National Institute for Health and Care Excellence

FINAL

Depression in adults

[G] Psychotic depression

NICE guideline NG222

Evidence review underpinning recommendations 1.12.1 to 1.12.6 and research recommendations in the NICE guideline

June 2022

Final

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May 2024: We have simplified the guideline by removing recommendations on general principles of care that are covered in other NICE guidelines (for example, the NICE guideline on service user experience in adult mental health).

This is a presentational change only, and no changes to practice are intended.

Disclaimer

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Psychotic depression

Review question

For adults with psychotic depression what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination (as first-line treatment or relapse prevention)?

Introduction

Psychosis in depression commonly manifests as nihilistic delusions, delusions of guilt, inadequacy and disease, or derogatory auditory hallucinations. People with psychotic depression also demonstrate more severe psychomotor disturbance and greater psychosocial impairment than those without psychosis. Psychotic symptoms are more common in samples of older patients than in younger patients and people with psychotic depression are more likely to require inpatient treatment and to die from suicide or medical causes in the years following their admission. There is also some evidence that people with major depression with psychotic features exhibit more frequent relapses or recurrences than patients with non-psychotic depression. Psychotic depression is often not diagnosed accurately, even in specialist settings, because the psychosis may be subtle, intermittent or concealed, and consequently, it is often inadequately treated.

The majority of international treatment guidelines on pharmacological approaches to psychotic depression advocate the combination of an antidepressant and antipsychotic medication. However, antipsychotic use is associated with weight gain and metabolic effects and the use of antidepressant-antipsychotic combinations increases the risks of arrhythmia and cardiac arrest.

In reviewing the evidence for further-line treatment (see Evidence rereview D), the committee agreed that it was not meaningful to separate out subgroups with psychotic depression, coexisting personality disorders, 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 psychotic depression 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 psychotic depression in the current evidence report, and the evidence for further-line treatment of psychotic depression 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 treatment or relapse prevention strategy for adults with psychotic depression.

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 psychotic depression (a depressive episode with psychotic features, i.e. delusions and/or hallucinations in the context of a major depressive disorder)

Intervention	• Psychological interventions (including behavioural therapies, cognitive and cognitive behavioural therapies, counselling, family interventions/couples therapy, interpersonal psychotherapy (IPT), psychodynamic psychotherapies, psychoeducational interventions, self-help [with or without support], art therapy, music therapy, eye movement desensitization and reprocessing [EMDR, for depression, not PTSD]) • Psychosocial interventions (including peer support, mindfulness, meditation or relaxation [including mindfulness-based stress reduction, MBSR]) • Pharmacological interventions (including SSRIs, TCAs, SNRIs, antipsychotics, lithium, omega-3 fatty acids) • Physical interventions (including acupuncture, ECT, exercise, yoga, light therapy [for depression, not SAD])
Comparison	• Treatment as usual • Waitlist • No treatment • Placebo • Any other active comparison
Outcome	**Critical:** • Depression symptomatology • Response • Remission • Relapse • Discontinuation due to any reason • Discontinuation due to side effects (for pharmacological trials) **Important:** • Quality of life • Personal, social, and occupational functioning

EMDR: eye movement desensitization and reprocessing; ECT: electroconvulsive therapy; IPT: interpersonal therapy; MBSR: mindfulness-based stress reduction; PTSD: post-traumatic stress disorder; SAD: seasonal affective disorder; SNRI: serotonin-noradrenaline reuptake inhibitor; 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

Eight randomised controlled trials (RCTs) were included in this review.

Four RCTs (Kunzel 2009, Mulsant 2001, Spiker 1985 and Wijkstra 2010) compared antipsychotic augmentation of antidepressants versus antidepressants alone (or with placebo) for the treatment of depression.

Two RCTs (Flint 2019, Meyers 2001) compared antipsychotic augmentation of antidepressants versus antidepressants (plus placebo) for the prevention of relapse.

Two RCTS (Meyers 2009, Spiker 1985) compared antidepressant augmentation of antipsychotics versus antipsychotics (plus placebo) for the treatment of depression.

One RCT (Spiker 1985) compared perphenazine (plus placebo) versus amitriptyline (plus placebo) for the treatment of depression.

One RCT (Wijkstra 2010) compared venlafaxine versus imipramine for the treatment of depression.

One RCT (Navarro 2008) compared continuation electroconvulsive therapy (ECT) plus nortriptyline versus nortriptyline plus treatment as usual for the prevention of relapse.

The included studies are summarised in Table 2.

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

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2 to Table 7.

Table 2: Summary of included studies for Comparison 1. Antipsychotic plus antidepressant versus antidepressant (alone or plus placebo) for the treatment of depression

Study	Population	Intervention	Comparison	Comments
Kunzel 2009 RCT Austria, Germany and Switzerland	N=94 Baseline severity: More severe Mean age (range): 51.1 years (range NR) Sex (% female): 60 Ethnicity (% BME): NR Setting: Secondary care	Haloperidol + amitriptyline (target daily dose of 7.5mg of haloperidol + 200mg amitriptyline; mean final dose 6.3mg of haloperidol [SD=2] and 185mg of amitriptyline [SD=24])	Trimipramine (target daily dose of 400mg; mean final dose 356mg [SD=61])	Treatment duration: 6 weeks Outcomes: • Depression symptomatology • Response • Remission (of depression) • Discontinuation due to any reason • Discontinuation due to side effects
Mulsant 2001 RCT	N=36	Perphenazine + nortriptyline (maximum dose of 24mg/day of	Nortriptyline + placebo (target blood level 100ng/ml for	Treatment duration: 2-16 weeks

Study	Population	Intervention	Comparison	Comments
US	Baseline severity: More severe Mean age (range): 72.4 years (≥50 – NR) Sex (% female): 73 Ethnicity (% BME): 3 Setting: Secondary care	perphenazine + target blood level 100ng/ml for nortriptyline [range 50-150ng/ml]; mean final dose 19mg perphenazine [SD=5] + 63mg of nortriptyline [SD=45])	nortriptyline [range 50-150ng/ml]; mean final dose 76mg of nortriptyline [SD=35] + 19mg placebo [SD=5])	Outcomes: • Depression symptomatology • Remission (of depression) • Remission (of depression and psychotic symptoms) • Discontinuation due to any reason • Discontinuation due to side effects
Spiker 1985 RCT US	N=58 Baseline severity: More severe Mean age (range):44.1 (range NR) Sex (% female): 62 Ethnicity (% BME): 7 Setting: Secondary care	Perphenazine + amitriptyline (target daily dose of 64mg of perphenazine + 200mg of amitriptyline; mean daily dose of 54mg of perphenazine [SD=17] + 170mg of amitriptyline [SD=46])	Amitriptyline (target blood level of 200ng/mL; mean daily dose 218mg [SD=47])	Treatment duration: 5 weeks Outcomes: • Remission (of depression and psychotic symptoms) • Discontinuation due to any reason • Discontinuation due to side effects
Wijkstra 2010 RCT Netherlands	N=122 Baseline severity: More severe Mean age (range): 50.6 years (range NR) Sex (% female): 51 Ethnicity (% BME): NR Setting: Secondary care	Quetiapine + venlafaxine (target daily dose of 600mg of quetiapine + 375mg of venlafaxine; mean maximum dose quetiapine 599mg/day [SD=15] and venlafaxine 373mg/day [SD=11])	Venlafaxine (target daily dose 375mg; mean maximum dose 372mg/day [SD=14])	Treatment duration: 7 weeks Outcomes: • Depression symptomatology • Response • Remission (of depression) • Discontinuation due to any reason • Discontinuation due to side effects

BME: black, minority, ethnic; N: number; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Table 3: Summary of included studies for Comparison 2. Antipsychotic plus antidepressant versus antidepressant plus placebo, for relapse prevention

Study	Population	Intervention	Comparison	Treatment duration
Flint 2019 RCT Canada, US	N=126 Baseline severity: less severe Mean age (range): 55.3 years Sex (% female): 62 Ethnicity (% BME): 18 Setting: Secondary care	Olanzapine (target daily dose of 15-20mg) + sertraline (target daily dose of 150-200mg)	Sertraline (target daily dose of 150-200mg) + placebo	Treatment duration: 36 weeks Outcome: • Relapse (of depression or psychotic symptoms)
Meyers 2001 RCT US	N=29 Baseline severity: Less severe Mean age (range): 72.2 years (range 50-84) Sex (% female): 68 Ethnicity (% BME): NR Setting: Secondary care	Perphenazine + nortriptyline (or sertraline). Nortriptyline was the primary study antidepressant, but sertraline was allowed if this medication was contraindicated or for those who had failed a nortriptyline trial before receiving ECT (1 participant in this group [6%] received sertraline). Target dose of 12-16mg/day of perphenazine and target blood level 50-150ng/ml for nortriptyline (or target dose 50-100mg/day of sertraline); Mean daily dose 10mg of perphenazine (SD=3) + 54mg of nortriptyline (SD=16)	Nortriptyline (or sertraline) + placebo (2 participants in this group [15%] received sertraline). Target blood level 50-150ng/ml for nortriptyline (or target dose 50-100mg/day of sertraline) + target dose of 12-16mg/day of placebo; Mean daily dose 70mg of nortriptyline (SD=13) + 11mg of placebo perphenazine (SD=2)	Treatment duration: 26 weeks Outcome: • Relapse (of depression or psychotic symptoms)

BME: black, minority, ethnic; ECT: electroconvulsive therapy; N: number; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Table 4: Summary of included studies for Comparison 3. Antidepressant plus antipsychotic versus antipsychotic plus placebo for the treatment of depression

Study	Population	Intervention	Comparison	Treatment duration
Meyers 2009 RCT US and Canada	N=259 Baseline severity: More severe Mean age (range): 58 years (range 18-93) Sex (% female): 64 Ethnicity (% BME): 15 Setting: Secondary care	Sertraline + olanzapine (target [minimum] daily dose of 150mg of sertraline + 15mg of olanzapine; mean final dose 169mg of sertraline [SD=44] + 14mg of olanzapine [SD=5])	Olanzapine + placebo (target [minimum] daily dose of 15mg of olanzapine + 150mg of placebo; mean final dose 15mg of olanzapine [SD=5] + 170mg of placebo [SD=35])	Treatment duration: 12 weeks Outcomes: • Remission (of depression and psychotic symptoms) • Discontinuation due to any reason • Discontinuation due to side effects
Spiker 1985 RCT US	N=58 Baseline severity: More severe Mean age (range): 44.1 years (range NR) Sex (% female): 62 Ethnicity (% BME): 7 Setting: Secondary care	Amitriptyline + perphenazine (target daily dose of 200mg of amitriptyline + 64mg of perphenazine; mean daily dose of 170mg of amitriptyline [SD=46] + 54mg of perphenazine [SD=17])	Perphenazine + placebo (target daily dose of 64mg; mean daily dose 50mg [SD=15])	Treatment duration: 5 weeks Outcomes: • Depression symptomatology • Remission (of depression and psychotic symptoms) • Discontinuation due to any reason • Discontinuation due to side effects

BME: black, minority, ethnic; N: number; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Table 5: Summary of included studies for Comparison 4. Perphenazine (plus placebo) versus amitriptyline (plus placebo) for the treatment of depression

Study	Population	Intervention	Comparison	Treatment duration
Spiker 1985 RCT US	N=58 Baseline severity: More severe	Perphenazine + placebo (target daily dose of 64mg; mean daily dose 50mg [SD=15])	Amitriptyline + placebo (target blood level of 200ng/mL; mean daily dose 218mg [SD=47])	Treatment duration: 5 weeks Outcomes:

Study	Population	Intervention	Comparison	Treatment duration
	Mean age (range): 44.1 years (range NR) Sex (% female): 62 Ethnicity (% BME): 7 Setting: Secondary care			• Depression symptomatology • Remission (of depression and psychotic symptoms) • Discontinuation due to any reason • Discontinuation due to side effects

BME: black, minority, ethnic; N: number; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Table 6: Summary of included studies for Comparison 5. Venlafaxine versus imipramine for the treatment of depression

Study	Population	Intervention	Comparison	Treatment duration
Wijkstra 2010 RCT Netherlands	N=122 Baseline severity: More severe Mean age (range): 50.5 (range NR) Sex (% female): 51 Ethnicity (% BME): NR Setting: Secondary care	Venlafaxine (target daily dose 375mg; mean maximum dose 372mg/day [SD=14])	Imipramine (target blood level of 200-300 µg/ml; mean daily dose 254mg [SD=101]; mean plasma level 294µg/ml [SD=75])	Treatment duration: 7 weeks Outcomes: • Depression symptomatology • Response • Remission • Discontinuation due to any reason • Discontinuation due to side effects

BME: black, minority, ethnic; N: number; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Table 7: Summary of included studies for Comparison 6. Continuation ECT plus nortriptyline versus nortriptyline plus treatment as usual, for relapse prevention

Study	Population	Intervention	Comparison	Treatment duration
Navarro 2008 RCT Spain	N=33 Baseline severity: Less severe	ECT + nortriptyline (16 ECT sessions + target blood level of 80-120ng/mL [maximum dose	Nortriptyline (target blood level of 80-120ng/mL [maximum dose 100mg/day]) + TAU. The non-ECT subgroup	Treatment duration: 104 weeks Outcome: • Relapse

Study	Population	Intervention	Comparison	Treatment duration
	Mean age (range): 70.5 (range ≥60-NR) Sex (% female): 64 Ethnicity (% BME): NR Setting: Secondary care	100mg/day] for nortriptyline)	received combined treatment with risperidone in a dose of up to 2mg/day for 6weeks, which was then withdrawn by tapering the dose over a 4-week period.	

