinuation due to any reason associated with CBT relative to IPT for adults with depression and coexisting personality disorder, however this effect is not statistically significant.

Important outcomes

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 4: Cognitive behavioural therapy versus short-term psychodynamic psychotherapy

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=24-27) shows neither a clinically important nor statistically significant difference between CBT and short-term psychodynamic psychotherapy on depression symptomatology at endpoint and at 3-month and 12-month follow-up, for adults with depression and coexisting personality disorder.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- Very low quality evidence from 1 RCT (N=24-27) shows neither a clinically important nor statistically significant difference between CBT and short-term psychodynamic psychotherapy on interpersonal problems at endpoint and at 3-month and 12-month follow-up, for adults with depression and coexisting personality disorder.

Comparison 5: Cognitive behavioural therapy versus pill placebo

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=93) shows a statistically significant but not clinically important benefit of CBT, relative to pill placebo, on depression symptomatology at endpoint for adults with depression and coexisting personality disorder.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 6: Cognitive behavioural therapy versus antidepressant

Critical outcomes

Depression symptomatology

- Low quality evidence from 1 RCT (N=89) shows neither a clinically important nor statistically significant difference between CBT and imipramine on depression symptomatology at endpoint, for adults with depression and coexisting personality disorder.

Remission

- Very low quality evidence from 1 RCT (N=86) shows a lower rate of remission associated with CBT relative to paroxetine for adults with depression and coexisting personality disorder, however this effect is not statistically significant.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=86) shows a higher rate of discontinuation due to any reason associated with CBT relative to paroxetine for adults with depression and coexisting personality disorder, however this effect is not statistically significant.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 7: CBT + fluoxetine versus IPT + fluoxetine

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=26) shows neither a clinically important nor statistically significant difference between combined CBT and fluoxetine and combined IPT and fluoxetine on depression symptomatology at endpoint, for adults with depression and coexisting personality disorder.

Remission

- Very low quality evidence from 1 RCT (N=32) shows neither a clinically important nor statistically significant difference between combined CBT and fluoxetine and combined IPT and fluoxetine on the rate of remission, for adults with depression and coexisting personality disorder.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=32) shows a higher rate of discontinuation due to any reason associated with combined CBT and fluoxetine relative to combined IPT and fluoxetine for adults with depression and coexisting personality disorder, however this effect is not statistically significant.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- Low quality evidence from 1 RCT (N=26) shows a clinically important but not statistically significant benefit of combined CBT and fluoxetine, relative to combined IPT and fluoxetine, on global functioning at endpoint for adults with depression and coexisting personality disorder.

Comparison 8: IPT versus pill placebo

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=89) shows neither a clinically important nor statistically significant difference between IPT and pill placebo on depression symptomatology at endpoint, for adults with depression and coexisting personality disorder.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 9: IPT versus imipramine

Critical outcomes

Depression symptomatology

- Low quality evidence from 1 RCT (N=85) shows neither a clinically important nor statistically significant difference between IPT and imipramine on depression symptomatology at endpoint, for adults with depression and coexisting personality disorder.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 10: IPT + fluoxetine versus fluoxetine

Critical outcomes

Depression symptomatology

- Low quality evidence from 1 RCT (N=32) shows a clinically important and statistically significant benefit of combined IPT and fluoxetine, relative to fluoxetine-only, on depression symptomatology at endpoint for adults with depression and coexisting personality disorder.

Remission

- Very low quality evidence from 1 RCT (N=39) shows a higher rate of remission associated with combined IPT and fluoxetine relative to fluoxetine-only for adults with depression and coexisting personality disorder, however this effect is not statistically significant.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=39) shows a lower rate of discontinuation due to any reason associated with combined IPT and fluoxetine relative to fluoxetine-only for adults with depression and coexisting personality disorder, however this effect is not statistically significant.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 11: Short-term psychodynamic psychotherapy + any antidepressant versus any antidepressant

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=85) shows a statistically significant but not clinically important benefit of combined short-term psychodynamic psychotherapy and antidepressant treatment, relative to antidepressant treatment alone, on depression symptomatology at endpoint for adults with depression and coexisting personality disorder.

Remission

- Very low quality evidence from 1 RCT (N=85) shows a clinically important and statistically significant benefit of combined short-term psychodynamic psychotherapy and antidepressant treatment, relative to antidepressant treatment alone, on the rate of remission for adults with depression and coexisting personality disorder.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes:

Quality of life

- Very low quality evidence from 1 RCT (N=85) shows a clinically important and statistically significant benefit of combined short-term psychodynamic psychotherapy and antidepressant treatment, relative to antidepressant treatment alone, on quality of life for adults with depression and coexisting personality disorder.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 12: Fluoxetine versus nortriptyline

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=83) shows neither a clinically important nor statistically significant difference between fluoxetine and nortriptyline on depression

symptomatology at endpoint, for adults with depression and coexisting personality disorder.

Remission

No evidence was identified for this outcome.

Response

- Very low quality evidence from 1 RCT (N=83) shows neither a clinically important nor statistically significant difference between fluoxetine and nortriptyline on the rate of response, for adults with depression and coexisting personality disorder.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=83) shows a lower rate of discontinuation due to any reason associated with fluoxetine relative to nortriptyline for adults with depression and coexisting personality disorder, however this effect is not statistically significant.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 13: Imipramine versus pill placebo

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=92) shows neither a clinically important nor statistically significant difference between imipramine and pill placebo on depression symptomatology at endpoint, for adults with depression and coexisting personality disorder.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to identify the most effective treatments for depression in people with a coexisting personality disorder, so the committee prioritised depression symptomatology, remission and response as critical outcomes. Where interventions were targeted at keeping people who were in full or partial remission well, relapse was identified as a critical outcome. As a treatment can only be effective if it is utilised by the person with depression, discontinuation due to side effects and discontinuation due to any reason were also prioritised by the committee as critical outcomes.

The aim of treating depression is to improve people's life and so health-related quality of life and personal, social and occupational functioning were chosen as important outcomes. The committee were cognisant that for people with depression, quality of life may be the most valued outcome, however, it was not prioritised as a critical outcome as the committee were aware that the data for this outcome was very limited, and so was less useful for making decisions

Due to the difficulties in engaging this group of people in treatment and the perception that outcomes may be poorer in this group, the committee placed the greatest emphasis on remission data and discontinuation rates.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. Overall the evidence was of low to very low quality. It was downgraded due to high risk of bias across multiple domains and wide confidence intervals (imprecision commonly associated with small sample sizes). Additionally, although there were a large number of comparisons, these largely included only single studies.

Depression symptomatology was reported for all comparisons, but only 4 comparisons reported remission and 1 reported response. Five comparisons reported discontinuation rates, 2 reported functional outcomes and only 1 reported quality of life.

Benefits and harms

The committee discussed the fact that in some cases people with personality disorders were not treated for comorbid depression, and that it was important to ensure they were treated for depression. They therefore made a recommendation to state this based on their own experience and knowledge.

The committee noted that there was some evidence of benefit on depression symptomatology for 2 of the comparisons of monotherapies: CBT alone compared to pill placebo, and behavioural therapy alone compared to short-term psychodynamic psychotherapy. There was also evidence for clinical benefit from studies with combined psychological (either IPT or short-term psychodynamic psychotherapy) and pharmacological treatment when compared with pharmacological monotherapy. Other evidence comparing psychological treatments to pill placebo, pharmacological treatments to pill placebo, one psychological treatment with another, one pharmacological treatment with another, or a psychological treatment to a pharmacological treatment showed no significant differences. The committee therefore recommended that in people with depression and coexisting personality disorder, their depression should be treated with a combination of an antidepressant and a psychological therapy.

The committee noted that although, based on the evidence, treatments combining an antidepressant with a high-intensity psychological intervention appeared to be the most effective, the evidence base for this question was limited in volume, with only small RCTs of low or very low quality. Consequently, they were only able to recommend combination treatment be 'considered' and they were not able to recommend a specific antidepressant or psychological therapy, but agreed that this would depend on the person's preference.

The committee were aware, based on their clinical experience and knowledge, of the significant problems in engaging, and ensuring uptake of treatment, for people with depression and a coexisting personality disorder. They therefore recommended that support should be provided to encourage uptake and engagement. A multi-disciplinary setting was considered by the committee to be important due to the complexity of the difficulties experienced by this population, as this allows access to appropriate expertise. On the basis of their knowledge and clinical experience, and their concerns that some people may not receive an adequate 'dose' of treatment, the committee decided that it was important to specify that it may be necessary to extend the duration of treatment, relative to the length and frequency of treatment that individuals experiencing a depressive episode without a coexisting personality disorder may receive. They noted that this will not always be appropriate, and therefore decided to add the qualifying statement 'if needed' to indicate that this is best left to clinical judgement.

The committee noted that this review covered people with depression comorbid with a personality disorder, but that there are different types of personality disorder and it was not always clear from the evidence which types had been included, or if all types had been combined and considered. The committee agreed that one of the most common types is emotionally unstable personality disorder (previously known as borderline personality disorder) and they were aware that there is existing NICE guidance about the treatment of people with borderline personality disorders with comorbid depression which recommends treatment within a well-structured treatment programme for borderline personality disorder. The committee therefore wanted to make recommendations that were in line with the existing NICE guideline on borderline personality disorder, and so recommended that referral to a specialist personality treatment disorder programme should be considered.

The committee considered that possible harms would be inadequate duration and intensity of treatment or the provision of ineffective treatment, or the potential for pharmacological treatment to exacerbate mood instability, adding to the importance of prospective mood monitoring for these patients during treatment initiation or change. However, they agreed that the percentage of people who were likely to benefit from these recommendations would be higher than those experiencing any harms.

Longer-term follow-up

The committee noted that very few studies of depression with coexisting PD reported any follow-up data. The committee considered this limited evidence, and noted that there was no evidence for sustained clinically important and statistically significant benefits on depression outcomes associated with any of the interventions included in the review. This was consistent with broader uncertainty associated with the limited evidence base and contributed to the committee agreement that they were only able to recommend that combination psychological and antidepressant treatment be 'considered'.

Quality of life and functioning outcomes

The committee also noted that there was very little data for quality of life or functioning outcomes. There was no evidence for clinically important and statistically significant effects on quality of life or functioning associated with any of the interventions included in the review. Given the sparsity of this evidence, and that it is broadly consistent with the findings observed for the critical outcomes, the committee did not consider it necessary to make any changes to recommendations based on effects observed for quality of life and functioning outcomes.

Cost effectiveness and resource use

No evidence on the cost-effectiveness of interventions for adults with depression and a coexisting personality disorder was identified and no further economic analysis was undertaken.

The committee considered that these recommendations would bring practice in line with what has been recommended in the NICE guideline on borderline personality disorder and therefore there were unlikely to be any additional costs associated with these recommendations. They also agreed that better treatment of depression with coexisting personality disorder would probably lead to a reduction in downstream costs associated with not dealing with this condition effectively.

The committee considered the results of the guideline economic analysis on treatment of new episodes of more severe depression (evidence report B, appendix J), which suggested that combination of antidepressant and high-intensity psychological intervention (CBT) was one of the most cost-effective treatments among those assessed, and expressed the opinion that, since this treatment showed clinical superiority over pharmacological treatment alone in people with depression and coexisting personality disorder, it was likely to be cost-effective as well, especially considering the high costs of care associated with sub-optimal treatment of this population.

The committee acknowledged that referral to a specialist personality disorder treatment programme for people with depression comorbid with personality disorder involves use of additional healthcare resources at extra cost; however they noted that this reflects current practice and is in line with existing NICE guideline on borderline personality disorder. The committee expressed the view that referral to specialists with expertise in personality disorder treatment is essential to deal with the complex needs of this population and that specialist care is likely to lead to improved outcomes regarding both the personality disorder and, subsequently, depression (as treatment of the personality disorder by specialist services

may lead to an improvement in depression), which are likely to outweigh costs associated with referral.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.11.1 to 1.11.4 in the NICE guideline.

