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Pharmacological interventions for treatment-resistant depression in adults (Review)

Davies P, Ijaz S, Williams CJ, Kessler D, Lewis G, Wiles N

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[Intervention Review]

Pharmacological interventions for treatment-resistant depression in adults

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A B S T R A C T

Background

Although antidepressants are often a first-line treatment for adults with moderate to severe depression, many people do not respond adequately to medication, and are said to have treatment-resistant depression (TRD). Little evidence exists to inform the most appropriate 'next step' treatment for these people.

Objectives

To assess the effectiveness of standard pharmacological treatments for adults with TRD.

Search methods

We searched the Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR) (March 2016), CENTRAL, MEDLINE, Embase, PsycINFO and Web of Science (31 December 2018), the World Health Organization trials portal and ClinicalTrials.gov for unpublished and ongoing studies, and screened bibliographies of included studies and relevant systematic reviews without date or language restrictions.

Selection criteria

Randomised controlled trials (RCTs) with participants aged 18 to 74 years with unipolar depression (based on criteria from DSM-IV-TR or earlier versions, International Classification of Diseases (ICD)-10, Feighner criteria or Research Diagnostic Criteria) who had not responded to a minimum of four weeks of antidepressant treatment at a recommended dose. Interventions were:

(1) increasing the dose of antidepressant monotherapy;

(2) switching to a different antidepressant monotherapy;

(3) augmenting treatment with another antidepressant;

(4) augmenting treatment with a non-antidepressant.

All were compared with continuing antidepressant monotherapy. We excluded studies of non-standard pharmacological treatments (e.g. sex hormones, vitamins, herbal medicines and food supplements).

Data collection and analysis

Two reviewers used standard Cochrane methods to extract data, assess risk of bias, and resolve disagreements. We analysed continuous outcomes with mean difference (MD) or standardised mean difference (SMD) and 95% confidence interval (CI). For dichotomous outcomes, we calculated a relative risk (RR) and 95% CI. Where sufficient data existed, we conducted meta-analyses using random-effects models.

Main results

We included 10 RCTs (2731 participants). Nine were conducted in outpatient settings and one in both in- and outpatients. Mean age of participants ranged from 42 - 50.2 years, and most were female.

One study investigated switching to, or augmenting current antidepressant treatment with, another antidepressant (mianserin). Another augmented current antidepressant treatment with the antidepressant mirtazapine. Eight studies augmented current antidepressant treatment with a non-antidepressant (either an anxiolytic (buspirone) or an antipsychotic (cariprazine; olanzapine; quetiapine (3 studies); or ziprasidone (2 studies)). We judged most studies to be at a low or unclear risk of bias. Only one of the included studies was not industry-sponsored.

There was no evidence of a difference in depression severity when current treatment was switched to mianserin (MD on Hamilton Rating Scale for Depression (HAM-D) = -1.8, 95% CI -5.22 to 1.62, low-quality evidence)) compared with continuing on antidepressant monotherapy. Nor was there evidence of a difference in numbers dropping out of treatment (RR 2.08, 95% CI 0.94 to 4.59, low-quality evidence; dropouts 38% in the mianserin switch group; 18% in the control).

Augmenting current antidepressant treatment with mianserin was associated with an improvement in depression symptoms severity scores from baseline (MD on HAM-D -4.8, 95% CI -8.18 to -1.42; moderate-quality evidence). There was no evidence of a difference in numbers dropping out (RR 1.02, 95% CI 0.38 to 2.72; low-quality evidence; 19% dropouts in the mianserin-augmented group; 38% in the control). When current antidepressant treatment was augmented with mirtazapine, there was little difference in depressive symptoms (MD on Beck Depression Inventory (BDI-II) -1.7, 95% CI -4.03 to 0.63; high-quality evidence) and no evidence of a difference in dropout numbers (RR 0.50, 95% CI 0.15 to 1.62; dropouts 2% in mirtazapine-augmented group; 3% in the control).