BME: black, minority, ethnic; ECT: electroconvulsive therapy; N: number; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

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

Quality assessment of studies included in the evidence review

See the 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 - Economic evidence 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

Comparison 1. Antipsychotic plus antidepressant versus antidepressant (alone or plus placebo) for the treatment of depression

Critical outcomes

Depression symptomatology

- Very low quality evidence from 3 RCTs (N=167) shows neither a clinically important nor statistically significant difference between combined antipsychotic and antidepressant

treatment and antidepressant treatment only on depression symptomatology change from baseline to endpoint, for adults with psychotic depression.

Response

- Very low quality evidence from 2 RCTs (N=174) shows neither a clinically important nor statistically significant difference between combined antipsychotic and antidepressant treatment and antidepressant treatment only on the rate of response, for adults with psychotic depression.

Remission (of depression)

- Very low quality evidence from 3 RCTs (N=210) shows neither a clinically important nor statistically significant difference between combined antipsychotic and antidepressant treatment and antidepressant treatment only on the rate of remission (of depression), for adults with psychotic depression.

Remission (of depression and psychotic symptoms)

- Very low quality evidence from 2 RCTs (N=77) shows a clinically important but not statistically significant benefit of combined antipsychotic and antidepressant treatment, relative to antidepressant treatment only, on the rate of remission of depression and psychotic symptoms, for adults with psychotic depression.

Discontinuation due to any reason

- Very low quality evidence from 4 RCTs (N=251) shows a higher rate of discontinuation due to any reason associated with combined antipsychotic and antidepressant treatment, relative to antidepressant treatment only for adults with psychotic depression, however this effect is not statistically significant.

Discontinuation due to side effects

- Very low quality evidence from 4 RCTs (N=251) shows a higher rate of discontinuation due to side effects associated with combined antipsychotic and antidepressant treatment relative to antidepressant treatment only for adults with psychotic depression, however this effect is not statistically significant.

Important outcomes

No evidence was identified for quality of life or functioning outcomes for this comparison.

Comparison 2. Antipsychotic plus antidepressant versus antidepressant plus placebo, for relapse prevention

Critical outcomes

Relapse

- Very low quality evidence from 2 RCTs (N=155) shows neither a clinically important nor statistically significant difference between combined antipsychotic and antidepressant treatment and antidepressant treatment (with placebo) on the rate of relapse of depression or psychotic symptoms, for adults with remitted psychotic depression.

Important outcomes

No evidence was identified for quality of life or functioning outcomes for this comparison.

Comparison 3. Antidepressant plus antipsychotic versus antipsychotic plus placebo for the treatment of depression

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=34) shows a clinically important and statistically significant benefit of combined antidepressant and antipsychotic treatment, relative to antipsychotic treatment (with placebo), on depression symptomatology for adults with psychotic depression.

Remission (of depression and psychotic symptoms)

- Very low quality evidence from 2 RCTs (N=298) shows a clinically important and statistically significant benefit of combined antidepressant and antipsychotic treatment, relative to antipsychotic treatment (with placebo), on the rate of remission of depression and psychotic symptoms for adults with psychotic depression.

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=298) shows neither a clinically important nor statistically significant difference between combined antidepressant and antipsychotic treatment and antipsychotic treatment (with placebo), on discontinuation due to any reason for adults with psychotic depression.

Discontinuation due to side effects

- Very low quality evidence from 2 RCTs (N=298) shows a lower rate of discontinuation due to side effects associated with combined antidepressant and antipsychotic treatment relative to antipsychotic treatment (with placebo) for adults with psychotic depression, however this effect is not statistically significant.

Important outcomes

No evidence was identified for quality of life or functioning outcomes for this comparison.

Comparison 4. Perphenazine (plus placebo) versus amitriptyline (plus placebo) for the treatment of depression

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=33) shows neither a clinically important nor statistically significant difference between perphenazine and amitriptyline on depression symptomatology for adults with psychotic depression.

Remission (of depression and psychotic symptoms)

- Very low quality evidence from 1 RCT (N=36) shows a higher rate of remission of depression and psychotic symptoms associated with amitriptyline relative to perphenazine for adults with psychotic depression, however this effect is not statistically significant.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=36) shows a higher rate of discontinuation due to any reason associated with amitriptyline relative to perphenazine for adults with psychotic depression, however this effect is not statistically significant.

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=36) shows a higher rate of discontinuation due to side effects associated with perphenazine relative to amitriptyline for adults with psychotic depression, however this effect is not statistically significant.

Important outcomes

No evidence was identified for quality of life or functioning outcomes for this comparison.

Comparison 5. Venlafaxine versus imipramine for the treatment of depression

Critical outcomes

Depression symptomatology

- Very low quality evidence from 1 RCT (N=81) shows neither a clinically important nor statistically significant difference between venlafaxine and imipramine on depression symptomatology change from baseline to endpoint, for adults with psychotic depression.

Response

- Very low quality evidence from 1 RCT (N=81) shows a higher rate of response associated with imipramine relative to venlafaxine for adults with psychotic depression, however this effect is not statistically significant.

Remission (of depression)

- Very low quality evidence from 1 RCT (N=81) shows a higher rate of remission of depression associated with venlafaxine relative to imipramine for adults with psychotic depression, however this effect is not statistically significant.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=81) shows neither a clinically important nor statistically significant difference between venlafaxine and imipramine on discontinuation due to any reason for adults with psychotic depression.

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=81) shows a higher rate of discontinuation due to side effects associated with imipramine relative to venlafaxine for adults with psychotic depression, however this effect is not statistically significant.

Important outcomes

No evidence was identified for quality of life or functioning outcomes for this comparison.

Comparison 6. Continuation ECT plus nortriptyline versus nortriptyline plus treatment as usual, for relapse prevention

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=33) shows a clinically important and statistically significant benefit of continuation ECT plus nortriptyline compared to nortriptyline plus treatment as usual, on preventing relapse for adults with psychotic depression.

Important outcomes

No evidence was identified for quality of life or functioning outcomes for this comparison.

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 determine which treatments are effective at treating psychotic depression so the committee identified depression symptomatology, response and remission as critical outcomes that would measure whether and to what extent symptoms had improved. An episode of psychotic depression can be frightening and leave people anxious about recurrence, so it is important to people that it does not recur, and therefore relapse was also prioritised by the committee as a critical outcome for comparisons that included a population of people who had remitted from depression. Discontinuation for any reason was used by the committee as a marker of acceptability of the treatment and for pharmacological treatments discontinuation due to side effects was prioritised as an indicator of the tolerability of the treatment. As discontinuation can lead to a poor treatment response these outcomes were both prioritised as critical outcomes.

Quality of life and functioning were prioritised as important outcomes. The committee were aware that these outcomes are very important to people with depression, but that there was likely to be less evidence for these outcomes so they would not be as useful to the committee's decision-making process.

The quality of the evidence

The quality of evidence for outcomes was assessed using GRADE and ranged from moderate to very low.

The evidence identified covered a range of pharmacological interventions, but was generally from single RCTs with a small sample size, and was of very low quality. The quality of the evidence was most frequently downgraded due to a high or unclear risk of bias or due to imprecision.

Benefits and harms

As with other treatment recommendations in the guideline, the committee agreed that treatment options should be discussed with people who have psychotic depression in order to involve them in making shared treatment decisions. However, they recognised that people with psychotic depression may lack capacity to make treatment decisions.

The committee also discussed whether people with psychotic depression could be safely and effectively cared for within primary care services and agreed, based on their expertise and experience, that due to their complex symptoms their needs could be better met by specialist mental health services, and so recommended referral to specialist mental health services. The committee specifically discussed whether GPs would be confident commencing prescriptions for antipsychotics to augment antidepressant treatment. The committee agreed, based on their knowledge and experience, that this would often not be the case. Consequently, they recommended that the treatment in specialist mental health services should include a risk assessment, and an assessment of needs, a programme of coordinated multi-professional care and access to psychological interventions after improvement of psychotic symptoms, so that the complex needs of those with psychotic depression could be treated effectively.

The committee considered the evidence for combined treatment with antipsychotics and antidepressants. Evidence from the comparison of an antipsychotic plus antidepressant compared to an antidepressant alone was inconsistent. However, there was some evidence for clinical benefits (on the rate of response) associated with quetiapine for acute treatment and olanzapine for relapse prevention. The committee therefore recommended that combination treatment with both an antidepressant and an antipsychotic should be considered for people with psychotic depression, and the specific antipsychotics that showed clearer benefits were given as examples. The committee also knew that quetiapine has antidepressant effects as well as antipsychotic effects so it was theoretically a good choice, and is often used for psychotic depression. However, the committee discussed that not everyone with psychotic depression may want to take antipsychotic medication. They also considered the evidence from the comparison of an antidepressant plus antipsychotic relative to an antipsychotic (plus placebo) that showed clinical benefits associated with the antidepressant treatment (on depression symptomatology, and remission of depression and psychotic symptoms), and therefore recommended that in such cases antidepressant treatment alone should be offered.

The committee agreed that the combination of an antidepressant and an antipsychotic may lead to increased side effects and that it was therefore important to monitor the combination for side effects and discontinue the antipsychotic as soon as possible. The committee discussed the cessation of the antipsychotic and agreed, based on their expertise and experience, that GPs may not be confident to make the decision to discontinue the prescription, and that the decision would be better made in conjunction with or by specialist mental health services and so they made this recommendation.

There was evidence from single studies comparing an antipsychotic to an antidepressant or different types of antidepressants. However, based on the absence of any clinically important and statistically significant differences between individual drugs, the committee agreed not to recommend any specific class or individual antidepressant over another.

The committee thought that it was important to emphasise that there was more information on how to prescribe and monitor antipsychotics available in the NICE guideline on psychosis and schizophrenia in adults, and therefore signposted the recommendations on prescribing and monitoring antipsychotics in that guideline.

The committee discussed the evidence for ECT in the treatment of psychotic depression. There was no evidence for ECT in the acute treatment of psychotic depression, although the committee were aware of data that suggests a higher remission rate in psychotic depression compared with non-psychotic depression. There was evidence from a small single study of the benefit of ECT in relapse prevention that was considered too limited to form the basis of a treatment recommendation.

The committee discussed that no evidence on psychological interventions for people with psychotic depression had been identified. Based on their knowledge and experience of the use of psychological interventions in the treatment of psychosis, the committee agreed that

psychological interventions delivered by practitioners with experience and specialist training in working with people with psychosis and depression may also be effective for psychotic depression. As there was no evidence for psychological or psychosocial interventions and such limited evidence for pharmacological treatment and ECT the committee made a research recommendation.

Longer-term follow-up

The committee noted that none of the studies on psychotic depression reported any follow-up data. The committee agreed that this created uncertainty about the sustainability of clinical benefits. 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 antidepressant and antipsychotic medication be 'considered'.

Quality of life and functioning outcomes

The committee also noted that none of the studies on psychotic depression reported any quality of life or functioning outcomes. As with the absence of follow-up data, the committee agreed that the lack of quality of life and functioning outcomes contributed to the limitations of the evidence base, and consequently the committee could only recommend that combination antidepressant and antipsychotic medication be 'considered'.