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Appendices

Appendix A – Review protocol

Review protocol for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Table 15: Review protocol for depression with personality disorder

Field (based on PRISMA-P)	Content
Review question	For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?
Objectives	To identify the most effective first-line treatment or relapse prevention strategy for adults with depression and a coexisting personality disorder
Population	Adults with depression and a coexisting personality disorder If some, but not all, of a study's participants are eligible for the review, then we will include a study if at least 80% of its participants are eligible for this review
Exclude	Trials of women with antenatal or postnatal depression Trials of children and young people (mean age under 18 years) Trials of people with learning disabilities Trials of people with bipolar disorder Trials of adults in contact with the criminal justice system (not solely as a result of being a witness or victim) Trials that specifically recruit participants with a physical health condition in addition to depression (e.g. depression in people with diabetes) Trials of further-line treatment following no/inadequate/limited response
Intervention	Interventions listed below are examples of interventions which may be included either alone or in combination.

Field (based on PRISMA-P)	Content
	Psychological interventions • Behavioural therapies (including behavioural activation, behavioural therapy [Lewinsohn 1976], coping with depression group) • Cognitive and cognitive behavioural therapies (including CBT individual or group, problem solving, rational emotive behaviour therapy [REBT] and third-wave cognitive therapies individual or group) • Counselling (including emotion-focused therapy [EFT], non-directive/supportive/ person-centred counselling and relational client-centred therapy) • Family interventions/couples therapy • Psychodynamic psychotherapies (including short-term psychodynamic psychotherapy, long-term psychodynamic psychotherapy and psychodynamic counselling) • Self-help with or without support (including cognitive bibliotherapy with or without support, computerised CBT [CCBT] with or without support, computerised psychodynamic therapy with or without support) • Art therapy • Music therapy • Eye movement desensitization and reprocessing (EMDR) (for depression, not PTSD) Psychosocial interventions • Peer support (including befriending, mentoring, and community navigators) • Mindfulness, meditation or relaxation (including mindfulness-based stress reduction [MBSR]) Pharmacological interventions • Selective serotonin reuptake inhibitors • Tricyclic antidepressants • Serotonin-norepinephrine reuptake inhibitors • Other antidepressant drugs (including mirtazapine and trazodone) • Antipsychotics • Lithium • Omega-3 fatty acids

Field (based on PRISMA-P)	Content
	Physical interventions • Acupuncture • ECT • Exercise • Yoga • Light therapy (for depression, not SAD)
Comparison	Treatment as usual Waitlist No treatment Placebo Other active intervention (must also meet inclusion criteria above)
Outcomes	**Critical outcomes:** Efficacy • Depression symptomatology (mean endpoint score or change in depression score from baseline) • Remission (usually defined as a cut off on a depression scale) • Response (usually defined as at least 50% improvement from the baseline score on a depression scale) • Relapse (number of participants who relapsed) The following depression scales will be included in the following hierarchy: • MADRS • HAMD • QIDS • PHQ • CGI (for dichotomous outcomes only) • CES-D • BDI • HADS-D (depression subscale)

Field (based on PRISMA-P)	Content
	• HADS (full scale) Acceptability/tolerability Discontinuation due to any reason (including side effects) Discontinuation due to side effects (for pharmacological trials) **Important, but not critical, outcomes:** Quality of life • Quality of life; as assessed with a validated scale, including the o 12-item/36-item Short-Form Survey [SF-12/SF-36], o 26-item short version of the World Health Organization Quality of Life assessment [WHOQOL-BREF], o EuroQoL [EQ5D], o Quality of Life Depression Scale [QLDS], o Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q], o Quality of Life Inventory [QoLI], o World Health Organization 5-item Well-Being Index [WHO-5] o Personal, social, and occupational functioning • Global functioning; as assessed with a validated scale, including o Global Assessment of Functioning [GAF], o Global Assessment Scale [GAS], o Social and Occupational Functioning Assessment Scale [SOFAS]) • Functional impairment; as assessed with a validated scale, including o Sheehan Disability Scale [SDS], o Social Adjustment Scale [SAS], o Work and Social Adjustment Scale [WSAS] • Sleeping difficulties; as assessed with a validated scale, including o Insomnia Severity Index [ISI] o Pittsburgh Sleep Quality Index [PSQI]

Field (based on PRISMA-P)	Content
	• Employment (for instance, % unemployed) • Interpersonal problems (as assessed with a validated scale, including Inventory of Interpersonal Problems [IIP]) Outcomes will be assessed at endpoint and follow-up (data for all available follow-up periods of at least 1-month post-intervention will be extracted and will be grouped into categories for analysis, for instance, 1-3 months, 4-6 months, 7-9 months, 10-12 months, 13-18 months, 19-24 months, and >2 years).
Study design	RCTs Systematic reviews of RCTs
Include unpublished data?	Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted from elsewhere (for instance, from the previous guideline)
Restriction by date?	All relevant studies from previous searches (pre-2016) will be carried forward. No restriction on date for the updated search, studies published between database inception and the date the searches are run will be sought.
Minimum sample size	N = 10 in each arm Studies with <50% completion data (drop out of >50%) will be excluded.
Study setting	Primary, secondary, tertiary and social care settings. Non-English-language papers will be excluded (unless data can be obtained from an existing review).
The review strategy	Data Extraction (selection and coding) Citations from each search will be downloaded into EndNote and duplicates removed. Titles and abstracts of identified studies will be screened by two reviewers for inclusion against criteria, until a good inter-rater reliability has been observed (percentage agreement =>90%). Initially 10% of references will be double-screened. If inter-rater agreement is good then the remaining references will be screened by one reviewer. All primary-level studies included after the first scan of citations will be acquired in full and re-evaluated for eligibility at the time they are being entered into a study database (standardised template created in Microsoft Excel). At least 10% of data extraction will be double-coded. Discrepancies or difficulties with coding will be resolved through discussion between reviewers or the opinion of a third reviewer will be sought. Data Analysis

Field (based on PRISMA-P)	Content
	A meta-analysis using a random-effects model will be conducted to combine results from similar studies. An intention to treat (ITT) approach will be taken where possible. Risk of bias will be assessed at the study level using the Cochrane risk of bias tool. This assessment includes: adequacy of randomisation (sufficient description of randomisation method, allocation concealment and any baseline difference between groups); blinding (of participants, intervention administrators and outcome assessors); attrition ('at risk of attrition bias' defined as a dropout of more than 20% and completer analysis used, or a difference of >20% between the groups); selective reporting bias (is the protocol registered, are all outcomes reported); other bias (for instance, conflict of interest in funding). Risk of bias will also be assessed at the outcome level using GRADE. For heterogeneity, outcomes will be downgraded once if I2>50%, twice if I2 >80%. For imprecision, outcomes will be downgraded using rules of thumb. If the 95% CI is imprecise i.e. crosses the line of no effect and the threshold for clinical benefit/harm, 0.8 or 1.25 (dichotomous) or -0.5 or 0.5 SMD (for continuous), the outcome will be downgraded. Outcomes will be downgraded one or two levels depending on how many lines it crosses. If the 95% CI is not imprecise, we will consider whether the criterion for Optimal Information Size is met (for dichotomous outcomes, 300 events; for continuous outcomes, 400 participants), if not we will downgrade one level.
Heterogeneity (sensitivity analysis and subgroups)	No sub-analyses are planned
Notes	Studies investigating further-line treatment of depression with coexisting personality disorder will be considered under RQ 2.4 and any differences in efficacy due to coexisting personality disorder will be examined through sub-analysis in that review
Information sources – databases and dates	Database(s): Embase 1974 to Present, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Cochrane Library; WEB OF SCIENCE
Identify if an update	Update of CG90 (2009)
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B.

Field (based on PRISMA-P)	Content
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual 2014
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Navneet Kapur in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	Not applicable

BDI: Beck depression inventory;(C)CBT: (computerised) cognitive behavioural therapy; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CES-D: Centre of epidemiology studies – depression; CGI: clinical global impressions; CI: confidence interval; DARE: Database of Abstracts of

Reviews of Effects; DSM: Diagnostic and statistical manual; ECT: electroconvulsive therapy; EFT: emotion-focused therapy; EMDR: eye movement desensitization and reprocessing; EQ-5D: European quality of life 5 dimensions; GAF: global assessment of functioning; GAS: global assessment scale; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HADS (D): hospital anxiety and depression scale (depression); HAMD: Hamilton Depression Rating Scale; ICD: International classification of diseases; IIP: inventory of interpersonal problems; ISI: insomnia severity index; ITT: intention to treat; MADRS: Montgomery–Åsberg Depression Rating Scale; MBSR: Mindfulness-based stress reduction; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PHQ-9: patient health questionnaire-9; PSQI: Pittsburgh sleep quality index; PTSD: post-traumatic stress disorder; QIDS: quick inventory of depressive symptomatology; QLDS: quality of life depression scale; Q-LES-Q: quality of life enjoyment and satisfaction questionnaire QOLI: quality of life inventory RCT: randomised controlled trial; REBT: rational emotive behaviour therapy; RoB: risk of bias; SAD: seasonal affective disorder; SAS: social adjustment scale; SDS: Sheehan disability scale; SF12/SF36 – short form 12 or 36 items; SMD: standardised mean difference; SOFAS: social and occupational functioning assessment scale; WHOQOL-BRIEF: World health organization quality of life assessment (brief); WHO-5: world health organization 5-item wellbeing index; WSAS: work and social adjustment scale

Appendix B – Literature search strategies

Literature search strategies for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Clinical search

Database(s): Embase 1974 to 2019 Week 20, Emcare 1995 to present, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 20, 2019, PsycINFO 1806 to May Week 2 2019

Date of search: 21/05/2019

Search updated: 06/04/2020

#	Searches
1	(depression/ or agitated depression/ or atypical depression/ or depressive psychosis/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or melancholia/ or "mixed anxiety and depression"/ or reactive depression/ or recurrent brief depression/ or treatment resistant depression/) use oemezd,emcr
2	(Depression/ or Depressive Disorder/ or Depressive Disorder, Major/ or Depressive Disorder, Treatment-Resistant/ or Disorders, Psychotic/ or Dysthymic Disorder/) use ppez
3	("depression (emotion)"/ or exp major depression/ or affective disorders/ or atypical depression/) use psyh
4	(depress* or dysthym* or melancholic* or ((affective or mood) adj disorder*)).tw.
5	((sever* or serious* or major* or chronic* or complex* or critical* or endur* or persist* or resist* or acute) adj2 (anxiety or (mental adj2 (disorder* or health or illness* or ill-health)) or (obsessive adj2 disorder*) or OCD or panic attack* or panic disorder* or phobi* or personality disorder* or psychiatric disorder* or psychiatric illness* or psychiatric ill-health*)).tw.
6	or/1-5
7	exp personality disorder/ use oemezd,emcr
8	exp personality disorders/ use ppez,psyh
9	comorbidity/
10	psychiatric diagnosis/ use oemezd,emcr
11	"Diagnosis, Dual (Psychiatry)"/ use ppez
12	dual diagnosis/ use psyh
13	((coexist* or co-exist* or comorbid* or co-morbid* or concomitant or concurrent or cooccurr* or co-occur* or multifactorial or multi-factorial or multimorbid* or multi-morbid* or polymorbid* or poly-morbid* or plural* or polypathy) adj (condition* or diagnos* or disorder* or morbidit* or personalit* or psychiatr*)).tw.
14	(or/7-8) and (or/9-12)
15	13 or 14
16	6 and 15
17	(exp psychotherapy/ or exp counseling/ or mindfulness/ or problem solving/ or psychiatric treatment/ or psychoeducation/ or self help/ or exp support group/) use oemezd,emcr
18	(exp Psychotherapy/ or Bibliotherapy/ or exp Cognitive Behavioral Therapy/ or exp Counseling/ or Problem Solving/ or Self Care/ or Self Efficacy/ or Self-Help Groups/) use ppez
19	(exp psychotherapy/ or behavioral activation system/ or bibliotherapy/ or cognitive therapy/ or exp counseling/ or group intervention/ or mindfulness/ or exp problem solving/ or psychoeducation/ or exp self-help techniques/ or support groups/) use psyh
20	((behavio* or abreact* or act* out* or age regression or assertive or autogenic or experiential) adj2 (activation or analys* or cathar* or conditioning or intervention* or modification* or therap* or training or treatment*)).tw.
21	((cognitive adj2 (behavior* or therap*)) or (CBT* or CBASP or biofeedback or contingency management or covert conditioning or covert sensiti?ation or defusion or MBCT* or neurofeedback or problem focus* or problem solving or rational emotive or REBT or schema or solution focus*) or ((third wave or 3rd wave) adj2 (intervention* or therap* or treatment*))).tw.
22	(counsel* or ((art or creative or compassion* or conversation* or dialectic* or emotion* or group* or insight or narrative or non-directive or nondirective or non-specific or nonspecific or rational or client-centred or client-centered or humanistic or integrative or interpersonal or person-centred or person-centered or personal construct or persuasion or Rogerian or talking or time-limited) adj2 (intervention* or therap* or training or treatment*))).tw.
23	(psychotherap* or (psycho* adj (aid* or help* or intervention* or support* or therap* or training or treatment*)) or (balint group or group program* or mindfulness* or mind training or role play* or support group*)).tw.
24	(self-help or bibliotherap* or meditat* or self-analy* or self-esteem or self-control or self-imag* or self-validat* or stress manag* or (computer* adj2 (intervention* or program* or therap* or treatment*)) or CCBT).tw.
25	[couple therapy/ use oemezd,emcr or couples therapy/ use ppez or ((family therapy/ or marital therapy/) use oemezd,emcr,ppez)]
26	[((exp family/ or marriage/) use oemezd,emcr,ppez) and exp psychotherapy/ use oemezd,emcr,ppez]
27	(couples therapy/ or family intervention/ or marriage counseling/) use psyh