Augmentation with buspirone provided no evidence of a benefit in terms of a reduction in depressive symptoms (MD on Montgomery and Asberg Depression Rating Scale (MADRS) -0.30, 95% CI -9.48 to 8.88; low-quality evidence) or numbers of drop-outs (RR 0.60, 95% CI 0.23 to 1.53; low-quality evidence; dropouts 11% in buspirone-augmented group; 19% in the control).

Severity of depressive symptoms reduced when current treatment was augmented with cariprazine (MD on MADRS -1.50, 95% CI -2.74 to -0.25; high-quality evidence), olanzapine (MD on HAM-D -7.9, 95% CI -16.76 to 0.96; low-quality evidence; MD on MADRS -12.4, 95% CI -22.44 to -2.36; low-quality evidence), quetiapine (SMD -0.32, 95% CI -0.46 to -0.18; I2 = 6%, high-quality evidence), or ziprasidone (MD on HAM-D -2.73, 95% CI -4.53 to -0.93; I2 = 0, moderate-quality evidence) compared with continuing on antidepressant monotherapy.

However, a greater number of participants dropped out when antidepressant monotherapy was augmented with an antipsychotic (cariprazine RR 1.68, 95% CI 1.16 to 2.41; quetiapine RR 1.57, 95% CI: 1.14 to 2.17; ziprasidone RR 1.60, 95% CI 1.01 to 2.55) compared with antidepressant monotherapy, although estimates for olanzapine augmentation were imprecise (RR 0.33, 95% CI 0.04 to 2.69). Dropout rates ranged from 10% to 39% in the groups augmented with an antipsychotic, and from 12% to 23% in the comparison groups. The most common reasons for dropping out were side effects or adverse events.

We also summarised data about response and remission rates (based on changes in depressive symptoms) for included studies, along with data on social adjustment and social functioning, quality of life, economic outcomes and adverse events.

Authors' conclusions

A small body of evidence shows that augmenting current antidepressant therapy with mianserin or with an antipsychotic (cariprazine, olanzapine, quetiapine or ziprasidone) improves depressive symptoms over the short-term (8 to 12 weeks). However, this evidence is mostly of low or moderate quality due to imprecision of the estimates of effects. Improvements with antipsychotics need to be balanced against the increased likelihood of dropping out of treatment or experiencing an adverse event. Augmentation of current antidepressant therapy with a second antidepressant, mirtazapine, does not produce a clinically important benefit in reduction of depressive symptoms (high-quality evidence). The evidence regarding the effects of augmenting current antidepressant therapy with buspirone or switching current antidepressant treatment to mianserin is currently insufficient.

Further trials are needed to increase the certainty of these findings and to examine long-term effects of treatment, as well as the effectiveness of other pharmacological treatment strategies.

P L A I N   L A N G U A G E   S U M M A R Y

Are there effective medications for treating depression that does not improve with the first medication used?

Background

Depression is a common problem often treated with antidepressant medication. However, many people do not get better with antidepressant treatment and have 'treatment-resistant depression' (TRD). Several different treatment approaches can be tried - such as increasing the dose of the current medication, adding another medication, or switching to a different antidepressant.

Cochrane reviewers looked at the available evidence to see which of these options may be the best treatment for people with TRD.

Search date

In December 2018, we searched eight medical databases for suitable clinical trials.

Study characteristics

We included 10 randomised controlled trials (RCTs) with 2731 participants (RCTs produce the most robust evidence). These trials investigated three different treatment strategies:

1. changing to a different antidepressant,

2. adding a second antidepressant to the current antidepressant treatment, or

3. adding a different type of medication to current antidepressant treatment - an anti-anxiety medication or an antipsychotic

We found no trials of increasing the dose of current antidepressant medication. Nine of the 10 studies included in this review were sponsored by pharmaceutical companies.

Key results

One small study investigated changing current antidepressant treatment to a different antidepressant (mianserin) or adding mianserin to current treatment. We are uncertain about the effect changing treatment to mianserin has on depressive symptoms or the likelihood of dropping out of treatment. People who added mianserin to their current antidepressant treatment showed fewer depressive symptoms, but the likelihood of dropping out was not clear.

Adding the antidepressant mirtazapine to current antidepressant treatment had little or no effect on depressive symptoms or on the likelihood of dropping out of treatment.