Cost effectiveness and resource use

No evidence on the cost-effectiveness of interventions for adults with depression with psychotic symptoms was identified and no further economic analysis was undertaken. The committee considered the costs associated with the treatment of people with depression with psychotic symptoms, including costs of inpatient care in psychiatric wards and, potentially, of Accident and Emergency visits. The committee acknowledged that referring people with depression with psychotic symptoms to specialist mental health services was likely to incur additional costs compared with no referral; however, they agreed that specialist services can deal more effectively with the complex needs of this population, including conducting a risk assessment, providing coordinated multi-professional care, and having expertise in initiation of antipsychotics to augment antidepressant treatment so as to deal with psychotic symptoms prior to initiation of psychological therapy. They agreed that specialist care is likely to lead to better outcomes (improvement in both psychotic and depressive symptoms) and also cost-savings resulting from better treatment effects and thus a reduction in the need to change treatments (which comes at a cost) as well as in the need for costly inpatient psychiatric care. Therefore, they expressed the opinion that referral costs were likely to be at least partially offset by cost-savings and improved outcomes in this population. The committee discussed the costs of antipsychotics, and given that a wide range of antipsychotics are currently available in a generic form, they estimated that augmentation of the current treatment plan with antipsychotic medicine was likely to lead to small resource implications.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.12.1 to 1.12.6 and research recommendations in the NICE guideline.

References

Flint 2019

Flint AJ, Meyers BS, Rothschild AJ, Whyte EM, Alexopoulos GS, Rudorfer MV et al. Stop-Pd Ii Study Grp. Effect of Continuing Olanzapine vs Placebo on Relapse Among Patients With Psychotic Depression in Remission The STOP-PD II Randomized Clinical Trial. Jama-Journal of the American Medical Association. 2019. 322(7): 622-631.

Kunzel 2009

Künzel HE, Ackl N, Hatzinger M, Held K, Holsboer-Trachsler E, Ising M, Kaschka W, Kasper S, Konstantinidis A, Sonntag A, Uhr M. Outcome in delusional depression comparing trimipramine monotherapy with a combination of amitriptyline and haloperidol–a double-blind multicenter trial. Journal of Psychiatric Research. 2009 Apr 1;43(7):702-10.

Meyers 2001

Meyers BS, Klimstra SA, Gabriele M, Hamilton M, Kakuma T, Tirumalasetti F, Alexopoulos GS. Continuation treatment of delusional depression in older adults. The American Journal of Geriatric Psychiatry. 2001 Sep 1;9(4):415-22.

Meyers 2009

Meyers BS, Flint AJ, Rothschild AJ, Mulsant BH, Whyte EM, Peasley-Miklus C, Papademetriou E, Leon AC, Heo M. A double-blind randomized controlled trial of olanzapine plus sertraline vs olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). Archives of General Psychiatry. 2009 Aug 1;66(8):838-47.

Mulsant 2001

Mulsant BH, Sweet RA, Rosen J, Pollock BG, Zubenko GS, Flynn T, Begley AE, Mazumdar S. A double-blind randomized comparison of nortriptyline plus perphenazine versus nortriptyline plus placebo in the treatment of psychotic depression in late life. The Journal of Clinical Psychiatry. 2001 Aug;62(8):597-604.

Navarro 2008

Navarro V, Gastó C, Torres X, Masana G, Penadés R, Guarch J, Vazquez M, Serra M, Pujol N, Pintor L, Catalan R. Continuation/maintenance treatment with nortriptyline versus combined nortriptyline and ECT in late-life psychotic depression: a two-year randomized study. The American Journal of Geriatric Psychiatry. 2008 Jun 1;16(6):498-505.

Spiker 1985

Spiker DG, Weiss JC, Dealy RS, Griffin SJ, Hanin I, Neil JF, Perel JM, Rossi AJ, Soloff PH. The pharmacological treatment of delusional depression. Am J Psychiatry. 1985 Apr 4;142(4):430-6.

Wijkstra 2010

Wijkstra J, Burger H, Van den Broek WW, Birkenhäger TK, Janzing JG, Boks MP, Bruijn JA, Van Der Loos ML, Breteler LM, Ramaekers GM, Verkes RJ. Treatment of unipolar psychotic depression: a randomized, double-blind study comparing imipramine, venlafaxine, and venlafaxine plus quetiapine. Acta Psychiatrica Scandinavica. 2010 Mar;121(3):190-200.

Appendices

Appendix A – Review protocol

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

Table 8: Review protocol for psychotic depression

Field (based on PRISMA-P)	Content
Review question	For adults with psychotic depression what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination (as first-line treatment or relapse prevention)?
Type of review question	Intervention review
Objective of the review	To identify the most effective first-line treatment or relapse prevention strategy for adults with psychotic depression
Population	Adults with psychotic depression (a depressive episode with psychotic features, i.e. delusions and/or hallucinations in the context of a major depressive disorder)
Exclude	Trials of women with postnatal depression Trials of people 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 particular physical health condition in addition to depression (e.g. depression in people with diabetes) Depression occurring in a primary psychotic illness, such as schizophrenia or dementia 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. Psychological interventions • Behavioural therapies (including behavioural activation, behavioural therapy [Lewinsohn 1976], coping with depression group)

Field (based on PRISMA-P)	Content
	• Cognitive and cognitive behavioural therapies (including CBT individual or group, problem solving, rational emotive behaviour therapy [REBT] and third-wave cognitive therapies) • Counselling (including emotion-focused therapy [EFT], non-directive/supportive/ person-centred counselling and relational client-centred therapy) • Family interventions/couples therapy • Interpersonal psychotherapy • Psychodynamic psychotherapies (including short-term psychodynamic psychotherapy, long-term psychodynamic psychotherapy and psychodynamic counselling) • Psychoeducational interventions (including psychoeducational group programmes) • 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 • Antipsychotics • Lithium • Omega-3 fatty acids Physical interventions: • Acupuncture • ECT • Exercise • Yoga • Light therapy (for depression, not SAD)

Field (based on PRISMA-P)	Content
Comparison	• Treatment as usual • Waitlist • No treatment • Placebo • Any other active comparison
Outcomes	**Critical outcomes:** • Depression symptomatology (mean endpoint score or change in depression score from baseline) • Response (usually defined as at least 50% improvement from the baseline score on a depression scale) • Remission (usually defined as a score below clinical threshold on a depression scale) • Relapse (number of people who returned to a depressive episode whilst in remission) 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) • HADS (full scale) • Discontinuation due to any reason (including side effects) • Discontinuation due to side effects (for pharmacological trials) **Important outcomes:** • Quality of life: ○ Quality of life (as assessed with a validated scale, including the 12-item/36-item Short-Form Survey [SF-12/SF-36], 26-item short version of the World Health Organization Quality of Life assessment [WHOQOL-BRIEF], EuroQoL [EQ5D], Quality of Life Depression Scale [QLDS], Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q], Quality of Life Inventory [QoLI], and World Health Organization 5-item Well-Being Index [WHO-5]) • Personal, social, and occupational functioning:

Field (based on PRISMA-P)	Content
	○ Global functioning (as assessed with a validated scale, including Global Assessment of Functioning [GAF], Global Assessment Scale [GAS], and Social and Occupational Functioning Assessment Scale [SOFAS]) ○ Functional impairment (as assessed with a validated scale, including Sheehan Disability Scale [SDS], Social Adjustment Scale [SAS], and Work and Social Adjustment Scale [WSAS]) ○ Sleeping difficulties (as assessed with a validated scale, including Insomnia Severity Index [ISI] and Pittsburgh Sleep Quality Index [PSQI]) ○ 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 existing reviews from the 2009 guideline and from previous searches (pre-2016) will be carried forward. Studies published between 2016 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.

Field (based on PRISMA-P)	Content
	Data Analysis 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
Data management (software)	Endnote was used to sift through the references identified by the search. Data was extracted into a standardised template created in Microsoft Excel. Pairwise meta-analyses and production of forest plots was done using Cochrane Review Manager (RevMan5). 'GRADEpro' was used to assess the quality of evidence for each outcome.
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.
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).

Field (based on PRISMA-P)	Content
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; CBASP: cognitive behavioural analysis system of psychotherapy; CBT: cognitive behavioural therapy; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CES-D: Centre of epidemiology studies – depression; CG: clinical guideline; CGI: clinical global impressions; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; DSM: diagnostic and statistical manual of mental disorder; 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; HAMD: Hamilton depression rating scale; ICD: international classification of diseases; IIP: inventory of interpersonal problems; IPT: interpersonal therapy; ISI: insomnia severity index; ITT: intention to treat; MADRS: Montgomery–åsberg depression rating scale MAOI: monoamine oxidase inhibitor; MBCT: mindfulness-based cognitive therapy; MBSR: mindfulness-based stress reduction; MDD: major depressive disorder; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PHQ: patient health questionnaire; PSQI: Pittsburgh sleep quality index; PTSD: post-traumatic stress disorder; QIDS: quick inventory of depression 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; SD: standard

deviation; SDS: sheehan disability scale; SF12/36: 12-/36-item short form health survey ; SMD: standardised mean difference; SNRI: serotonin noradrenaline reuptake inhibitor; SOFAS: Social and occupational functioning assessment scale; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TeCA: tetracyclic antidepressant; 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 psychotic depression what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination (as first-line treatment or relapse prevention)?

Clinical search

Database(s): Embase 1974 to 2019 Week 12, Emcare 1995 to present, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 26, 2019, PsycINFO 1806 to March Week 3 2019

Date of Search: 27/03/2019

Search updated: 04/03/2021

#	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 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 melanchol* or ((affective or mood) adj disorder*)).tw.
5	((severe or serious or persistent or major or critical or clinical or acute) adj2 (anxiety or (mental adj2 (disorder* 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	(depressive psychosis/ or affective psychosis/ or exp delusion/ or exp hallucination/) use oemezd,emcr
8	(Affective Disorder, Psychotic/ or Psychotic Disorders/ or Delusions/ or Hallucinations/) use ppez
9	(Affective Psychosis/ or Acute Psychosis/ or Chronic Psychosis/ or Delusions/ or Hallucinosis/ or Psychosis/ or Reactive Psychosis/) use psyh
10	(psychotic* or psychosis or psychoses or delusion* or hallucinat*).tw.
11	or/7-10
12	6 and 11
13	(exp psychotherapy/ or exp counseling/ or problem solving/ or self help/) use oemezd,emcr
14	(exp Psychotherapy/ or exp Counseling/ or Problem Solving/ or Self Care/ or Self Efficacy/ or Self-Help Groups/) use ppez
15	(exp psychotherapy/ or behavioral activation system/ or cognitive therapy/ or exp counseling/ or exp problem solving/ or exp self-help techniques/) use psyh
16	peer group/ use oemezd,emcr,ppez
17	peer relations/ use psyh
18	friendship/ use oemezd,emcr,psyh
19	Friends/ use ppez
20	mindfulness/
21	(psychotherap* or psycho-therap*).tw.
22	((behavi* or cognitive or couple* or family or families or interpersonal or psychiatr* or psychoanaly* or psycho-analy* or psychodynamic* or psycho-dynamic* or psycholog* or psychosocial or psycho-social) adj2 (intervention* or psychotherap* or therap* or treatment*)).tw.
23	(counsel* or mindfulness or problem solving or self-help or solution focus* or talking therap* or talking treatment*).tw.
24	(befriend* or friend* or mentor* or peer support or (communit* adj (navigat* or support*))).tw.
25	((non pharmacologic* or nonpharmacologic*) adj (intervention* or therap* or treatment*)).tw.
26	drug therapy.fs.
27	drug therapy/
28	exp neuroleptic agent/ use oemezd,emcr
29	exp tricyclic antidepressant agent/
30	exp neuroleptic drugs/ use psyh
31	exp tricyclic antidepressant drugs/ use psyh
32	exp Antipsychotic Agents/ use ppez
33	(antipsychotic* or anti-psychotic*).tw.
34	exp serotonin noradrenalin reuptake inhibitor/ use oemezd,emcr
35	exp "Serotonin and Noradrenaline Reuptake Inhibitors"/ use ppez
36	serotonin norepinephrine reuptake inhibitors/ use psyh
37	exp serotonin uptake inhibitor/ use oemezd,emcr
38	exp Serotonin Uptake Inhibitors/ use ppez