#	Searches
28	[((exp couples/ or exp family/ or family relations/ or exp marital relations/ or marriage/ or spouses/) use psyh) and exp psychotherapy/ use psyh]
29	((couple* or famil* or husband* or marriage* or marital or partner* or wife or wives) adj2 (counsel* or intervention* or psychotherap* or therap* or treatment*)).tw.
30	or/17-29
31	drug therapy/ or drug therapy.fs.
32	psychopharmacotherapy/ use oemezd,emcr,psyh
33	antidepressant agent/ use oemezd,emcr
34	Antidepressive Agents/ use ppez
35	antidepressant drugs/ use psyh
36	serotonin uptake inhibitor/ use oemezd,emcr
37	Serotonin Uptake Inhibitors/ use ppez
38	serotonin reuptake inhibitors/ use psyh
39	serotonin noradrenalin reuptake inhibitor/ use oemezd,emcr
40	"Serotonin and Noradrenaline Reuptake Inhibitors"/ use ppez
41	serotonin norepinephrine reuptake inhibitors/ use psyh
42	tricyclic antidepressant agent/ use oemezd,emcr
43	Antidepressive Agents, Tricyclic/ use ppez
44	tricyclic antidepressant drugs/ use psyh
45	amfebutamone/ or amineptine/ or amitriptyline/ or bupropion/ or clomipramine/ or chlorimipramine/ or citalopram/ or desipramine/ or duloxetine/ or Duloxetine Hydrochloride/ or escitalopram/ or fluvoxamine/ or fluoxetine/ or imipramine/ or lofepramine/ or mirtazapine/ or moclobemide/ or nefazadone/ or nortriptyline/ or paroxetine/ or sertraline/ or venlafaxine/ or Venlafaxine Hydrochloride/
46	(antidepress* or amfebutamone or amineptin* or amitr?ptylin* or bupropion or chlorimipramine or clomipramin* or citalopram or desipramin* or duloxetin* or escitalopram or fluvoxamin* or fluoxetin* or imipramin* or lofepramin* or mirtazapin* or moclobemide or nefazadon* or nortriptylin* or paroxetin* or psychopharmacologic* or psychopharmacotherap* or sertralin* or venlafaxin* or SNRI* or SSRI* or TCA* or tricyclic or (serotonin adj2 inhibitor*)).tw.
47	or/31-46
48	neuroleptic agent/ use oemezd,emcr
49	Antipsychotic Agents/ use ppez
50	neuroleptic drugs/ use psyh
51	amisulpride/ or aripiprazole/ or olanzapine/ or quetiapine/ or Quetiapine Fumarate/ or risperidone/ or ziprasidone/
52	(antipsychotic* or anti-psychotic* or amisulpride or aripiprazole or olanzapine or psychotropic* or quetiapine or risperidone or ziprasidone).tw.
53	or/48-52
54	lithium/ or lithium.tw.
55	omega 3 fatty acid/ use oemezd,emcr
56	Fatty Acids, Omega-3/ use ppez
57	fatty acids/ use psyh
58	(omega adj ("fatty acid*" or "polyunsaturated fatty acid*" or PUFA*)).tw.
59	or/55-58
60	acupuncture/ or acupuncture.tw.
61	electroconvulsive therapy/ use oemezd,emcr,ppez
62	electroconvulsive shock therapy/ use psyh
63	(ECT or ((electroconvulsive or electro-convulsive) adj2 (therap* or treatment*)) or electroshock or (shock adj (therapy or treatment))).tw.
64	exp exercise/
65	(exp Exercise Therapy/ or Physical Exertion/ or exp Physical Fitness/ or Bicycling/ or exp Running/ or Swimming/ or Walking/) use ppez
66	(exp kinesiotherapy/ or exp physical activity/ or fitness/ or exp sport/) use oemezd,emcr
67	(exp physical fitness/ or exp sports/) use psyh
68	yoga/
69	(exercis* or yoga or cycling or bicycling or jogging or running or sport* or swimming or walking).tw.
70	or/60-69
71	peer group/ or mentoring/
72	peer relations/ use psyh
73	friendship/
74	Friends/ use ppez
75	(befriend* or friend* or mentor* or peer support or (communit* adj (navigat* or support*))).tw.
76	or/71-75
77	or/30,47,53-54,59,70,76
78	16 and 77
79	Letter/ use ppez
80	letter.pt. or letter/ use oemezd,emcr
81	note.pt.
82	editorial.pt.
83	Editorial/ use ppez
84	News/ use ppez
85	exp Historical Article/ use ppez
86	Anecdotes as Topic/ use ppez

#	Searches
87	Comment/ use ppez
88	Case Report/
89	case study/ use oemezd,emcr
90	(letter or comment*).ti.
91	or/79-90
92	randomized controlled trial/
93	random*.ti,ab.
94	92 or 93
95	91 not 94
96	(animals/ not humans/) use ppez
97	(animal/ not human/) use oemezd,emcr
98	nonhuman/ use oemezd,emcr
99	exp animals/ use psyh
100	"primates (nonhuman)"/ use psyh
101	exp Animals, Laboratory/ use ppez
102	exp Animal Experimentation/ use ppez
103	exp animal experiment/ use oemezd,emcr
104	exp experimental animal/ use oemezd,emcr
105	exp Models, Animal/ use ppez
106	animal model/ use oemezd,emcr
107	animal models/ use psyh
108	animal research/ use psyh
109	exp Rodentia/ use ppez
110	exp rodent/ use oemezd,emcr
111	exp rodents/ use psyh
112	(rat or rats or mouse or mice).ti.
113	or/95-112
114	78 not 113
115	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi?ed or randomly).ab. or trial.ti.
116	115 use ppez
117	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi?ed or randomly or trial).ab.
118	117 use ppez
119	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
120	119 use oemezd,emcr
121	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti.
122	121 use psyh
123	116 or 118
124	120 or 122 or 123
125	Meta-Analysis/
126	exp Meta-Analysis as Topic/
127	systematic review/
128	meta-analysis/
129	(meta analy* or metanaly* or metaanaly*).ti,ab.
130	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
131	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
132	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
133	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
134	(search* adj4 literature).ab.
135	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
136	cochrane.jw.
137	((pool* or combined) adj2 (data or trials or studies or results)).ab.
138	(or/125-127,129,131-136) use ppez
139	(or/127-130,132-137) use oemezd,emcr
140	(or/125,129,131-136) use psyh
141	or/138-140
142	network meta-analysis/
143	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
144	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
145	or/142-144
146	or/124,141,145
147	114 and 146
148	limit 147 to english language

The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 3 of 12, March 2019; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2019

Date of Search: 21/05/2019

Search updated: 06/05/2020

ID	Search
#1	MeSH descriptor: [Depression] this term only
#2	MeSH descriptor: [Depressive Disorder] this term only
#3	MeSH descriptor: [Depressive Disorder, Major] this term only
#4	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
#5	MeSH descriptor: [Affective Disorders, Psychotic] this term only
#6	MeSH descriptor: [Dysthymic Disorder] this term only
#7	(depress* or dysphori* or dysthym* or melanchol* or ((affective or mood) next disorder*)):ti,ab
#8	((sever* or serious* or major* or acute or chronic* or complex* or endur* or persist* or resist*) next/2 anxiety or (mental next/2 (disorder* or health or illness* or ill-health)) or (obsessive next/2 disorder*) or OCD or "panic attack*" or "panic disorder*" or phobi* or "personality disorder*" or "psychiatric disorder*" or "psychiatric illness*" or "psychiatric ill-health*"):ti,ab
#9	{or #1-#8}
#10	MeSH descriptor: [Personality Disorders] explode all trees
#11	MeSH descriptor: [Comorbidity] this term only
#12	MeSH descriptor: [Diagnosis, Dual (Psychiatry)] this term only
#13	((coexist* or “co exist*” or comorbid* or “co morbid*” or concomitant or concurrent or cooccurr* or “co occur*” or multifactorial or “multi factoria”l or multimorbid* or “multi morbid*” or polymorbid* or “poly morbid*” or plural* or polypathy) next (condition* or diagnos* or disorder* or morbidit* or personalit* or psychiatr*))
#14	#10 and (#11 or #12)
#15	#13 or #14
#16	#9 and #15 in Cochrane Reviews, Cochrane Protocols, Trials

Health Economics search

Database(s): Embase 1974 to 2019 Week 08, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to February 26, 2019, PsycINFO 1806 to February Week 1 2019

Date of Search: 27/02/2019

Search updated: 02/03/2021

#	Searches
1	(depression/ or agitated depression/ or atypical depression/ or depressive psychosis/ or dysphoria/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or melancholia/ or "mixed anxiety and depression"/ or "mixed depression and dementia"/ or premenstrual dysphoric disorder/ or reactive depression/ or recurrent brief depression/ or seasonal affective disorder/ or treatment resistant depression/) use oemezd
2	((Depression/ or exp Depressive Disorder/ or Adjustment Disorders/ or Affective Disorders, Psychotic/ or Factitious Disorders/ or Premenstrual Dysphoric Disorder/) use ppez
3	("depression (emotion)"/ or exp major depression/ or affective disorders/ or atypical depression/ or premenstrual dysphoric disorder/ or seasonal affective disorder/) use psyh
4	(depress* or dysphori* or dysthym* or melanchol* or seasonal affective disorder* or ((affective or mood) adj disorder*)).tw.
5	or/1-4
6	Letter/ use ppez
7	letter.pt. or letter/ use oemezd
8	note.pt.
9	editorial.pt.
10	Editorial/ use ppez
11	News/ use ppez
12	exp Historical Article/ use ppez
13	Anecdotes as Topic/ use ppez
14	Comment/ use ppez
15	Case Report/
16	case study/ use oemezd
17	(letter or comment*).ti.
18	or/6-17
19	randomized controlled trial/
20	random*.ti,ab.
21	19 or 20
22	18 not 21
23	(animals/ not humans/) use ppez
24	(animal/ not human/) use oemezd
25	nonhuman/ use oemezd
26	exp animals/ use psyh

#	Searches
27	"primates (nonhuman)"/ use psyh
28	exp Animals, Laboratory/ use ppez
29	exp Animal Experimentation/ use ppez
30	exp animal experiment/ use oemezd
31	exp experimental animal/ use oemezd
32	exp Models, Animal/ use ppez
33	animal model/ use oemezd
34	animal models/ use psyh
35	animal research/ use psyh
36	exp Rodentia/ use ppez
37	exp rodent/ use oemezd
38	exp rodents/ use psyh
39	(rat or rats or mouse or mice).ti.
40	or/22-39
41	5 not 40
42	Economics/
43	Value of life/
44	exp "Costs and Cost Analysis"/
45	exp Economics, Hospital/
46	exp Economics, Medical/
47	Economics, Nursing/
48	Economics, Pharmaceutical/
49	exp "Fees and Charges"/
50	exp Budgets/
51	(or/42-50) use ppez
52	health economics/
53	exp economic evaluation/
54	exp health care cost/
55	exp fee/
56	budget/
57	funding/
58	(or/52-57) use oemezd
59	exp economics/
60	exp "costs and cost analysis"/
61	cost containment/
62	money/
63	resource allocation/
64	(or/59-63) use psyh
65	budget*.ti,ab.
66	cost*.ti.
67	(economic* or pharmaco?economic*).ti.
68	(price* or pricing*).ti,ab.
69	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
70	(financ* or fee or fees).ti,ab.
71	(value adj2 (money or monetary)).ti,ab.
72	or/65-70
73	51 or 58 or 64 or 72
74	Quality-Adjusted Life Years/ use ppez
75	Sickness Impact Profile/
76	quality adjusted life year/ use oemezd
77	"quality of life index"/ use oemezd
78	(quality adjusted or quality adjusted life year*).tw.
79	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
80	(illness state* or health state*).tw.
81	(hui or hui2 or hui3).tw.
82	(multiattibute* or multi attribute*).tw.
83	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
84	utilities.tw.
85	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
86	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
87	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
88	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
89	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
90	Quality of Life/ and ec.fs.
91	Quality of Life/ and (health adj3 status).tw.
92	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
93	(quality of life or qol).tw. and cost benefit analysis/ use oemezd
94	(quality of life or qol).tw. and "costs and cost analysis"/ use psyh

#	Searches
95	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
96	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
97	cost benefit analysis/ use oemezd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
98	"costs and cost analysis"/ use psyh and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
99	*quality of life/ and (quality of life or qol).ti.
100	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
101	quality of life/ and health-related quality of life.tw.
102	Models, Economic/ use ppez
103	economic model/ use oemezd
104	or/74-101
105	73 or 104
106	41 and 105
107	limit 106 to english language
108	limit 107 to yr="2016 -Current"

Database(s): NIHR Centre for Reviews and Dissemination: Health Technology Assessment Database (HTA)

Date of search: 26/02/2019

#	Searches
#1	MESH DESCRIPTOR: depressive disorder EXPLODE ALL TREES
#2	((depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder* or affective disorder* or mood disorder*))
#3	#1 or #2 IN HTA FROM 2016 TO 2019

Database(s): CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature) 1937-current, EBSCO Host

Date of initial search: 26/02/2019

Search updated: 02/03/2021

#	Query	Limiters/Expanders
S31	S4 AND S30	Limiters - Publication Year: 2016-2019; Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S30	S10 OR S29	Search modes - Boolean/Phrase
S29	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	Limiters - Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S28	(MH "Quality of Life") AND TX (health-related quality of life)	Search modes - Boolean/Phrase
S27	(MH "Quality of Life") AND TI (quality of life or qol)	Search modes - Boolean/Phrase
S26	AB ((qol or hrqol or quality of life) AND ((qol or hrqol* or quality of life) N2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)))	Search modes - Boolean/Phrase
S25	(MH "Cost Benefit Analysis") AND TX ((quality of life or qol) or (cost-effectiveness ratio* and (perspective* or life expectanc*))	Search modes - Boolean/Phrase
S24	(MH "Quality of Life") TX (health N3 status)	Search modes - Boolean/Phrase
S23	(MH "Quality of Life") AND TX ((quality of life or qol) N (score*1 or measure*1))	Search modes - Boolean/Phrase
S22	TX (time trade off*1 or time tradeoff*1 or tto or timetradeoff*1)	Search modes - Boolean/Phrase
S21	TX (sf36 or sf 36 or sf thirty six or sf thirtysix)	Search modes - Boolean/Phrase
S20	TX (euro* N3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*))	Search modes - Boolean/Phrase
S19	TX (eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol)	Search modes - Boolean/Phrase
S18	TI utilities	Search modes - Boolean/Phrase
S17	TX (utilit* N3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*))	Search modes - Boolean/Phrase

#	Query	Limiters/Expanders
S16	TX (multiattibute* or multi attribute*)	Search modes - Boolean/Phrase
S15	TX (hui or hui2 or hui3)	Search modes - Boolean/Phrase
S14	TX (illness state* or health state*)	Search modes - Boolean/Phrase
S13	TX (quality adjusted or quality adjusted life year*or qaly* or qal or qald* or qale* or qtime* or qwb* or daly)	Search modes - Boolean/Phrase
S12	(MH "Sickness Impact Profile")	Search modes - Boolean/Phrase
S11	(MH "Quality-Adjusted Life Years")	Search modes - Boolean/Phrase
S10	S5 OR S6 OR S7 OR S8 OR S9	Limiters - Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S9	TX (value N2 (money or monetary))	Search modes - Boolean/Phrase
S8	TX (cost* N2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*))	Search modes - Boolean/Phrase
S7	TI cost* or economic* or pharmaco?economic*	Search modes - Boolean/Phrase
S6	TX budget* or fee or fees or finance* or price* or pricing	Search modes - Boolean/Phrase
S5	(MH "Fees and Charges+") OR (MH "Costs and Cost Analysis+") OR (MH "Economics") OR (MH "Economic Value of Life") OR (MH "Economics, Pharmaceutical") OR (MH "Economic Aspects of Illness") OR (MH "Resource Allocation+")	Search modes - Boolean/Phrase
S4	S1 OR S2 OR S3	Limiters - Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S3	TX (depress* or dysphori* or dysthym* or melanchol* or seasonal affective disorder)	Search modes - Boolean/Phrase
S2	(MH "Adjustment Disorders+") OR (MH "Factitious Disorders") OR (MH "Affective Disorders, Psychotic")	Search modes - Boolean/Phrase
S1	(MH "Depression+") OR (MH "Premenstrual Dysphoric Disorder") OR (MH "Seasonal Affective Disorder")	Search modes - Boolean/Phrase

Additional EMDR search

Database(s): Embase 1980 to 2021 Week 43, Emcare 1995 to present, Ovid MEDLINE(R) ALL 1946 to November 03, 2021, APA PsycInfo 1806 to November Week 1 2021

Date of Search: 04/11/2021

#	Searches
1	(depression/ or agitated depression/ or atypical depression/ or depressive psychosis/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or melancholia/ or "mixed anxiety and depression"/ or reactive depression/ or recurrent brief depression/ or treatment resistant depression/) use emez,emcr
2	(Depression/ or Depressive Disorder/ or Depressive Disorder, Major/ or Depressive Disorder, Treatment-Resistant/ or Disorders, Psychotic/ or Dysthymic Disorder/) use medall
3	("depression (emotion)"/ or exp major depression/ or affective disorders/ or atypical depression/) use psyh
4	(depress* or dysthym* or melanchol* or ((affective or mood) adj disorder*)).tw.
5	((sever* or serious* or major* or chronic* or complex* or critical* or endur* or persist* or resist* or acute) adj2 (anxiety or (mental adj2 (disorder* or health or illness* or ill-health)) or (obsessive adj2 disorder*) or OCD or panic attack* or panic disorder* or phobi* or personality disorder* or psychiatric disorder* or psychiatric illness* or psychiatric ill-health*)).tw.
6	or/1-5
7	(eye movement desensiti?ation or EMDR).tw.
8	6 and 7
9	Meta-Analysis/
10	exp Meta-Analysis as Topic/
11	systematic review/
12	meta-analysis/
13	(meta analy* or metanaly* or metaanaly*).ti,ab.
14	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
15	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
16	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
17	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
18	(search* adj4 literature).ab.
19	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
20	cochrane.jw.
21	((pool* or combined) adj2 (data or trials or studies or results)).ab.
22	(or/9-11,13,15-20) use medall
23	(or/11-14,16-21) use emez,emcr
24	(or/9,13,15-20) use psyh

#	Searches
25	or/22-24
26	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi?ed or randomly).ab. or trial.ti.
27	26 use medall
28	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi?ed or randomly or trial).ab.
29	28 use medall
30	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
31	30 use emez,emcr
32	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti.
33	32 use psyh
34	27 or 29
35	31 or 33 or 34
36	network meta-analysis/
37	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
38	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
39	or/36-38
40	25 or 35 or 39
41	8 and 40
42	limit 41 to english language

The Cochrane Library, issue 10 of 12, October 2021

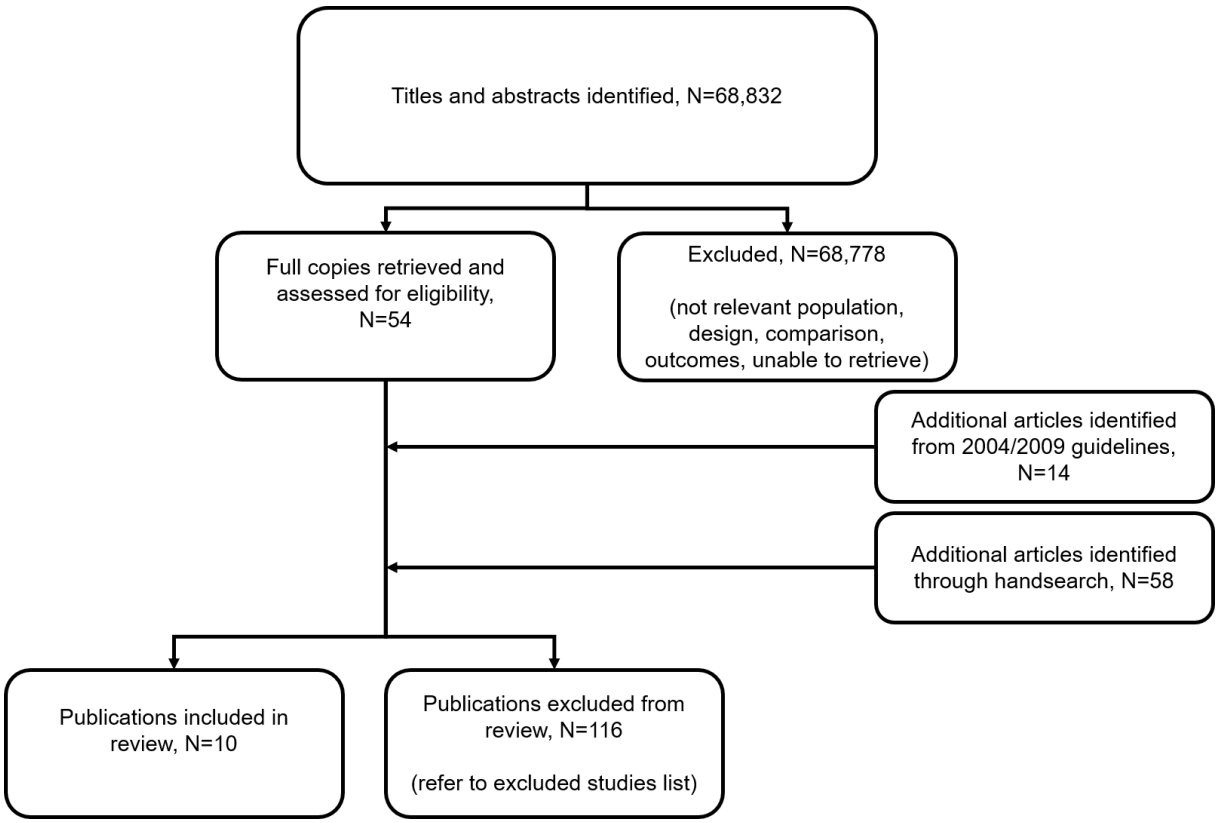
Date of search: 04/11/2021

ID	Search
#1	MeSH descriptor: [Depression] this term only
#2	MeSH descriptor: [Depressive Disorder] this term only
#3	MeSH descriptor: [Depressive Disorder, Major] this term only
#4	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
#5	MeSH descriptor: [Affective Disorders, Psychotic] this term only
#6	MeSH descriptor: [Dysthymic Disorder] this term only
#7	(depress* or dysphori* or dysthym* or melanchol* or ((affective or mood) next disorder*)):ti,ab
#8	((sever* or serious* or major* or acute or chronic* or complex* or endur* or persist* or resist*) next/2 anxiety or (mental next/2 (disorder* or health or illness* or "ill health")) or (obsessive next/2 disorder*) or OCD or "panic attack*" or "panic disorder*" or phobi* or "personality disorder*" or "psychiatric disorder*" or "psychiatric illness*" or "psychiatric ill-health*"):ti,ab
#9	{or #1-#8}
#10	("eye movement desensitisation" or "eye movement desensitization" or EMDR):ti,ab
#11	#9 and #10