#	Searches
39	exp serotonin reuptake inhibitors/ use psyh
40	(SNRI* or SSRI* or (serotonin adj2 inhibitor*)).tw.
41	(agomelatine or allegron or amitriptyline or anafranil or brintellix or cipralex or cipramil or citalopram or clomipramine or cymbalta or depefex or dosulepin or doxepin or duloxetine or edronax or efexor or escitalopram or faverin or fluoxetine or fluvoxamine or foraven or imipramine or isocarboxazid or lofepramine or lomont or lustral or manerix or mianserin or mirtazapine or moclobemide or molipaxin or nardil or nortriptyline or oxactin or parnate or paroxetine or phenelzine or politid or prothiaden or prozac or prozep or reboxetine or seroxat or sertraline or sinepin or sunveniz or surmontil or tofranil or tonpular or tranylcypromine or trazodone or trimipramine or triptafen or valdoxan or venadex or venaxx or venlafaxine or venlalic or viepax or vortioxetine or zispin).tw.
42	(abilify or amisulpride or anquil or aripiprazole or asenapine or atrolak or benperidol or biquelle or chlorpromazine or clopixol or clozapine or clozaril or denzapine or depixol or dolmatil or dozic or ebesque or fentazin or fluanxol or flupenthixol or flupentixol or fluphenazine decanoate or haldol or haloperidol or invega or largactil or latuda or levomepromazine or lurasidone or modecate or neulactil or nozinan or olanzapine or orap or paliperidone or pericyazine or perphenazine or pimozide or piportil or pipotiazine palmitate or prochlorperazine or promazine or quetiapine or risperdal or risperidone or serenace or seroquel or solian or stelazine or stemetil or sulpiride or sulpor or sycrest or tenprolide or trevicta or trifluoperazine or xeplion or zaluron or zuclopentixol or zypadhera or zyprexa).tw.
43	lithium/ use oemezd,emcr,ppez
44	lithium derivative/ use oemezd,emcr
45	exp Lithium Compounds/ use ppez
46	exp lithium/ use psyh
47	(lithium or camcolit or liskonum or priadel or lithonate or litarex or li-liquid).tw.
48	omega 3 fatty acid/ use oemezd,emcr
49	exp Fatty Acids, Omega-3/ use ppez
50	fatty acids/ use psyh
51	(omega adj ("fatty acid*" or "polyunsaturated fatty acid*" or PUFA*)).tw.
52	(docosahex* or DHA or eicosa* or EPA or linoleic or linolenic or (oil and (cod liver or fish or flax* or linseed or nut or nuts or rapeseed or seed or seeds or shellfish or sunflower or vegetable))).tw.
53	acupuncture/
54	acupuncture.tw.
55	electroconvulsive therapy/ use oemezd,emcr,ppez
56	electroconvulsive shock therapy/ use psyh
57	(ECT or ((electroconvulsive or electro-convulsive) adj2 (therap* or treatment*)) or electroshock or (shock adj (therapy or treatment))).tw.
58	exp exercise/
59	(exp Exercise Therapy/ or Physical Exertion/ or exp Physical Fitness/ or Bicycling/ or exp Running/ or Swimming/ or Walking/) use ppez
60	(exp kinesiotherapy/ or exp physical activity/ or fitness/ or exp sport/) use oemezd,emcr
61	(exp physical fitness/ or exp sports/) use psyh
62	yoga/
63	(exercis* or yoga or cycling or bicycling or jogging or running or sport* or swimming or walking).tw.
64	or/13-63
65	12 and 64
66	limit 65 to english language
67	Letter/ use ppez
68	letter.pt. or letter/ use oemezd, emcr
69	note.pt.
70	editorial.pt.
71	Editorial/ use ppez
72	News/ use ppez
73	exp Historical Article/ use ppez
74	Anecdotes as Topic/ use ppez
75	Comment/ use ppez
76	Case Report/
77	case study/ use oemezd, emcr
78	(letter or comment*).ti.
79	or/67-78
80	randomized controlled trial/
81	random*.ti,ab.
82	80 or 81
83	79 not 82
84	(animals/ not humans/) use ppez
85	(animal/ not human/) use oemezd, emcr
86	nonhuman/ use oemezd,emcr
87	exp animals/ use psyh
88	"primates (nonhuman)"/ use psyh
89	exp Animals, Laboratory/ use ppez
90	exp Animal Experimentation/ use ppez
91	exp animal experiment/ use oemezd, emcr
92	exp experimental animal/ use oemezd, emcr
93	exp Models, Animal/ use ppez
94	animal model/ use oemezd, emcr

#	Searches
95	animal models/ use psyh
96	animal research/ use psyh
97	exp Rodentia/ use ppez
98	exp rodent/ use oemezd, emcr
99	exp rodents/ use psyh
100	(rat or rats or mouse or mice).ti.
101	or/83-100
102	66 not 101
103	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.
104	103 use ppez
105	(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.
106	105 use ppez
107	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.
108	107 use oemezd, emcr
109	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti.
110	109 use psyh
111	104 or 106
112	108 or 110 or 111
113	Meta-Analysis/
114	exp Meta-Analysis as Topic/
115	systematic review/
116	meta-analysis/
117	(meta analy* or metanaly* or metaanaly*).ti,ab.
118	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
119	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
120	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
121	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
122	(search* adj4 literature).ab.
123	(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.
124	cochrane.jw.
125	((pool* or combined) adj2 (data or trials or studies or results)).ab.
126	(or/113-115,117,119-124) use ppez
127	(or/115-118,120-125) use oemezd, emcr
128	(or/113,117,119-124) use psyh
129	or/126-128
130	112 or 129
131	102 and 130
132	limit 131 to dc=20160601-20190327 use oemezd,emcr [Limit not valid in PsycINFO; records were retained]
133	limit 131 to ed=20160601-20190327 use ppez [Limit not valid in Embase,Ovid Emcare,PsycINFO; records were retained]
134	limit 131 to dt=20160601-20190327 use prem [Limit not valid in Embase,Ovid Emcare,PsycINFO; records were retained]
135	limit 131 to up=20160601-20190327 use psyh
136	132 or 133 or 134 or 135
137	remove duplicates from 136

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

Date of search: 27/03/2019

Search updated: 04/03/2021

ID	Search
#1	MeSH descriptor: [Depression] this term only
#2	MeSH descriptor: [Depressive Disorder] this term only
#3	MeSH descriptor: [Depressive Disorder, Major] explode all trees
#4	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
#5	MeSH descriptor: [Dysthymic Disorder] this term only
#6	(depress* or dysphori* or dysthym* or melanchol* or ((affective or mood) next disorder*)):ti,ab
#7	((sever* or serious* or resistant or persist* or major or endur* or chronic or clinical) next/2 (mental next/2 (disorder* or illness* or ill-health)) or (obsessive next/2 disorder*)):ti,ab
#8	((sever* or serious or persist* or major or endur* or chronic or clinical) next/2 (anxiety 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}

ID	Search
#10	MeSH descriptor: [Affective Disorders, Psychotic] this term only
#11	MeSH descriptor: [Psychotic Disorders] this term only
#12	MeSH descriptor: [Delusions] this term only
#13	MeSH descriptor: [Hallucinations] this term only
#14	(psychotic* or psychosis or psychoses or delusion* or hallucinat*):ti,ab
#15	{or #10-#14}
#16	#9 and #15 with Cochrane Library publication date Between Jun 2016 and Mar 2019

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: 27/02/12019

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 melancholi* 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
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"/

#	Searches
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
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 search: 26/02/2019

Search updated: 02/03/2021

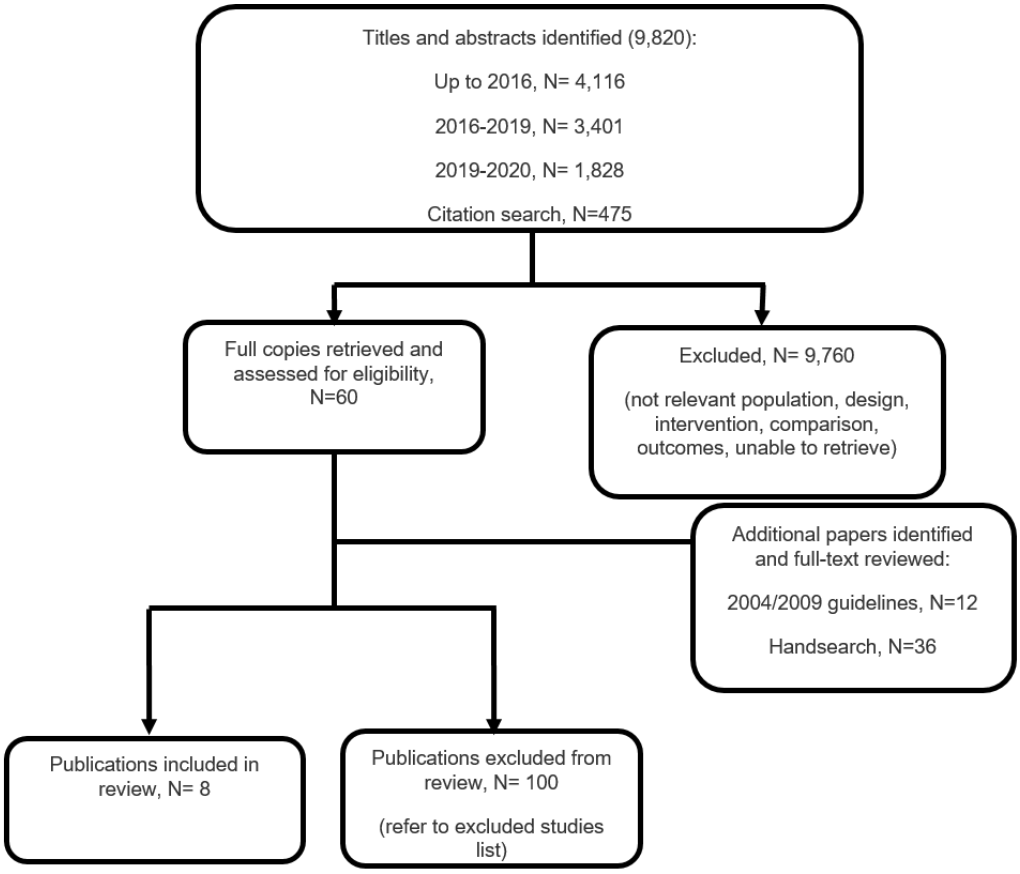
#	Query	Limiters/Expanders
S31	S4 AND S30	Limiters - Publication Year: 2016-2019; Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S30	S10 OR S29	Search modes - Boolean/Phrase
S29	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR 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
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

#	Query	Limiters/Expanders
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

Appendix C – Clinical evidence study selection

Study selection for review question: For adults with psychotic depression what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination (as first-line treatment or relapse prevention)?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Evidence tables for review question: For adults with psychotic depression what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination (as first-line treatment or relapse prevention)?

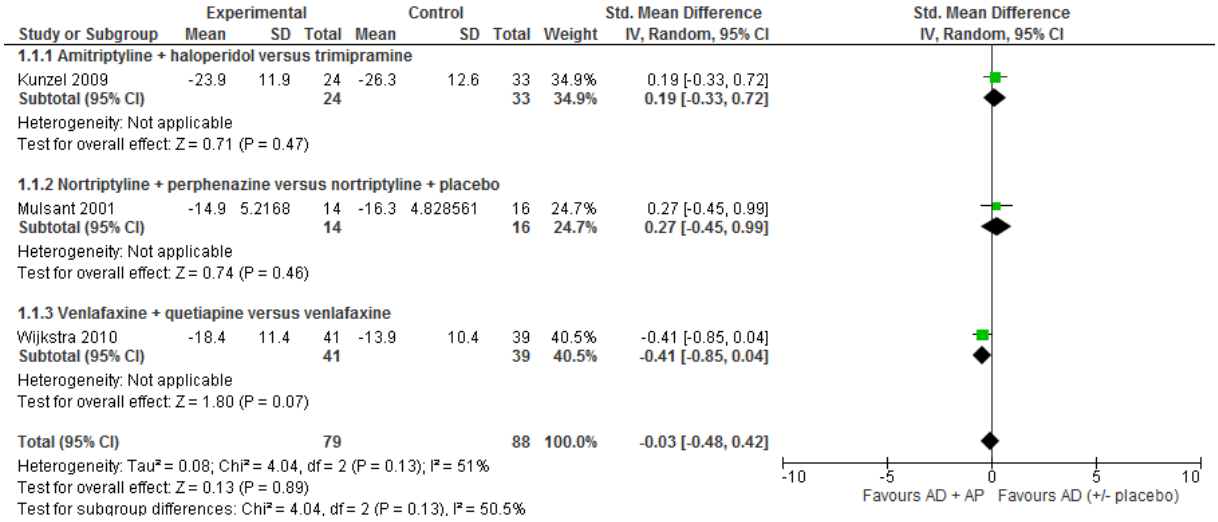
Please refer to the clinical evidence tables in supplement G – Clinical evidence tables for Evidence Review G Psychotic depression