Appendix C – Clinical evidence study selection

Clinical study selection for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Figure 1: Study selection flowchart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Please refer to the clinical evidence tables in supplement F– Clinical evidence tables for Evidence Review F Depression with personality disorder

Appendix E – Forest plots

Forest plots for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Comparison 1. Behavioural therapy versus short-term psychodynamic psychotherapy

Figure 2: Depression symptomatology at endpoint (BDI)

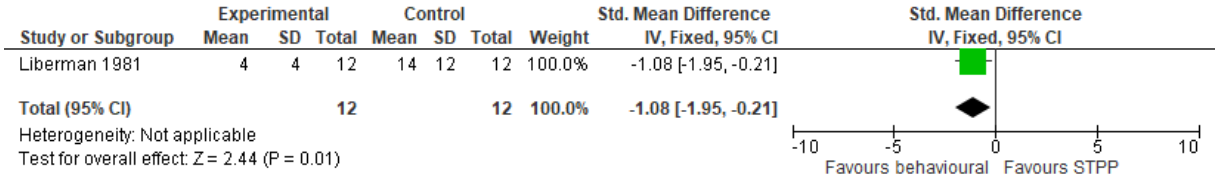


Figure 3: Depression symptomatology at 1-month follow-up (BDI)

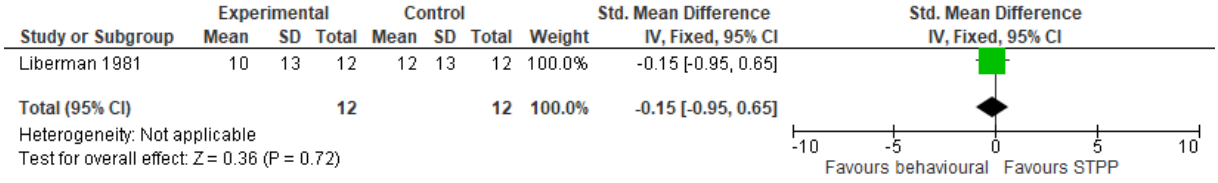


Figure 4: Depression symptomatology at 3-month follow-up (BDI)

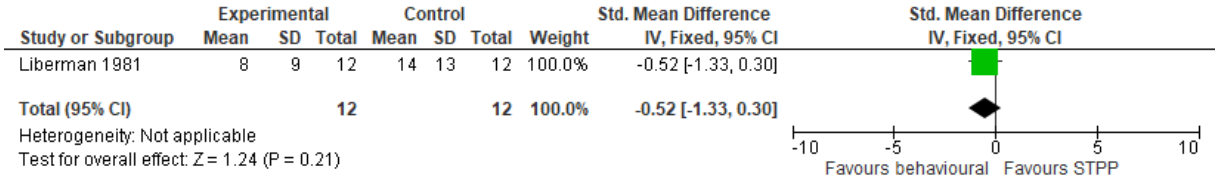


Figure 5: Depression symptomatology at 6-month follow-up (BDI)

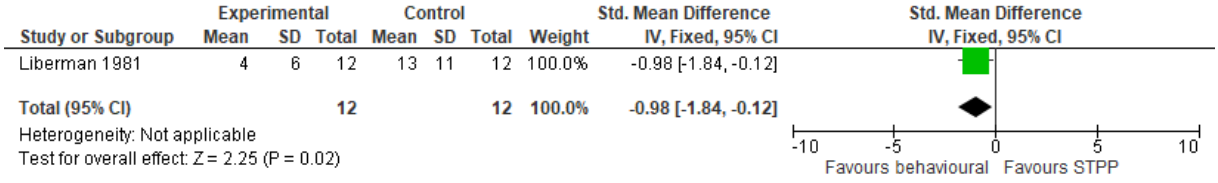
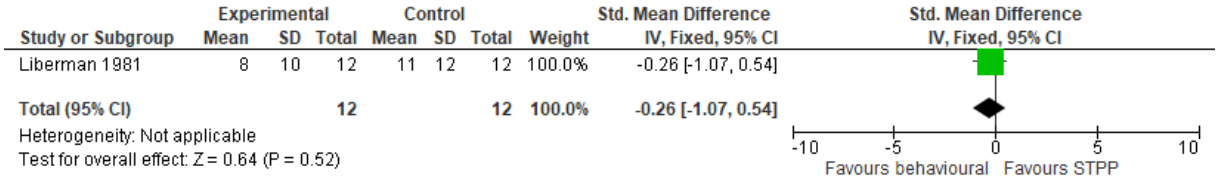
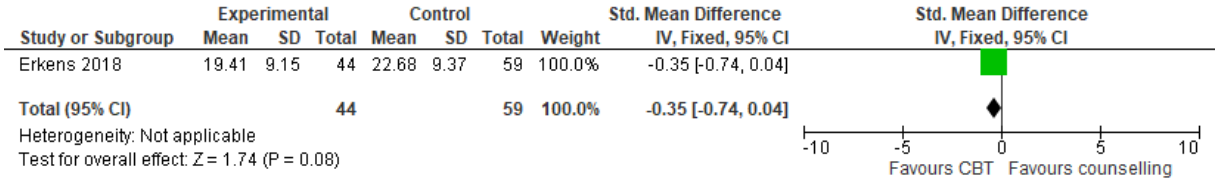


Figure 6: Depression symptomatology at 8-month follow-up (BDI)



Comparison 2. Cognitive behavioural therapy versus counselling

Figure 7: Depression symptomatology at endpoint (HAMD)



Comparison 3. Cognitive behavioural therapy versus interpersonal therapy

Figure 8: Depression symptomatology at endpoint (BDI-II/HAMD)

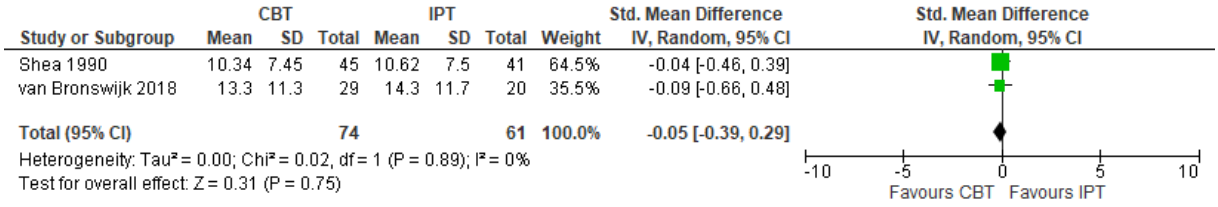


Figure 9: Depression symptomatology at 5-month follow-up (BDI-II)

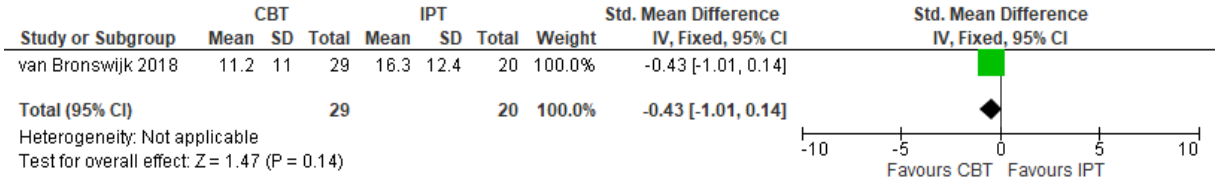
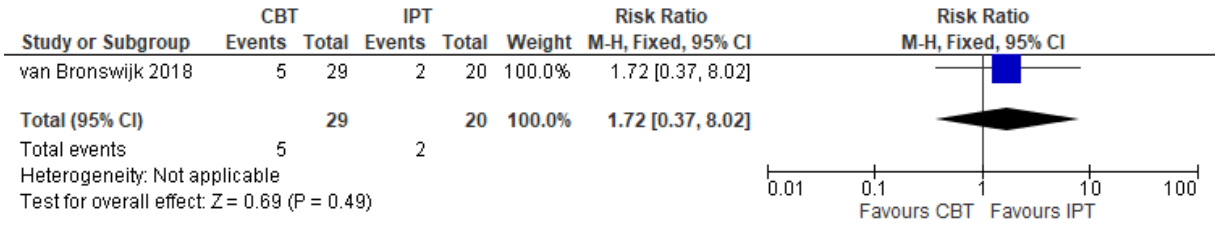


Figure 10: Discontinuation due to any reason



Comparison 4. Cognitive behavioural therapy versus short-term psychodynamic psychotherapy

Figure 11: Depression symptomatology at endpoint (BDI)

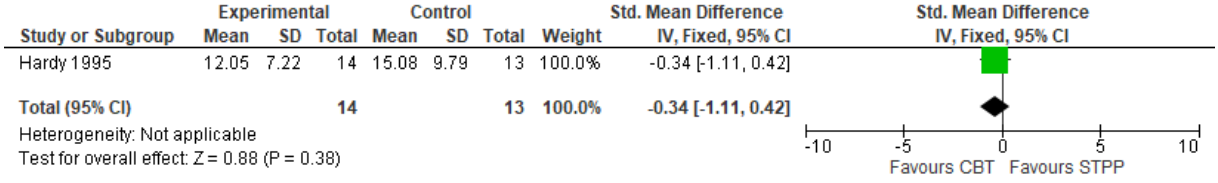


Figure 12: Depression symptomatology at 3-month follow-up (BDI)

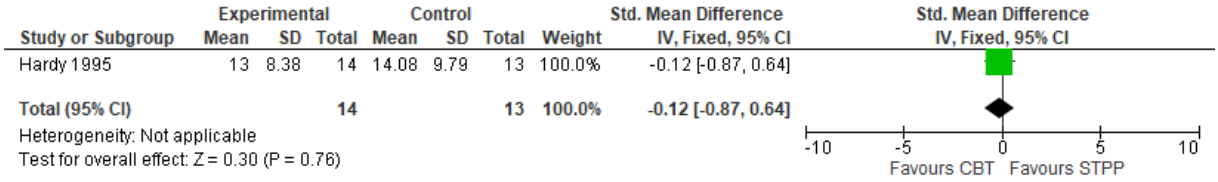


Figure 13: Depression symptomatology at 12-month follow-up (BDI)

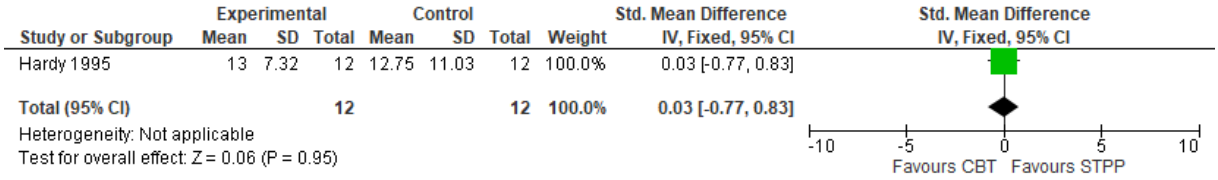


Figure 14: Interpersonal problems at endpoint (IIP)

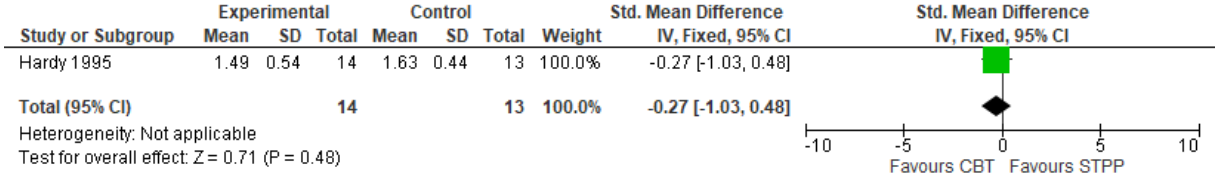


Figure 15: Interpersonal problems at 3-month follow-up (IIP)