Appendix E – Forest plots

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

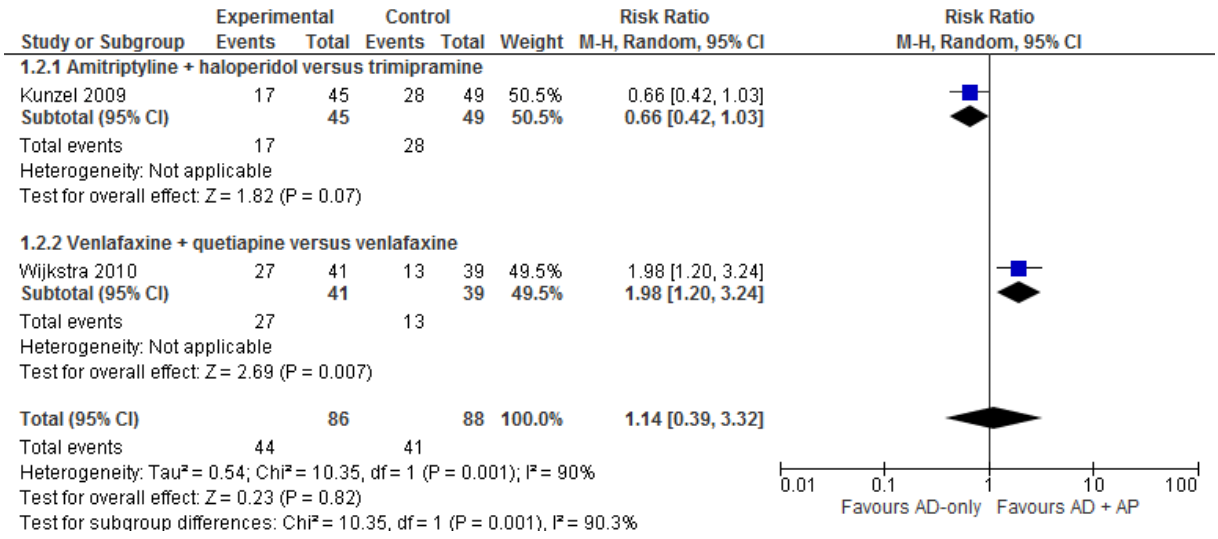
Comparison 1. Antipsychotic plus antidepressant versus antidepressant (alone or plus placebo) for acute treatment of psychotic depression in adults

Figure 2: Depression symptomatology (HAMD change score)



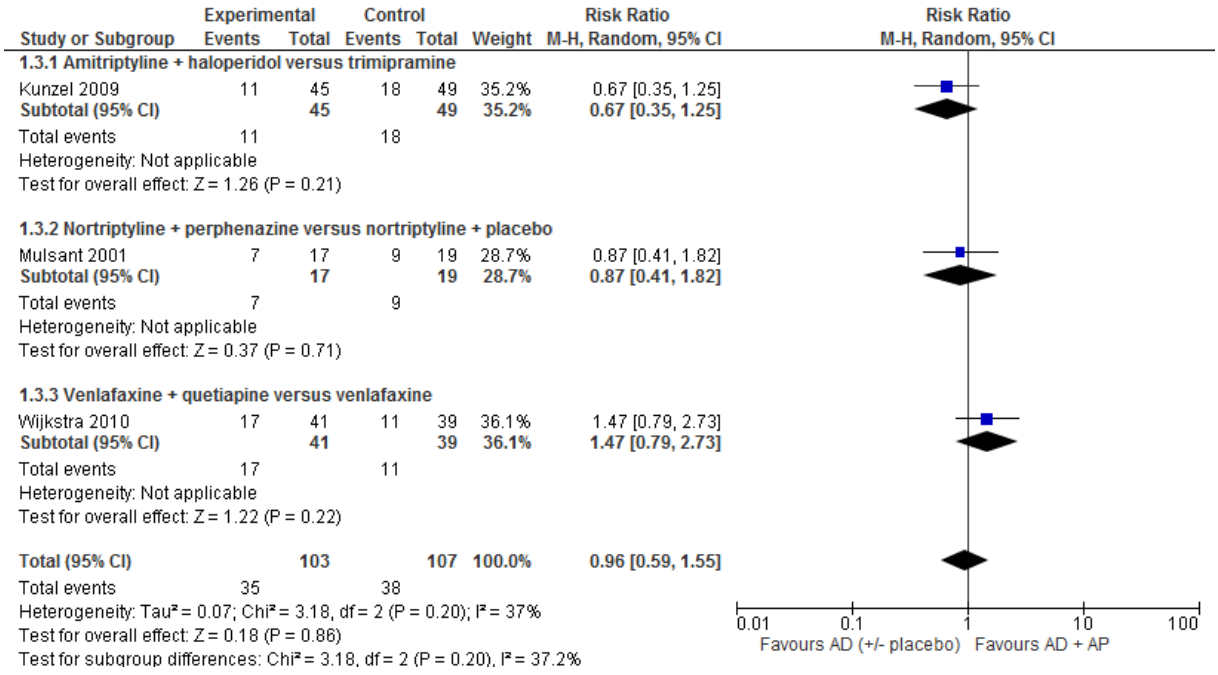
AD: antidepressant; AP: antipsychotic; HAMD: Hamilton Depression Rating Scale

Figure 3: Response (number of participants improving by at least 50% from baseline on HAMD)



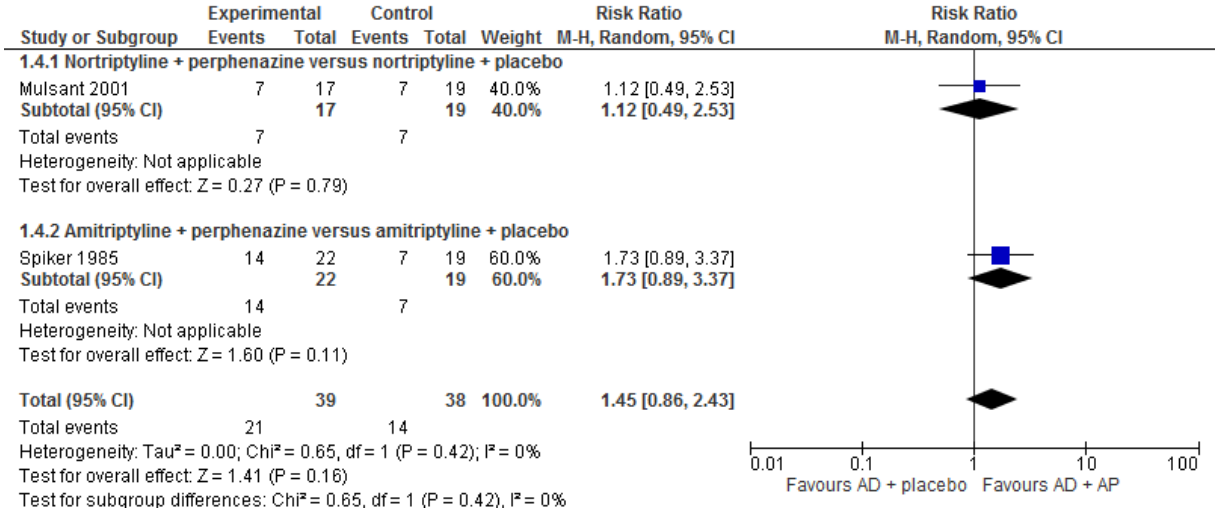
AD: antidepressant; AP: antipsychotic; HAMD: Hamilton Depression Rating Scale

Figure 4: Remission of depression (number of participants scoring HAMD<8/9/11)



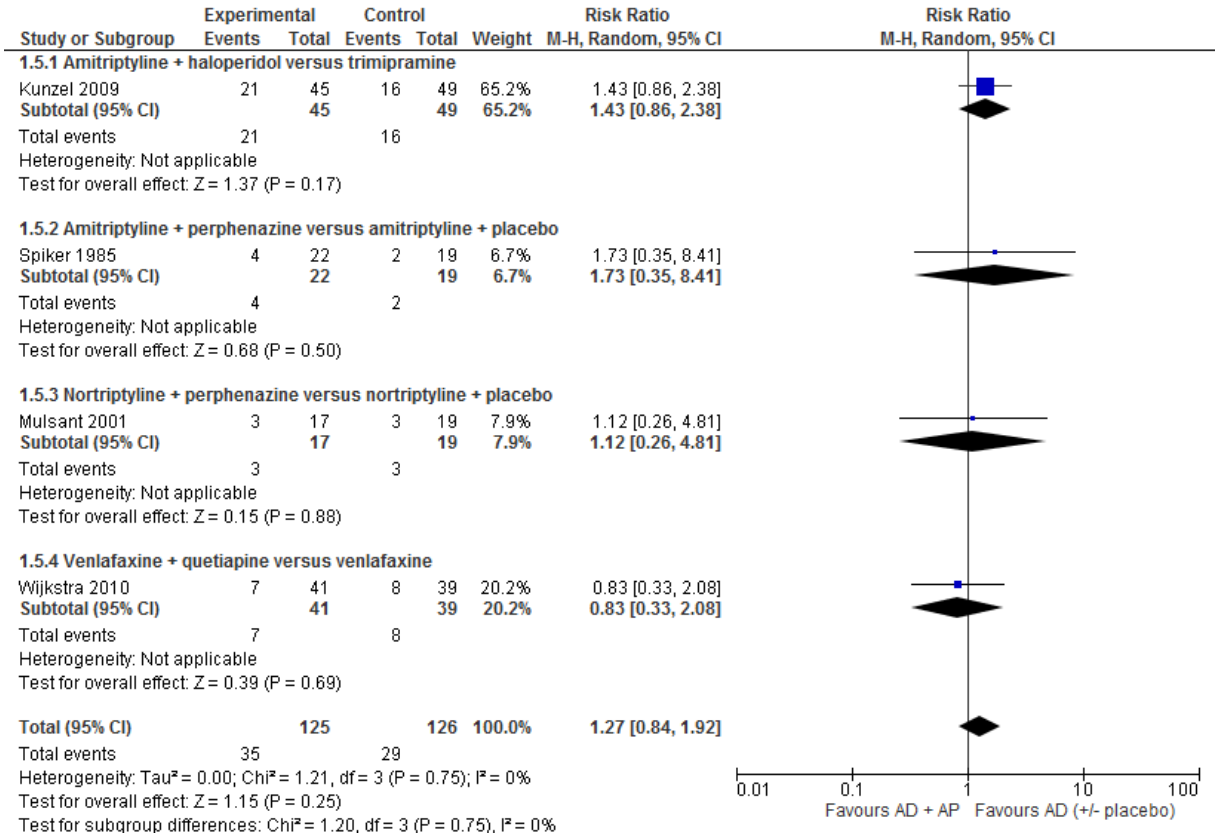
AD: antidepressant; AP: antipsychotic; HAMD: Hamilton Depression Rating Scale

Figure 5: Remission of depression and psychotic symptoms (HAMD<11/7 and absence of psychosis [scores of 1-2 for BPRS items 11, 12 & 15/SADS delusional rating score=1])



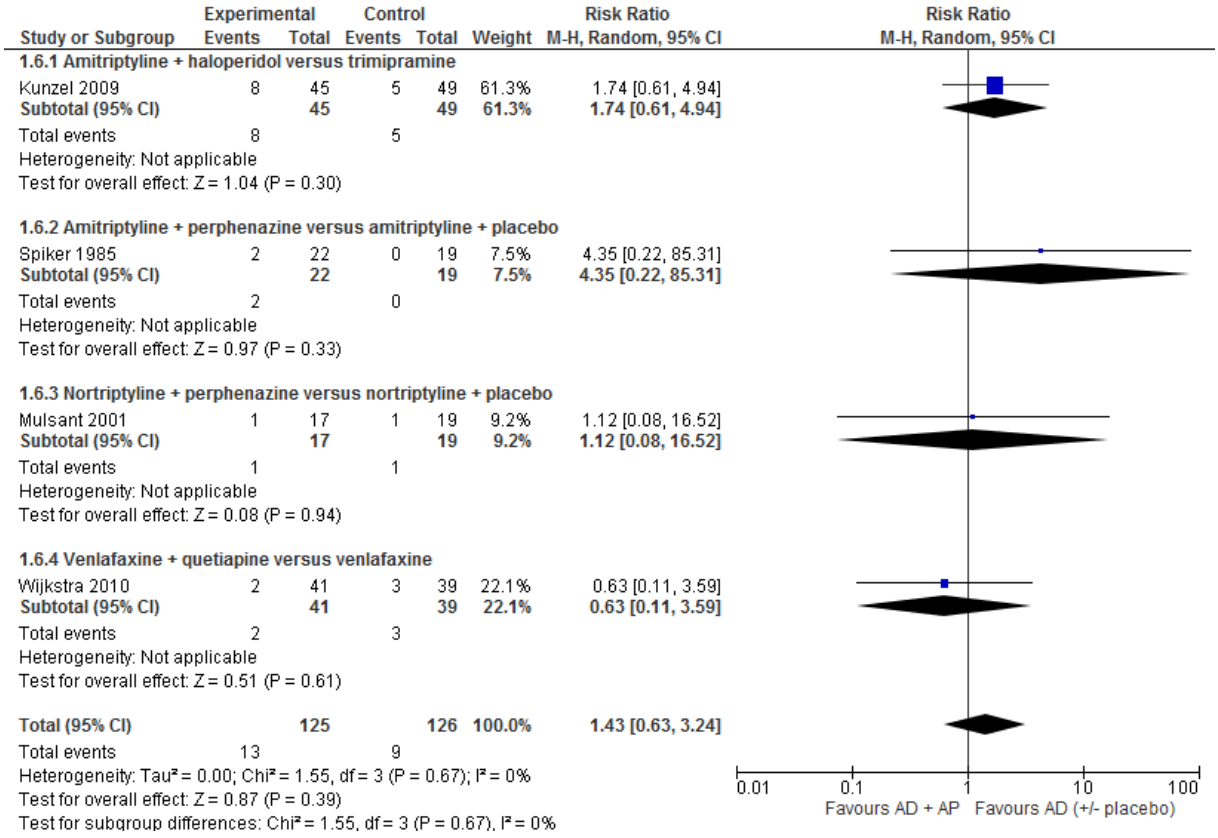
AD: antidepressant; AP: antipsychotic; HAMD: Hamilton Depression Rating Scale

Figure 6: Discontinuation due to any reason



AD: antidepressant; AP: antipsychotic

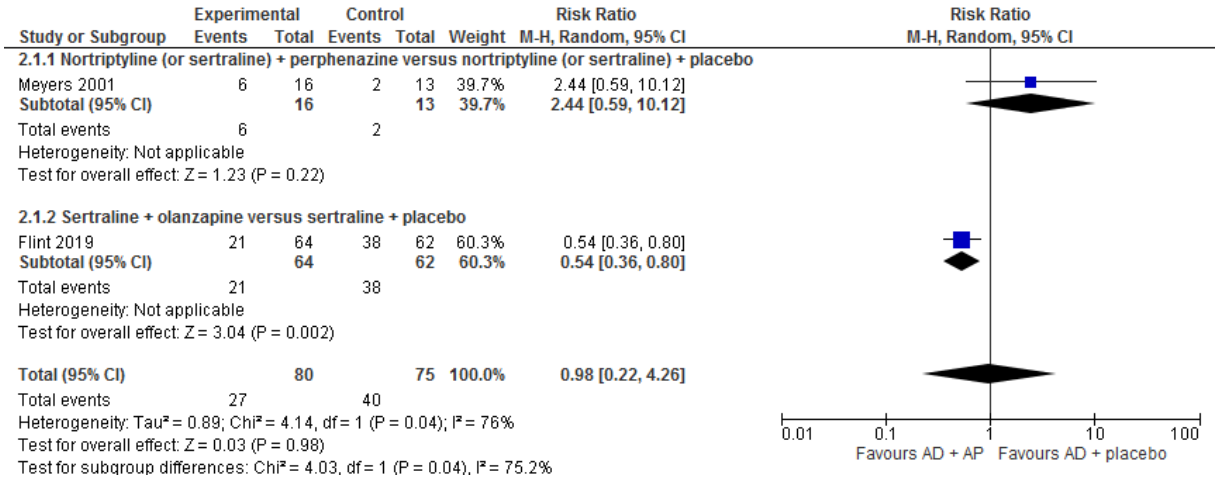
Figure 7: Discontinuation due to side effects



AD: antidepressant; AP: antipsychotic

Comparison 2. Antipsychotic plus antidepressant versus antidepressant plus placebo for relapse prevention in adults with psychotic depression

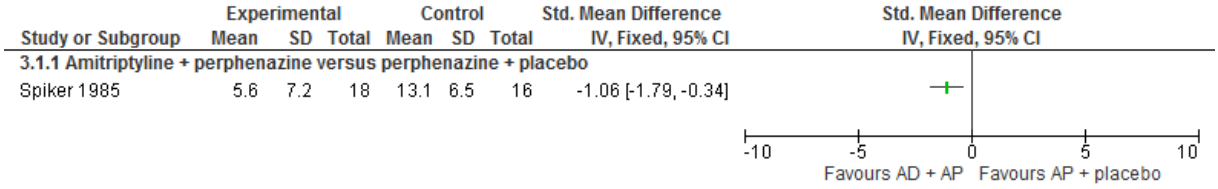
Figure 8: Relapse of depression or psychotic symptoms



AD: antidepressant; AP: antipsychotic; ECT: electroconvulsive therapy

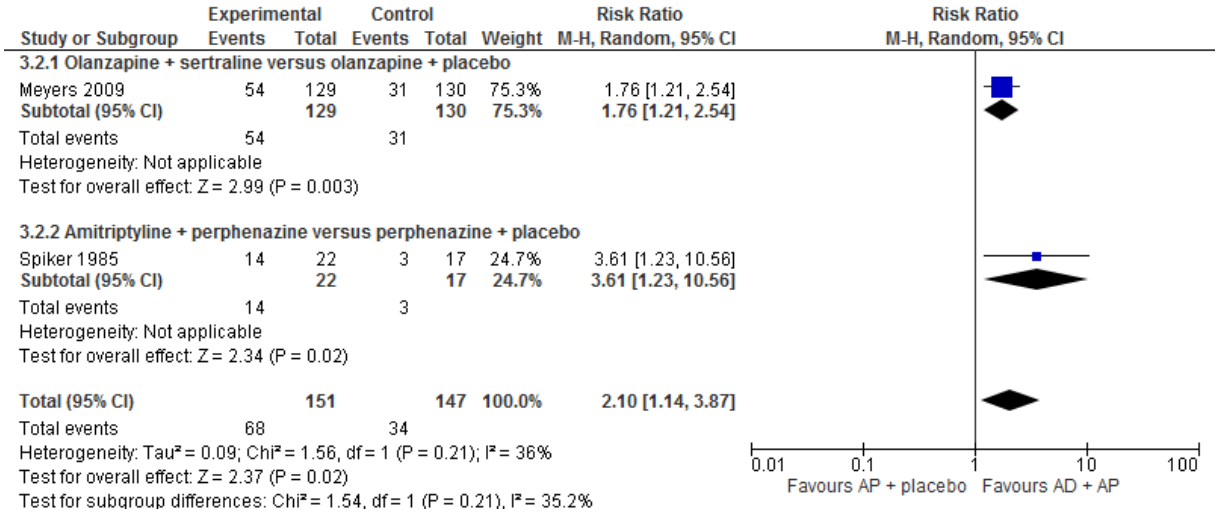
Comparison 3. Antidepressant plus antipsychotic versus antipsychotic plus placebo for the treatment of psychotic depression in adults

Figure 9: Depression symptomatology (HAMD)



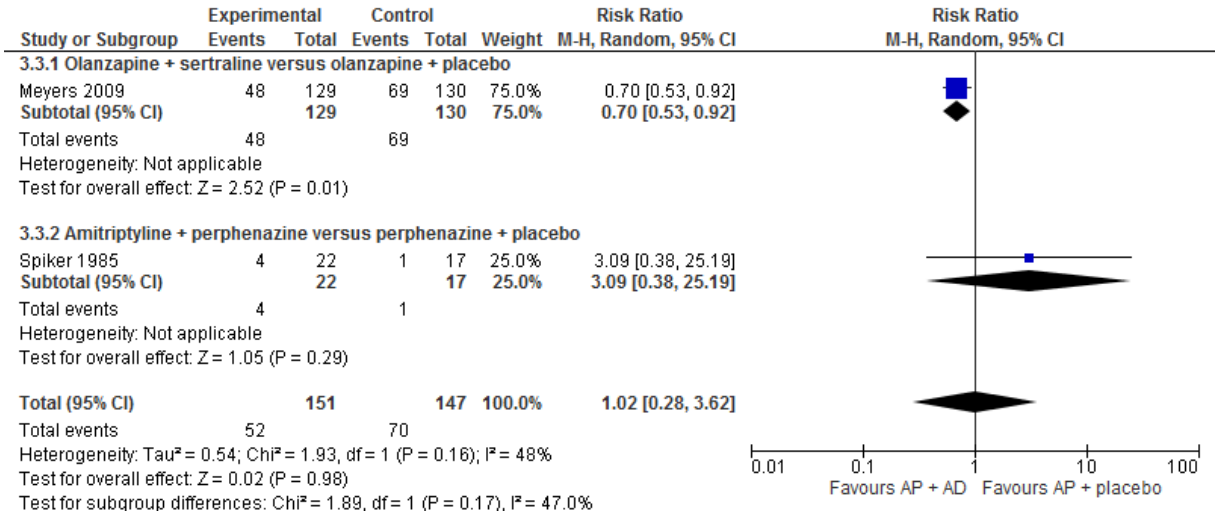
AD: antidepressant; AP: antipsychotic; HAMD: Hamilton Depression Rating Scale

Figure 10: Remission of depression and psychotic symptoms (HAMD<7/11 and absence of delusions [SADS delusional item score of 1])



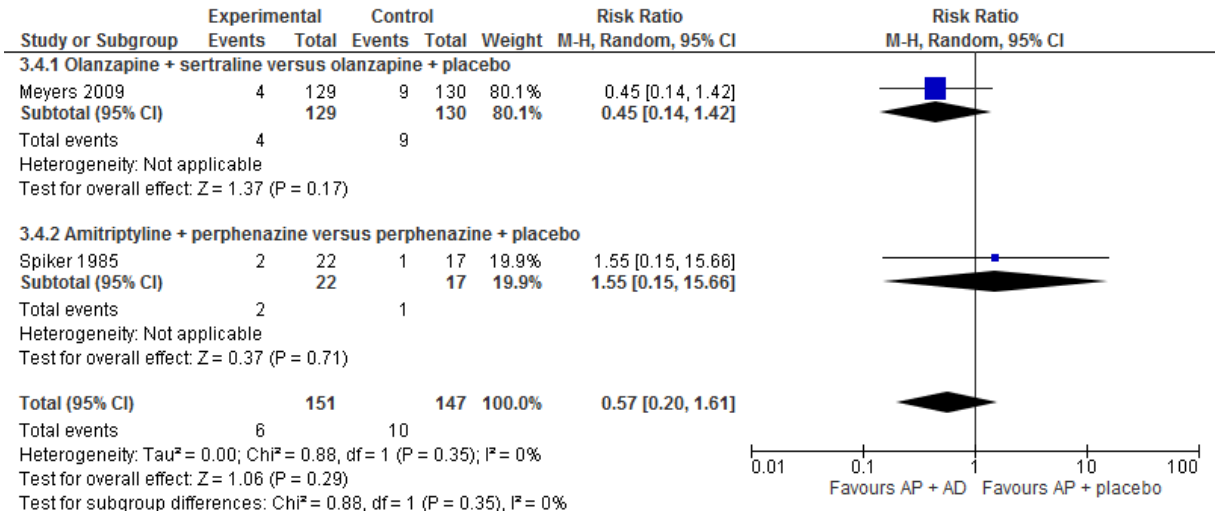
AD: antidepressant; AP: antipsychotic; HAMD: Hamilton Depression Rating Scale

Figure 11: Discontinuation due to any reason



AD: antidepressant; AP: antipsychotic

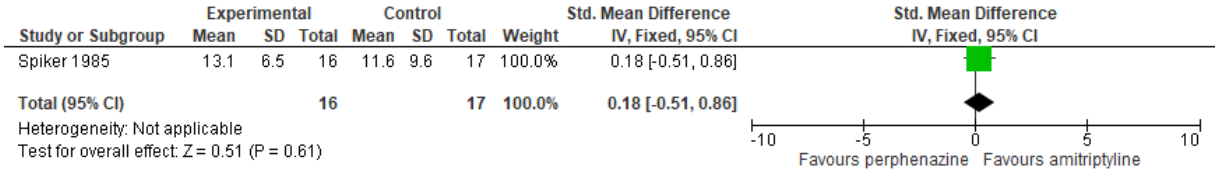
Figure 12: Discontinuation due to side effects