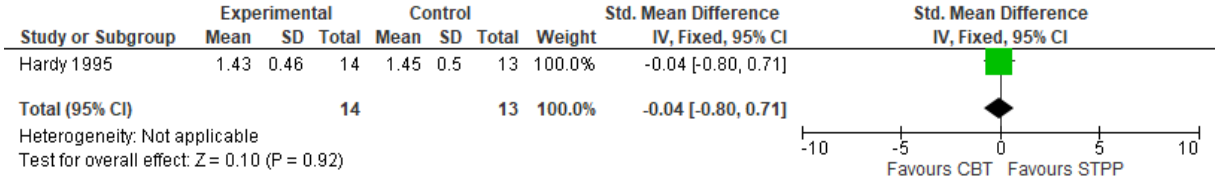
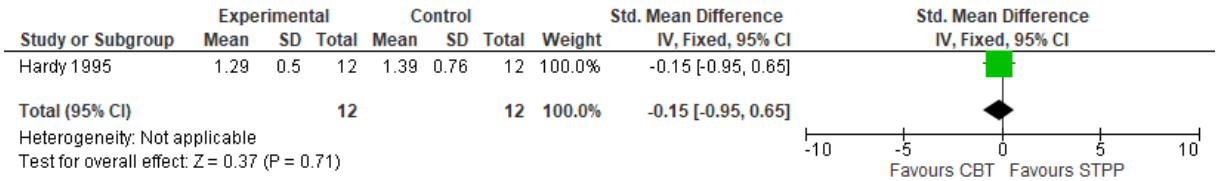
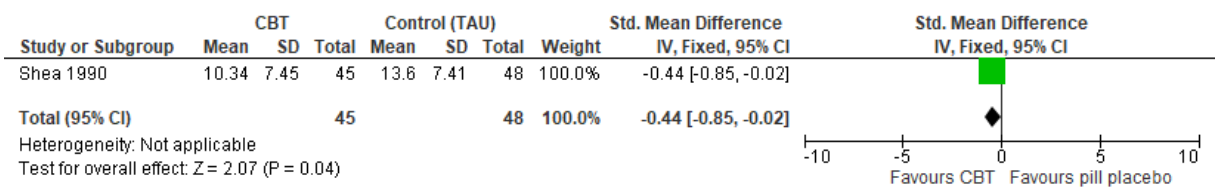


Figure 16: Interpersonal problems at 12-month follow-up (IIP)



Comparison 5. Cognitive behavioural therapy versus pill placebo

Figure 17: Depression symptomatology at endpoint (HAMD)



Comparison 6. Cognitive behavioural therapy versus antidepressant

Figure 18: Depression symptomatology at endpoint (HAMD)

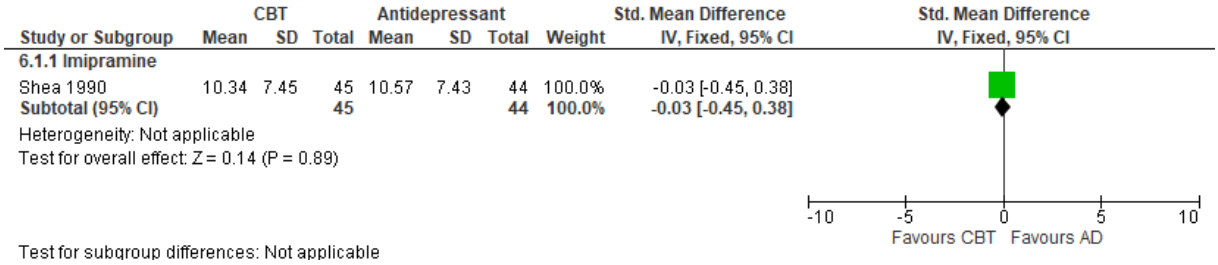


Figure 19: Remission (ITT)

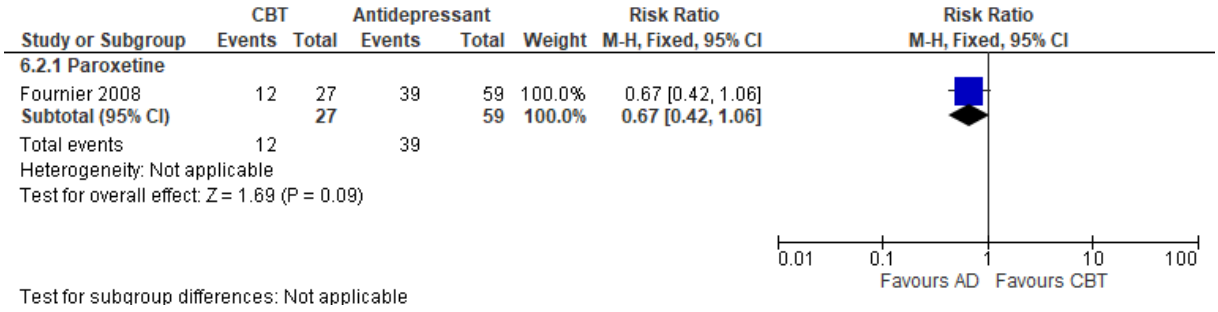
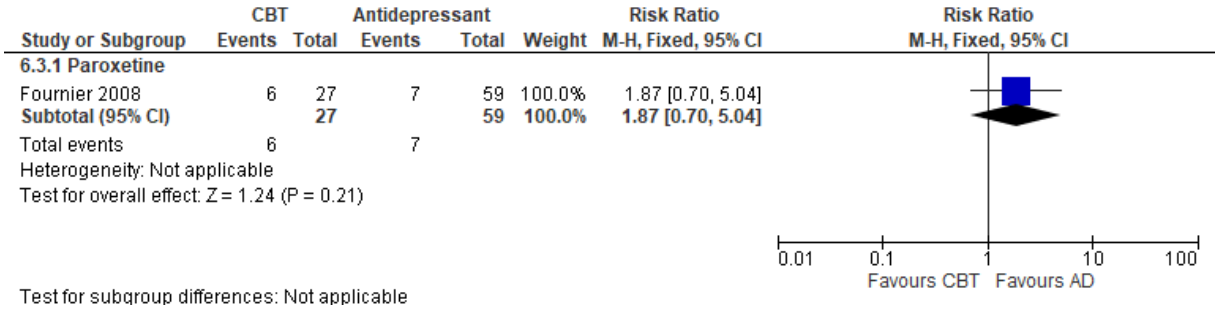


Figure 20: Discontinuation due to any reason



Comparison 7. CBT + fluoxetine versus IPT + fluoxetine

Figure 21: Depression symptomatology at endpoint (HAMD)

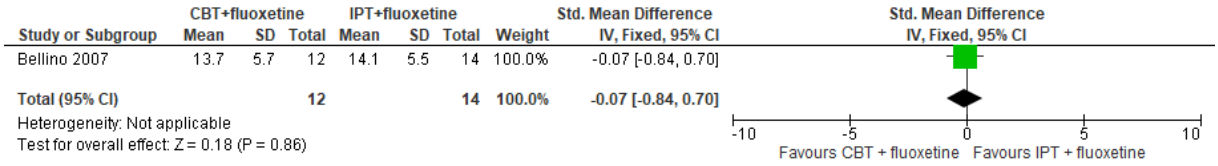


Figure 22: Remission (ITT)

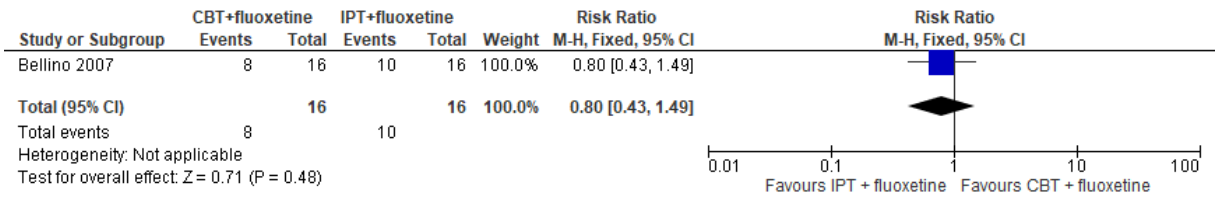


Figure 23: Discontinuation due to any reason

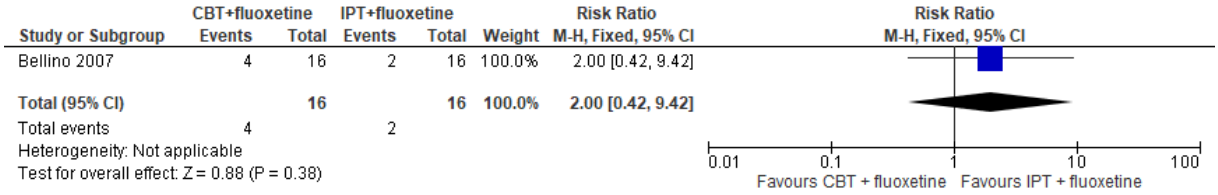
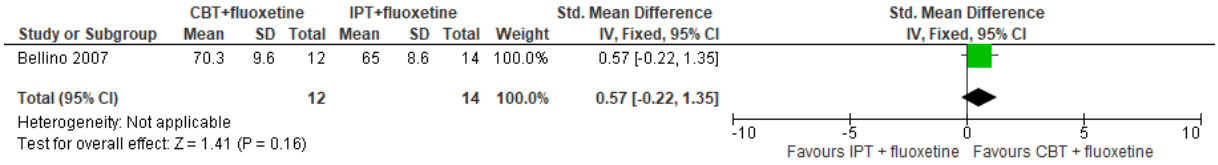
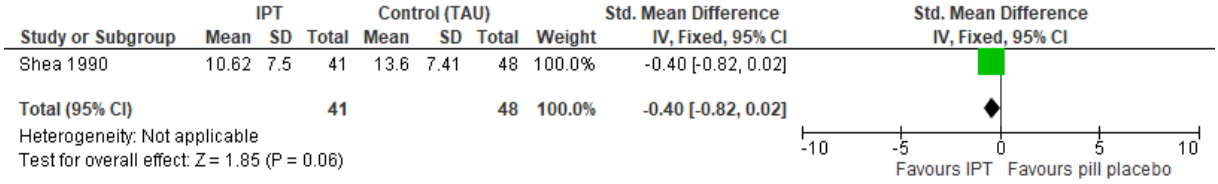


Figure 24: Global functioning at endpoint (SOFAS)



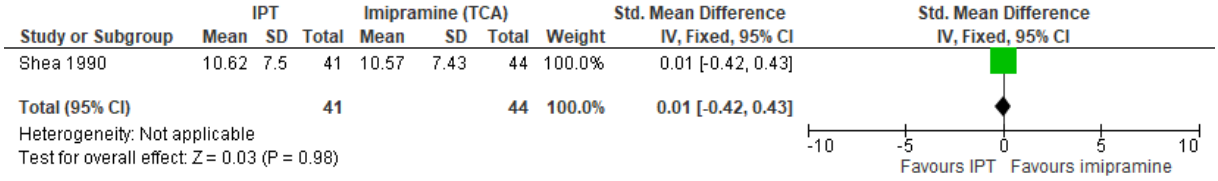
Comparison 8. IPT versus pill placebo

Figure 25: Depression symptomatology at endpoint (HAMD)



Comparison 9. IPT versus imipramine

Figure 26: Depression symptomatology at endpoint (HAMD)



Comparison 10. IPT + fluoxetine versus fluoxetine

Figure 27: Depression symptomatology at endpoint (HAMD)

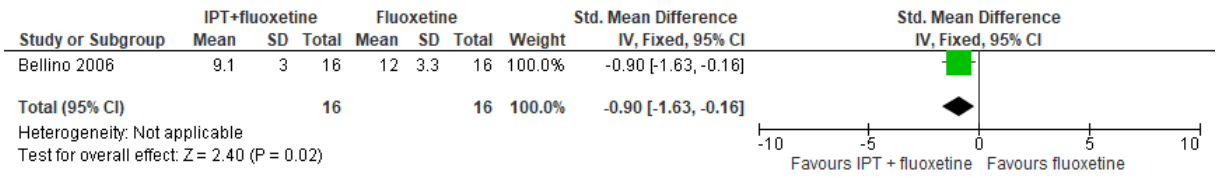


Figure 28: Remission (ITT)