AD: antidepressant; AP: antipsychotic

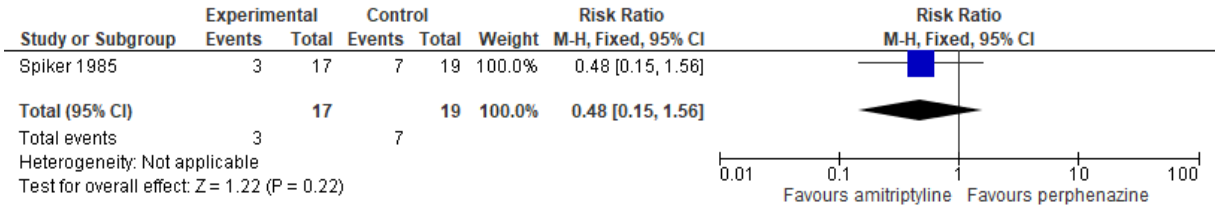
Comparison 4. Perphenazine (plus placebo) versus amitriptyline (plus placebo) for the treatment of psychotic depression in adults

Figure 13: Depression symptomatology (HAMD)



HAMD: Hamilton Depression Rating Scale

Figure 14: Remission of depression and psychotic symptoms (HAMD<7 and no longer delusional [SADS delusional rating score=1])



HAMD: Hamilton Depression Rating Scale

Figure 15: Discontinuation due to any reason

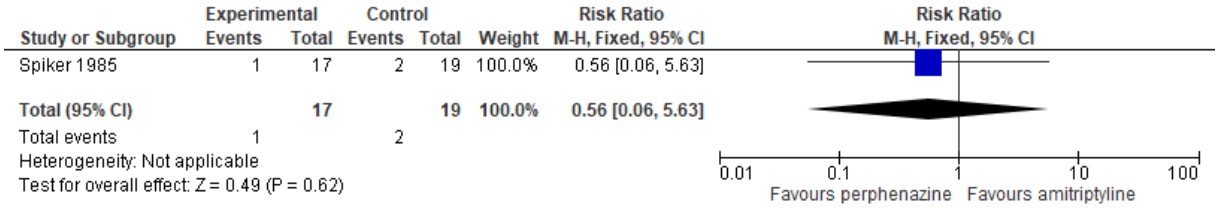
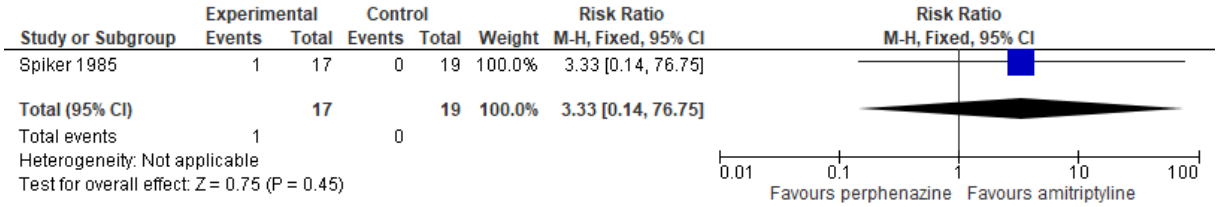
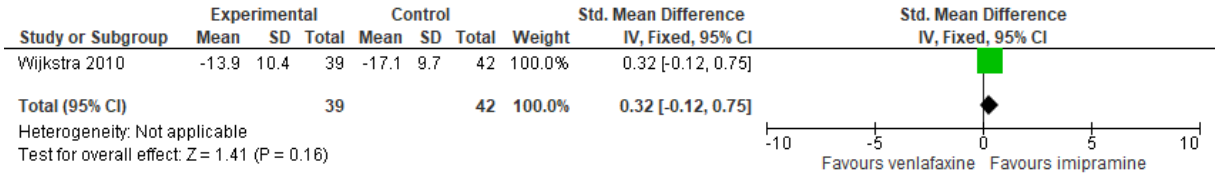


Figure 16: Discontinuation due to side effects



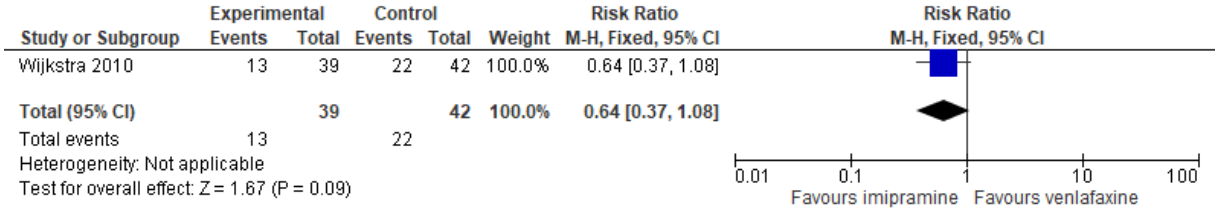
Comparison 5. Venlafaxine versus imipramine for the treatment of psychotic depression in adults

Figure 17: Depression symptomatology (HAMD change score)



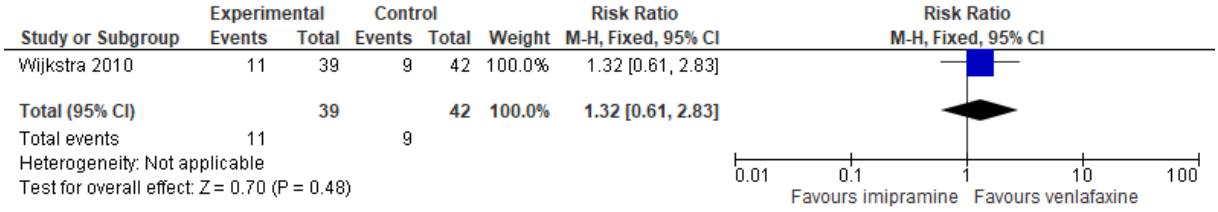
HAMD: Hamilton Depression Rating Scale

Figure 18: Response (at least 50% improvement from baseline on HAMD and a final HAMD score <15)



HAMD: Hamilton Depression Rating Scale

Figure 19: Remission (HAMD<8)



HAMD: Hamilton Depression Rating Scale

Figure 20: Discontinuation due to any reason

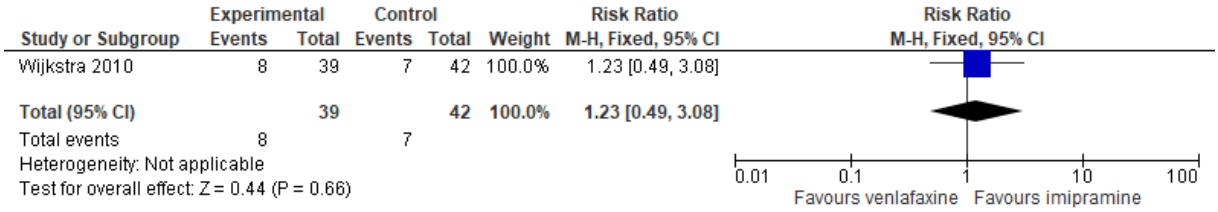
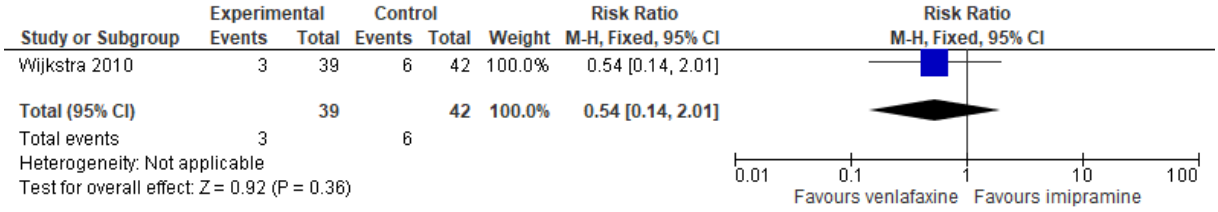
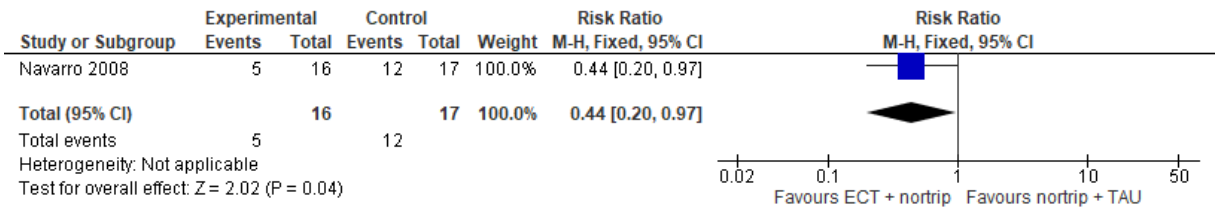


Figure 21: Discontinuation due to side effects



Comparison 6. Continuation ECT plus nortriptyline versus nortriptyline plus treatment as usual for relapse prevention

Figure 22: Relapse (met DSM-IV criteria for major depression and HAMD score≥16 in 2 consecutive visits)



ECT: electroconvulsive therapy; HAMD: Hamilton Depression Rating Scale

Appendix F – GRADE tables

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

Table 9: Clinical evidence profile for comparison 1. Antipsychotic plus antidepressant versus antidepressant (alone or plus placebo) for acute treatment of psychotic depression in adults

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic + antidepressant versus antidepressant (alone or + placebo) for acute treatment	Control	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (HAMD change score) (Better indicated by lower values)												
3 (Kunzel 2009, Mulsant 2001, Wijkstra 2010)	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	reporting bias[3]	79	88	-	SMD 0.03 lower (0.48 lower to 0.42 higher)	VERY LOW	CRITICAL
Response (number of participants improving by at least 50% from baseline on HAMD)												
2 (Kunzel 2009, Wijkstra 2010)	randomised trials	serious[1]	very serious[4]	no serious indirectness	very serious[5]	reporting bias[6]	44/86 (51.2%)	41/88 (46.6%)	RR 1.14 (0.39 to 3.32)	65 more per 1000 (from 284 fewer to 1000 more)	VERY LOW	CRITICAL
Remission of depression (number of participants scoring HAMD<8/9/11)												
3 (Kunzel 2009, Mulsant 2001, Wijkstra 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	35/103 (34%)	38/107 (35.5%)	RR 0.96 (0.59 to 1.55)	14 fewer per 1000 (from 146 fewer to 195 more)	VERY LOW	CRITICAL
Remission of depression and psychotic symptoms (HAMD<11/7 and absence of psychosis [scores of 1-2 for BPRS items 11,12 & 15/SADS delusional rating score=1])												
2 (Mulsant 2001, Spiker 1985)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[9]	21/39 (53.8%)	14/38 (36.8%)	RR 1.45 (0.86 to 2.43)	166 more per 1000 (from 52	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antipsychotic + antidepressant versus antidepressant (alone or + placebo) for acute treatment**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										fewer to 527 more)		
Discontinuation due to any reason												
4 (Kunzel 2009, Spiker 1985, Mulsant 2001, Wijkstra 2010)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[3]	35/125 (28%)	29/126 (23%)	RR 1.27 (0.84 to 1.92)	62 more per 1000 (from 37 fewer to 212 more)	VERY LOW	CRITICAL
Discontinuation due to side effects												
4 (Kunzel 2009, Spiker 1985, Mulsant 2001, Wijkstra 2010)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	13/125 (10.4%)	9/126 (7.1%)	RR 1.43 (0.63 to 3.24)	31 more per 1000 (from 26 fewer to 160 more)	VERY LOW	CRITICAL

CI: Confidence interval; HAMD: Hamilton Depression Rating Scale; RR: Risk ratio; SMD: Standardised mean difference
[1] *Risk of bias is unclear across multiple domains*
[2] *I^2>50%*
[3] *Two studies were funded by pharmaceutical company and in 1 study authors have financial interests in pharmaceutical companies*
[4] *I2 >80%*
[5] *95% CI crosses line of no effect and both clinical decision thresholds*
[6] *Funded by pharmaceutical company*
[7] *Risk of bias unclear or high across multiple domains*
[8] *95% CI crosses line of no effect and one clinical decision threshold*
[9] *Authors have financial interests in pharmaceutical companies*

Table 10: Clinical evidence profile for comparison 2. Antipsychotic plus antidepressant versus antidepressant plus placebo for relapse prevention in adults with psychotic depressions

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic + antidepressant versus antidepressant + placebo for relapse prevention	Control	Relative (95% CI)	Absolute		
Relapse of depression or psychotic symptoms												
2 (Flint 2019, Meyers 2001)	randomised trials	very serious[1]	serious[2]	no serious indirectness	very serious[3]	reporting bias[4]	27/80 (33.8%)	40/75 (53.3%)	RR 0.98 (0.22 to 4.26)	11 fewer per 1000 (from 416 fewer to 1000 more)	VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio
[1] Risk of bias unclear or high across multiple domains
[2] I^2>50%
[3] 95% CI crosses line of no effect and both clinical decision thresholds
[4] In 1 study drop-out is not reported and in another study authors have financial interests in pharmaceutical companies

Table 11: Clinical evidence profile for comparison 3. Antidepressant plus antipsychotic versus antipsychotic plus placebo for the treatment of psychotic depression in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant + antipsychotic versus antipsychotic + placebo	Control	Relative (95% CI)	Absolute		
Depression symptomatology (HAMD)												
1 (Spiker 1985)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	16	-	SMD 1.06 lower (1.79 to 0.34 lower)	VERY LOW	CRITICAL
Remission of depression and psychotic symptoms (HAMD<7/11 and absence of delusions [SADS delusional item score of 1])												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antidepressant + antipsychotic versus antipsychotic + placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
2 (Meyers 2009, Spiker 1985)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[4]	68/151 (45%)	34/147 (23.1 %)	RR 2.1 (1.14 to 3.87)	254 more per 1000 (from 32 more to 664 more)	VERY LOW	CRITICAL
Discontinuation due to any reason												
2 (Meyers 2009, Spiker 1985)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias4	52/151 (34.4%)	70/147 (47.6 %)	RR 1.02 (0.28 to 3.62)	10 more per 1000 (from 343 fewer to 1000 more)	VERY LOW	CRITICAL
Discontinuation due to side effects												
2 (Meyers 2009, Spiker 1985)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias4	6/151 (4%)	10/147 (6.8%)	RR 0.57 (0.2 to 1.61)	29 fewer per 1000 (from 54 fewer to 41 more)	VERY LOW	CRITICAL

CI: Confidence interval; HAMD: Hamilton Depression Rating Scale; RR: Risk ratio; SADS: Delusion Severity Item of the Schedule for Affective Disorders and Schizophrenia; SMD: Standardised mean difference

[1] High risk of bias associated with allocation method and unclear risk of bias associated with selective reporting

[2] 95% CI crosses one clinical decision threshold

[3] Risk of bias unclear or high across multiple domains

[4] In one study drop-out is not reported and also during the last 18 months of recruitment, the age eligibility criterion was reduced to 50 to increase the pool of potential subjects

[5] 95% CI crosses line of no effect and both clinical decision thresholds

Table 12: Clinical evidence profile for comparison 4. Perphenazine (plus placebo) versus amitriptyline (plus placebo) for the treatment of psychotic depression in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Perphenazine (+ placebo) versus amitriptyline (+ placebo)	Control	Relative (95% CI)	Absolute		
Depression symptomatology (HAMD) (Better indicated by lower values)												
1 (Spiker 1985)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	17	-	SMD 0.18 higher (0.51 lower to 0.86 higher)	VERY LOW	CRITICAL
Remission of depression and psychotic symptoms (HAMD<7 and no longer delusional [SADS delusional rating score=1])												
1 (Spiker 1985)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/17 (17.6%)	7/19 (36.8 %)	RR 0.48 (0.15 to 1.56)	192 fewer per 1000 (from 313 fewer to 206 more)	VERY LOW	CRITICAL
Discontinuation due to any reason												
1 (Spiker 1985)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/17 (5.9%)	2/19 (10.5 %)	RR 0.56 (0.06 to 5.63)	46 fewer per 1000 (from 99 fewer to 487 more)	VERY LOW	CRITICAL
Discontinuation due to side effects												
1 (Spiker 1985)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/17 (5.9%)	0/19 (0%)	RR 3.33 (0.14 to 76.75)	-	VERY LOW	CRITICAL

CI: Confidence interval; HAMD: Hamilton Depression Rating Scale; RR: Risk ratio; SADS: Delusion Severity Item of the Schedule for Affective Disorders and Schizophrenia; SMD: Standardised mean difference

[1] High risk of bias associated with allocation method and unclear risk of bias associated with selective reporting

[2] 95% CI crosses line of no effect and both clinical decision thresholds

Table 13: Clinical evidence profile for comparison 5. Venlafaxine versus imipramine for the treatment of psychotic depression in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine versus imipramine	Control	Relative (95% CI)	Absolute		
Depression symptomatology (HAMD change score) (Better indicated by lower values)												
1 (Wijkstra 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	39	42	-	SMD 0.32 higher (0.12 lower to 0.75 higher)	VERY LOW	CRITICAL
Response (at least 50% improvement from baseline on HAMD and a final HAMD score <15)												
1 (Wijkstra 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	13/39 (33.3%)	22/42 (52.4%)	RR 0.64 (0.37 to 1.08)	189 fewer per 1000 (from 330 fewer to 42 more)	VERY LOW	CRITICAL
Remission (HAMD<8)												
1 (Wijkstra 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	11/39 (28.2%)	9/42 (21.4%)	RR 1.32 (0.61 to 2.83)	69 more per 1000 (from 84 fewer to 392 more)	VERY LOW	CRITICAL
Discontinuation due to any reason												
1 (Wijkstra 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	8/39 (20.5%)	7/42 (16.7%)	RR 1.23 (0.49 to 3.08)	38 more per 1000 (from 85 fewer to 347 more)	VERY LOW	CRITICAL
Discontinuation due to side effects												
1 (Wijkstra 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	3/39 (7.7%)	6/42 (14.3%)	RR 0.54 (0.14 to 2.01)	66 fewer per 1000 (from 123 fewer to 144 more)	VERY LOW	CRITICAL

CI: Confidence interval; HAMD: Hamilton Depression Rating Scale; RR: Risk ratio; SMD: Standardised mean difference
[1] Unclear risk of bias concerning detection
[2] 95% CI crosses line of no effect and both clinical decision thresholds
[3] Funding from pharmaceutical company
[4] 95% CI crosses line of no effect and one clinical decision threshold

Table 14: Clinical evidence profile for comparison 6. Continuation ECT plus nortriptyline versus nortriptyline plus treatment as usual for relapse prevention

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Continuation ECT + nortriptyline versus nortriptyline + TAU for relapse prevention**	**Control**	**Relative (95% CI)**	**Absolute**		
Relapse (met DSM-IV criteria for major depression and HAMD score≥16 in 2 consecutive visits)												
1 (Navarro 2008)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/16 (31.3%)	12/17 (70.6%)	RR 0.44 (0.2 to 0.97)	395 fewer per 1000 (from 21 fewer to 565 fewer)	VERY LOW	CRITICAL

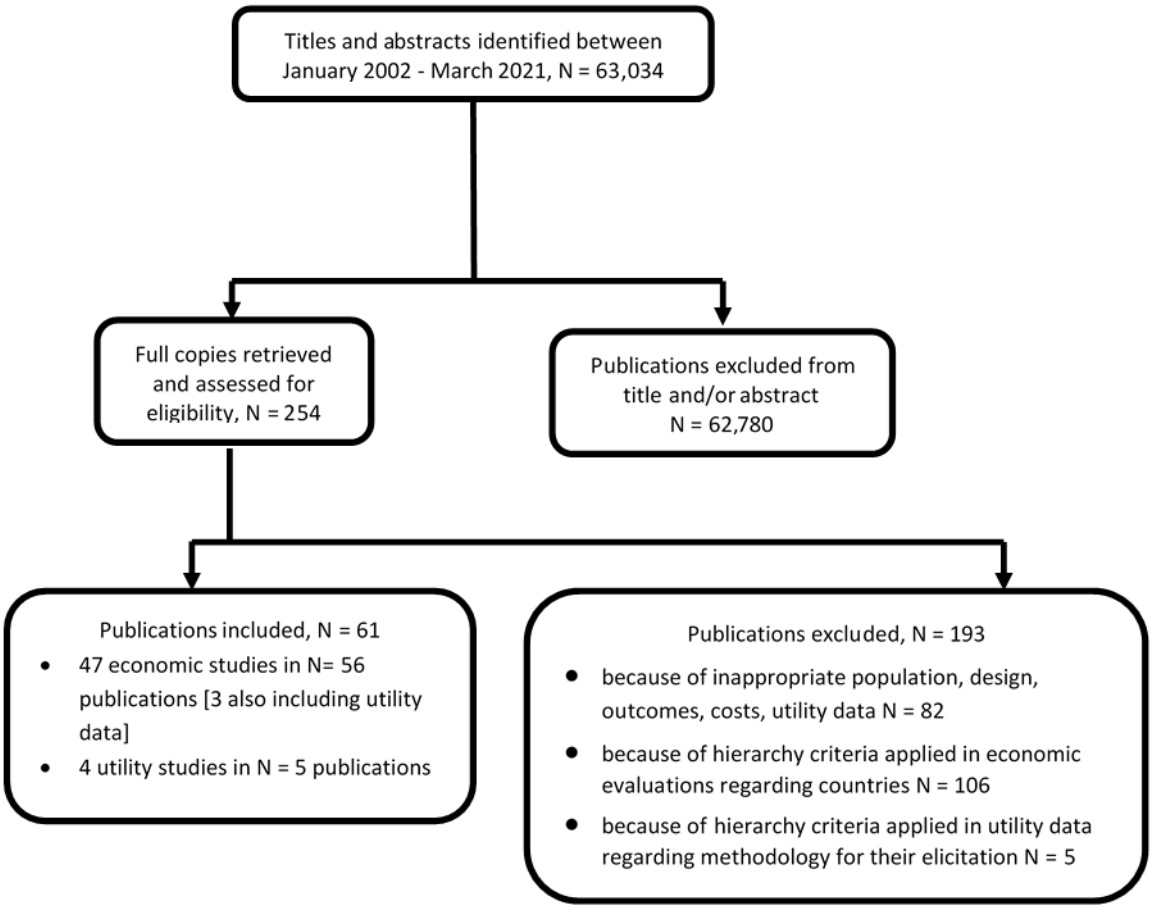
CI: Confidence interval; DSM: Diagnostic and Statistical Manual of Mental Disorders; HAMD: Hamilton Depression Rating Scale; ECT: electroconvulsive therapy; RR: Risk ratio
[1] High risk of bias associated with performance and unclear risk of bias associated with allocation concealment
[2] 95% CI crosses one clinical decision threshold

Appendix G – Economic evidence study selection

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

A global health economics search was undertaken for all areas covered in the guideline. Figure 23 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 23. 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 psychotic depression what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination (as first-line treatment or relapse prevention)?

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 psychotic depression what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination (as first-line treatment or relapse prevention)?

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 psychotic depression what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination (as first-line treatment or relapse prevention)?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: For adults with psychotic depression what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination (as first-line treatment or relapse prevention)?

Clinical studies

Please refer to the excluded studies in supplement G – Clinical evidence tables for Evidence Review G Psychotic depression

Economic studies

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

Appendix L – Research recommendations

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

Research question

What are the most effective and cost effective interventions for the treatment and management of psychotic depression (including consideration of pharmacological, psychological, psychosocial interventions and ECT)?

Why this is important

There is limited evidence on the most effective interventions for the treatment of psychotic depression. All identified evidence examined different pharmacological strategies, with no evidence identified for psychological or psychosocial interventions. Additionally, the current evidence for pharmacological interventions consisted primarily of small, low quality RCTs. The lack of evidence for psychological or psychosocial interventions alone or in combination with pharmacological is a further limitation. There is also very little data on the long-term outcomes for people with psychotic depression.

Table 15: Research recommendation rationale

Research question	What are the most effective and cost effective interventions for the treatment and management of psychotic depression (including consideration of pharmacological, psychological and psychosocial interventions)?
Importance to 'patients' or the population	Evidence of effectiveness and cost-effectiveness of treatments for psychotic depression may lead to the availability of a wider range of treatment options.
Relevance to NICE guidance	There is currently no guidance to help advise which psychological or psychosocial interventions are effective in psychotic depression.
Relevance to the NHS	Use of cost-effective options may lead to reduced costs for treating people with psychotic depression.
National priorities	The NHS Five Year Forward plan makes access to mental health services a key national priority
Current evidence base	No available evidence for psychological or psychosocial interventions alone, or in combination with pharmacological interventions
Equality	People with depression and comorbidities such as psychosis should have equal access to treatment of depression
Feasibility	This study would probably require a coordinated recruitment strategy across several treatment settings and services in order to achieve adequate statistical power.

Table 16: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults (18 years or older) with psychotic depression
Intervention	• Novel pharmacological interventions • Psychological or psychosocial interventions

Criterion	Explanation
	• Combination of psychological or psychosocial interventions with pharmacological interventions • ECT
Comparator	• Antidepressant treatment augmented with antipsychotic medication • Placebo • Treatment as usual • Wait-list
Outcomes	• Depression symptomatology • Response • Remission • Relapse • Discontinuation due to any reason • Discontinuation due to side effects (for pharmacological trials) • Quality of life • Cost-effectiveness
Study design	Randomised controlled trial
Timeframe	Follow-up to 24 months