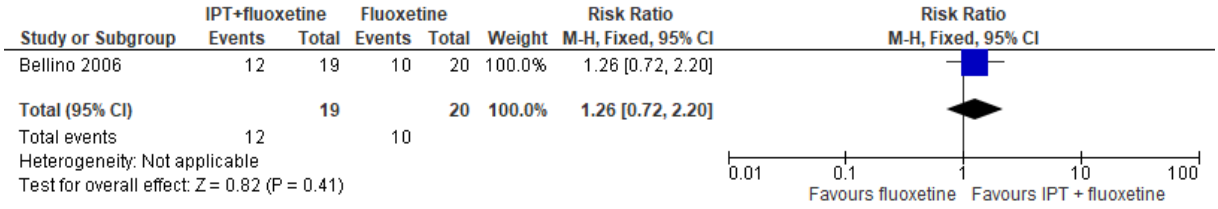
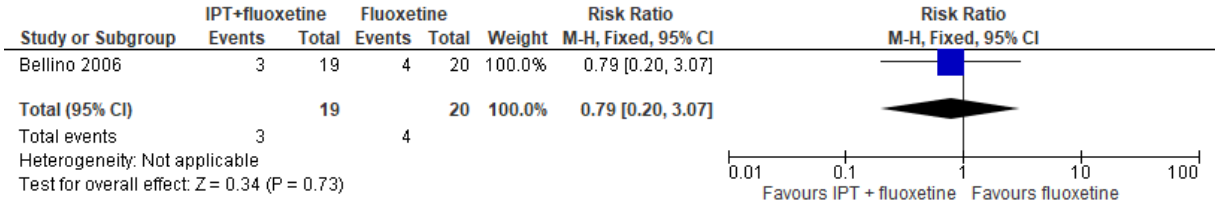


Figure 29: Discontinuation due to any reason



Comparison 11. Short-term psychodynamic psychotherapy + any antidepressant versus any antidepressant

Figure 30: Depression symptomatology at endpoint (HAMD)

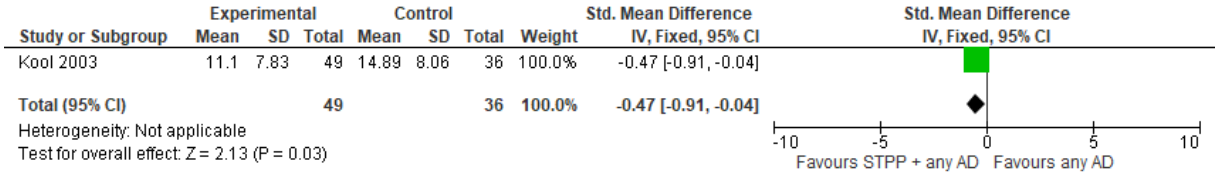


Figure 31: Remission (ITT)

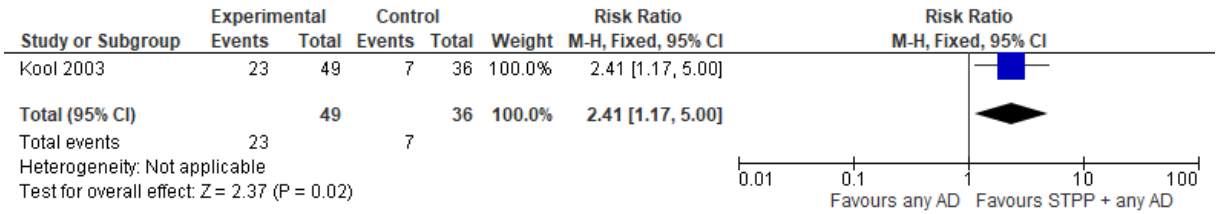
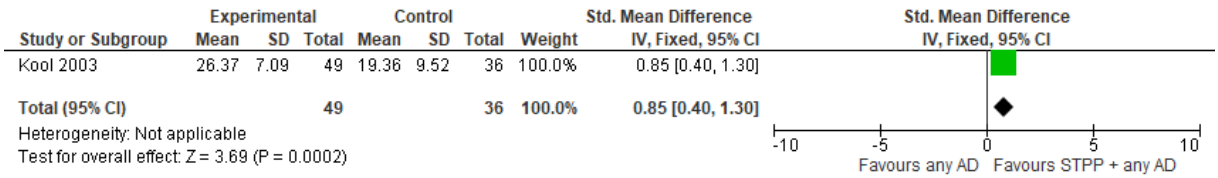


Figure 32: Quality of life at endpoint (QLDS)



Comparison 12. Fluoxetine versus nortriptyline

Figure 33: Depression symptomatology endpoint (MADRS)

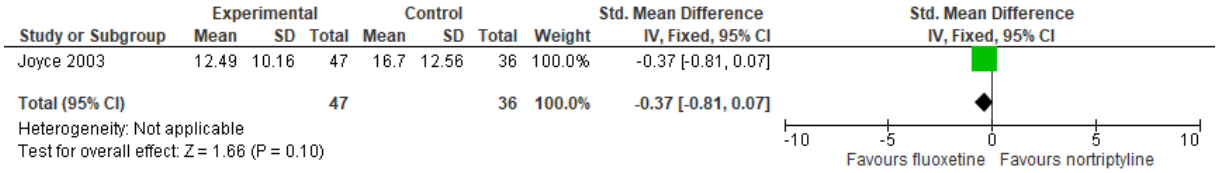


Figure 34: Response (ITT)

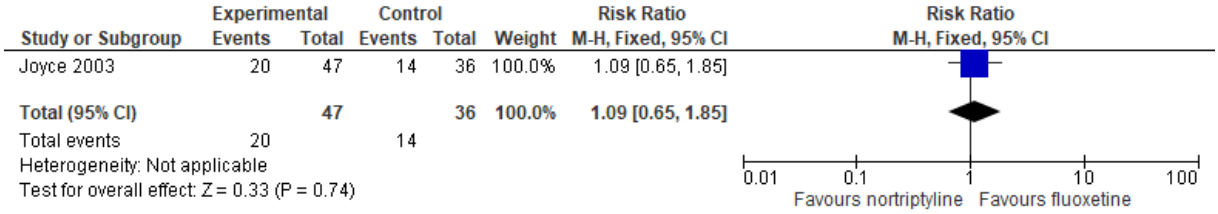
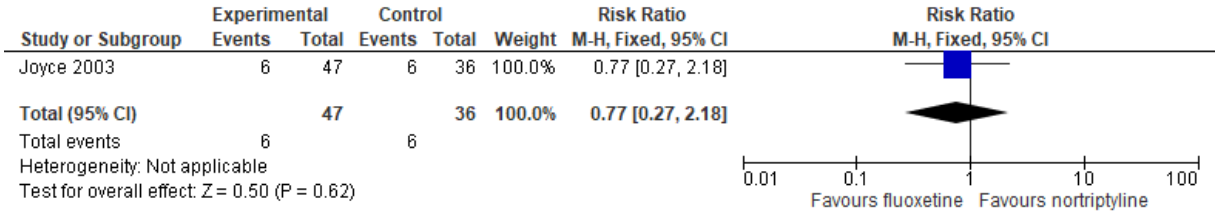
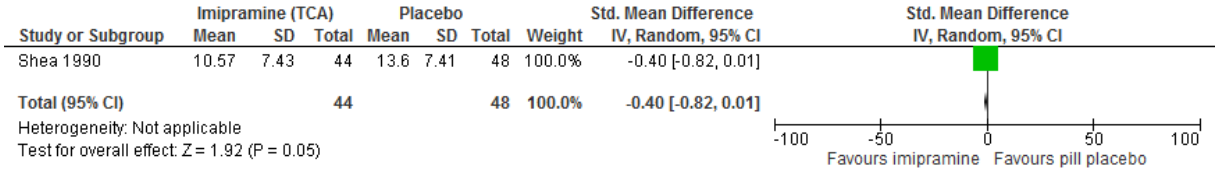


Figure 35: Discontinuation due to any reason



Comparison 13. Imipramine versus pill placebo

Figure 36: Depression symptomatology at endpoint (HAMD)



Appendix F – GRADE tables

GRADE tables for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Table 16: Clinical evidence profile for Comparison 1. Behavioural therapy versus short-term psychodynamic psychotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural therapy	Short-term psychodynamic psychotherapy	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up mean 1 weeks; measured with: Beck depression inventory (BDI); Better indicated by lower values)												
1 (Liberman 1981)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	SMD 1.08 lower (1.95 to 0.21 lower)	VERY LOW	CRITICAL
Depression symptomatology at 1-month follow-up (follow-up mean 1 months; measured with: Beck depression inventory (BDI); Better indicated by lower values)												
1 (Liberman 1981)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12	12	-	SMD 0.15 lower (0.95 lower to 0.65 higher)	VERY LOW	CRITICAL
Depression symptomatology at 3-month follow-up (follow-up mean 3 months; measured with: Beck depression inventory (BDI); Better indicated by lower values)												
1 (Liberman 1981)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	SMD 0.52 lower (1.33 lower to 0.3 higher)	VERY LOW	CRITICAL
Depression symptomatology at 6-month follow-up (follow-up mean 6 months; measured with: Beck depression inventory (BDI); Better indicated by lower values)												
1 (Liberman 1981)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	SMD 0.98 lower (1.84 to 0.12 lower)	VERY LOW	CRITICAL
Depression symptomatology at 8-month follow-up (follow-up mean 8 months; measured with: Beck depression inventory (BDI); Better indicated by lower values)												
1 (Liberman 1981)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12	12	-	SMD 0.26 lower (1.07 lower to 0.54 higher)	VERY LOW	CRITICAL

CI: confidence interval; SMD: standard mean difference

[1] Risk of bias is high or unclear across multiple domains

[2] 95% CI crosses thresholds for clinically important benefit and no effect

[3] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

Table 17: Clinical evidence profile for Comparison 2. Cognitive behavioural therapy versus counselling

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive behavioural therapy	Counselling	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up mean 20 weeks; measured with: Hamilton depression scale (HAMD); Better indicated by lower values)												
1 (Erkens 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	59	-	SMD 0.35 lower (0.74 lower to 0.04 higher)	LOW	CRITICAL

CI: confidence interval; SMD: standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important benefit and no effect

Table 18: Clinical evidence profile for Comparison 3. Cognitive behavioural therapy versus interpersonal therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive behavioural therapy	Interpersonal therapy	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up 16-30 weeks; measured with: Beck depression inventory (BDI-II)/Hamilton depression scale (HAMD); Better indicated by lower values)												
2 (Shea 1990, van Bronswijk 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74	61	-	SMD 0.05 lower (0.39 lower to 0.29 higher)	LOW	CRITICAL
Depression symptomatology at 5-month follow-up (follow-up mean 5 months; measured with: Beck depression inventory (BDI-II); Better indicated by lower values)												
1 (von Bronswijk 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	20	-	SMD 0.43 lower (1.01 lower to 0.14 higher)	VERY LOW	CRITICAL
Discontinuation due any reason (follow-up mean 30 weeks; assessed with: Number of participants who dropped out for any reason)												
1 (von Bronswijk 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/29 (17.2%)	2/20 (10%)	RR 1.72 (0.37 to 8.02)	72 more per 1000 (from 63 fewer to 702 more)	VERY LOW	CRITICAL

CI: confidence interval; RR: relative risk
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important benefit and no effect
[3] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

Table 19: Clinical evidence profile for Comparison 4. Cognitive behavioural therapy versus short-term psychodynamic psychotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive behavioural therapy	Short-term psychodynamic psychotherapy	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up 8-16 weeks; measured with: Beck depression inventory (BDI); Better indicated by lower values)												
1 (Hardy 1995)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14	13	-	SMD 0.34 lower (1.11 lower to 0.42 higher)	VERY LOW	CRITICAL
Depression symptomatology at 3-month follow-up (follow-up mean 3 months; measured with: Beck depression inventory (BDI); Better indicated by lower values)												
1 (Hardy 1995)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	14	13	-	SMD 0.12 lower (0.87 lower to 0.64 higher)	VERY LOW	CRITICAL
Depression symptomatology at 12-month follow-up (follow-up mean 12 months; measured with: Beck depression inventory (BDI); Better indicated by lower values)												
1 (Hardy 1995)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12	12	-	SMD 0.03 higher (0.77 lower to 0.83 higher)	VERY LOW	CRITICAL
Interpersonal problems at endpoint (follow-up 8-16 weeks; measured with: Inventory of interpersonal problems (IIP); Better indicated by lower values)												
1 (Hardy 1995)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14	13	-	SMD 0.27 lower (1.03 lower to 0.48 higher)	VERY LOW	IMPORTANT
Interpersonal problems at 3-month follow-up (follow-up mean 3 months; measured with: Inventory of interpersonal problems (IIP); Better indicated by lower values)												
1 (Hardy 1995)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	14	13	-	SMD 0.04 lower (0.8 lower to 0.71 higher)	VERY LOW	IMPORTANT
Interpersonal problems at 12-month follow-up (follow-up mean 12 months; measured with: Inventory of interpersonal problems (IIP); Better indicated by lower values)												
1 (Hardy 1995)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12	12	-	SMD 0.15 lower (0.95 lower to 0.65 higher)	VERY LOW	IMPORTANT

CI: confidence interval; SMD: standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important benefit and no effect
[3] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

Table 20: Clinical evidence profile for Comparison 5. Cognitive behavioural therapy versus pill placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive behavioural therapy	Pill placebo	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up mean 16 weeks; measured with: Hamilton depression scale (HAMD); Better indicated by lower values)												
1 (Shea 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45	48	-	SMD 0.44 lower (0.85 to 0.02 lower)	VERY LOW	CRITICAL

CI: confidence interval; SMD: standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important benefit (SMD 0.5/-0.5) and no effect

Table 21: Clinical evidence profile for Comparison 6. Cognitive behavioural therapy versus antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive behavioural therapy	Antidepressant	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up mean 16 weeks; measured with: Hamilton depression scale (HAMD); Better indicated by lower values)												
1 (Shea 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	45	44	-	SMD 0.03 lower (0.45 lower to 0.38 higher)	LOW	CRITICAL
Remission (ITT) (follow-up mean 16 weeks; assessed with: Number of participants with Hamilton depression scale (HAMD) less than or equal to 12)												
1 (Fournier 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	12/27 (44.4%)	39/59 (66.1%)	RR 0.67 (0.42 to 1.06)	218 fewer per 1000 (from 383 fewer to 40 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 16 weeks; assessed with: Number of participants who dropped out for any reason)												
1 (Fournier 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	6/27 (22.2%)	7/59 (11.9%)	RR 1.87 (0.7 to 5.04)	103 more per 1000 (from 36 fewer to 479 more)	VERY LOW	CRITICAL

CI: confidence interval; RR: relative risk
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important harm and no effect
[3] Authors have received financial support from pharmaceutical company
[4] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

Table 22: Clinical evidence profile for Comparison 7. CBT + fluoxetine versus IPT + fluoxetine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + fluoxetine	IPT + fluoxetine	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up mean 24 weeks; measured with: Hamilton depression scale (HAMD); Better indicated by lower values)												
1 (Bellino 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12	14	-	SMD 0.07 lower (0.84 lower to 0.7 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 24 weeks; assessed with: Hamilton depression scale (HAMD) score ≤8 and improved by at least 40% and clinical global impression-improvement (CGI-I) score=1-2)												
1 (Bellino 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/16 (50%)	10/16 (62.5%)	RR 0.8 (0.43 to 1.49)	125 fewer per 1000 (from 356 fewer to 306 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 24 weeks; assessed with: Number of participants who dropped out for any reason)												
1 (Bellino 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/16 (25%)	2/16 (12.5%)	RR 2 (0.42 to 9.42)	125 more per 1000 (from 73 fewer to 1000 more)	VERY LOW	CRITICAL
Global functioning at endpoint (follow-up mean 24 weeks; measured with: Social and occupational functioning assessment scale (SOFAS); Better indicated by higher values)												
1 (Bellino 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12	14	-	SMD 0.57 higher (0.22 lower to 1.35 higher)	LOW	IMPORTANT

CBT: cognitive behavioural therapy; CI: confidence interval; IPT: interpersonal therapy; RR: relative risk; SMD: standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm
[3] 95% CI crosses thresholds for clinically important benefit and no effect

Table 23: Clinical evidence profile for Comparison 8. IPT versus pill placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Pill placebo	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up mean 16 weeks; measured with: Hamilton depression scale (HAMD); Better indicated by lower values)												
1 (Shea 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41	48	-	SMD 0.4 lower (0.82 lower to 0.02 higher)	VERY LOW	CRITICAL

CI: confidence interval; IPT: interpersonal therapy; SMD: standard mean difference

[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important benefit and no effect

Table 24: Clinical evidence profile for Comparison 9. IPT versus imipramine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Imipramine	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (HAMD) (follow-up mean 16 weeks; measured with: Hamilton depression scale (HAMD); Better indicated by lower values)												
1 (shea 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	44	-	SMD 0.01 higher (0.42 lower to 0.43 higher)	LOW	CRITICAL

CI: confidence interval; IPT: interpersonal therapy; SMD: standard mean difference
[1] Risk of bias is high or unclear across multiple domains

Table 25: Clinical evidence profile for Comparison 10. IPT + fluoxetine versus fluoxetine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT + fluoxetine	Fluoxetine	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up mean 24 weeks; measured with: Hamilton depression scale (HAMD); Better indicated by lower values)												
1 (Bellino 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	16	-	SMD 0.9 lower (1.63 to 0.16 lower)	LOW	CRITICAL
Remission (ITT) (follow-up mean 24 weeks; assessed with: Hamilton depression scale (HAMD) score ≤8 and improved by at least 40% and clinical global impression-improvement (CGI-I) score=1-2)												
1 (Bellino 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/19 (63.2%)	10/20 (50%)	RR 1.26 (0.72 to 2.2)	130 more per 1000 (from 140 fewer to 600 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 24 weeks; assessed with: Number of participants who dropped out for any reason)												
1 (Bellino 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/19 (15.8%)	4/20 (20%)	RR 0.79 (0.2 to 3.07)	42 fewer per 1000 (from 160 fewer to 414 more)	VERY LOW	CRITICAL

CI: confidence interval; IPT: interpersonal therapy; RR: relative risk; SMD: standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important benefit and no effect
[3] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

Table 26: Clinical evidence profile for Comparison 11. Short-term psychodynamic psychotherapy + any antidepressant versus any antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-term psychodynamic psychotherapy + any antidepressant	Any antidepressant	Relative (95% CI)	Absolute		
Depression symptomatology at endpoint (follow-up mean 24 weeks; measured with: Hamilton depression scale (HAMD); Better indicated by lower values)												
1 (Kool 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	49	36	-	SMD 0.47 lower (0.91 to 0.04 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 24 weeks; assessed with: Number of participants with Hamilton depression scale (HAMD) score of less than or equal to 7)												
1 (Kool 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	23/49 (46.9%)	7/36 (19.4%)	RR 2.41 (1.17 to 5)	274 more per 1000 (from 33 more to 778 more)	VERY LOW	CRITICAL
Quality of life at endpoint (follow-up mean 24 weeks; measured with: Quality of life depression scale (QLDS); Better indicated by higher values)												
1 (Kool 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	49	36	-	SMD 0.85 higher (0.4 to 1.3 higher)	VERY LOW	IMPORTANT

CI: confidence interval; RR: relative risk; SMD: standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important benefit and no effect
[3] Trial funded by pharmaceutical company

Table 27: Clinical evidence profile for Comparison 12. Fluoxetine versus nortriptyline

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoxetine	Nortriptyline	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 6 weeks; measured with: Montgomery-Asberg depression rating scale (MADRS); Better indicated by lower values)												

1 (Joyce 2003)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	47	36	-	SMD 0.37 lower (0.81 lower to 0.07 higher)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 6 weeks; assessed with: Number of participants showing at least 60% improvement on Montgomery-Asberg depression rating scale (MADRS))												
1 (Joyce 2003)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	20/47 (42.6%)	14/36 (38.9%)	RR 1.09 (0.65 to 1.85)	35 more per 1000 (from 136 fewer to 331 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants who dropped out for any reason)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	6/47 (12.8%)	6/36 (16.7%)	RR 0.77 (0.27 to 2.18)	38 fewer per 1000 (from 122 fewer to 197 more)	VERY LOW	CRITICAL

CI: confidence interval; RR: relative risk; SMD: standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important benefit and no effect
[3] Study partially funded by pharmaceutical company
[4] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

Table 28: Clinical evidence profile for Comparison 13. Imipramine versus pill placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Imipramine**	**Pill placebo**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology at endpoint (follow-up mean 16 weeks; measured with: Hamilton depression scale (HAMD); Better indicated by lower values)												
1 (Shea 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	48	-	SMD 0.4 lower (0.82 lower to 0.01 higher)	VERY LOW	CRITICAL

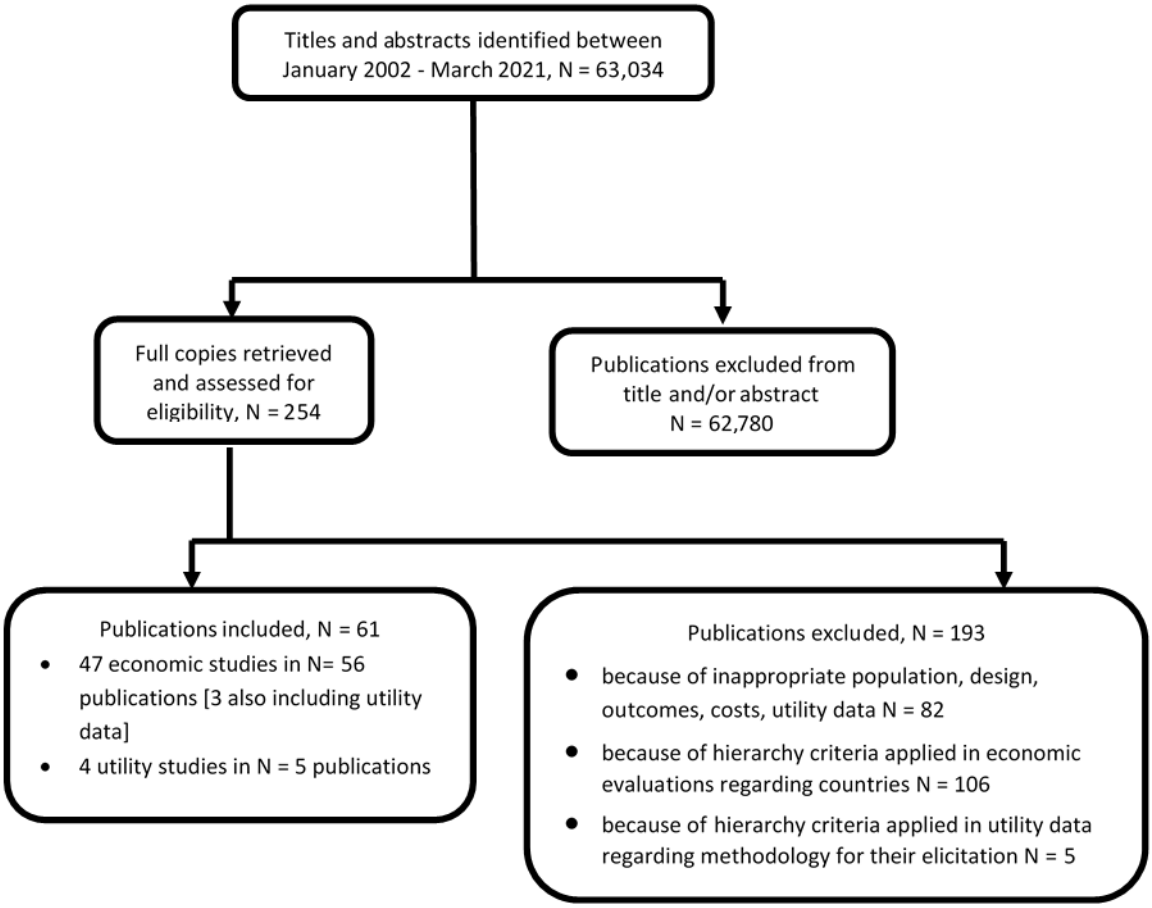
CI: confidence interval; SMD: standard mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for clinically important benefit and no effect

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

A global health economics search was undertaken for all areas covered in the guideline. Figure 37 shows the flow diagram of the selection process for economic evaluations of interventions and strategies for adults with depression and studies reporting depression-related health state utility data.

Figure 37. Flow diagram of selection process for economic evaluations of interventions and strategies for adults with depression and studies reporting depression-related health state utility data



Appendix H – Economic evidence tables

Economic evidence tables for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Clinical studies

Please refer to the excluded studies in supplement F– Clinical evidence tables for Evidence review F Depression with personality disorder

Economic studies

Please refer to supplement 3 - Economic evidence included & excluded studies.

Appendix L – Research recommendations

Research recommendations for review question: For adults with depression and a coexisting personality disorder what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions alone or in combination?

No research recommendations were made for this review question.