The effect of adding an anti-anxiety medication (buspirone) to ongoing antidepressant treatment on depressive symptoms or dropping out is currently uncertain. These findings were based on one small study.

Most studies looked at the effects of adding an antipsychotic medication (cariprazine, quetiapine, ziprasidone or olanzapine) to current antidepressant treatment. These suggested that adding cariprazine results in a small reduction in depressive symptoms; adding quetiapine reduces depressive symptoms; and adding ziprasidone probably results in a small reduction in depressive symptoms. However, our results also suggest that adding these medicines to current treatment probably increases the likelihood of dropping out of treatment. The most common reasons for dropping out were side effects or adverse events. Adding olanzapine to ongoing treatment may reduce depressive symptoms, but the effects on dropping out are uncertain (findings based on one small study).

Nearly all (9/10) of the studies assessed the effects of treatment in the short-term – six or eight weeks after beginning the new treatment – so the longer term effects of most treatments are unknown.

Quality of the evidence

We judged the quality of the evidence as high, moderate, or low for different outcomes. The main limitation we identified was that the evidence for many of the treatment options investigated came from only one study, and some of these studies also had few participants.

We rated the evidence to be low quality for:

1. switching from the current antidepressant treatment to another antidepressant (mianserin);

2. supplementing current antidepressant treatment with a second antidepressant (mianserin), or with an anti-anxiety medication (buspirone), or with the antipsychotic olanzapine.

This means we are uncertain about the effects of these treatments on depression symptoms or the likelihood of dropping out of treatment.

We rated the quality of the evidence for adding mirtazapine (an antidepressant), cariprazine (an antipsychotic) or quetiapine (an antipsychotic) to ongoing antidepressant treatment on depressive symptoms as high, meaning we are very confident in the effect of these treatment strategies.

We rated the quality of the evidence for adding the antipsychotic ziprasidone to ongoing antidepressant treatment on the effect on depressive symptoms as moderate, which means the true effect may be different from what we found, although findings are likely to be close.

We rated the quality of the evidence for adding mirtazapine (an antidepressant) to ongoing antidepressant treatment on the likelihood of dropping out of treatment as high. We rated the quality of the evidence for adding cariprazine, olanzapine or ziprasidone (all antipsychotics) on the likelihood of dropping out as moderate.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.   Switching to mianserin (60 mg/d) compared to continuing on current antidepressant (fluoxetine 20 mg/d) for treatment-resistant depression in adults

Switching to mianserin (60 mg/d) compared to continuing on current antidepressant (fluoxetine 20 mg/d) for treatment-resistant depression in adults

Patient or population: treatment-resistant depression in adults
Setting: inpatient and outpatient
Intervention: switching to mianserin (60 mg/d)
Comparison: continuing on current antidepressant (fluoxetine 20 mg/d)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with continuing on current antidepressant (fluoxetine 20 mg/d)	Risk difference with switching to mianserin (60 mg/d)
Depressive symptoms (HAM-D) Scale from: 0 to 54 (worse) follow-up: 6 weeks	71 (1 RCT)	⊕⊕⊖⊖ LOW [1]	MD - 1.8 (-5.23 to 1.63)	The mean depressive symptom score (HAM-D) was 15.6	MD 1.8 lower (5.23 lower to 1.63 higher)
Dropouts follow-up: 6 weeks	72 (1 RCT)	⊕⊕⊖⊖ LOW [2]	RR 2.08 (0.94 to 4.59)	Study population	
				184 per 1,000	199 more per 1,000 (11 fewer to 661 more)
Response (≥ 50% improvement in HAM-D score) follow-up: 6 weeks	71 (1 RCT)	⊕⊕⊖⊖ LOW [2]	RR 1.32 (0.76 to 2.27)	Study population	
				368 per 1,000	118 more per 1,000 (88 fewer to 468 more)
Remission (HAM-D total score ≤ 8) follow-up: 6 weeks	71 (1 RCT)	⊕⊕⊖⊖ LOW [3]	RR 1.97 (0.88 to 4.42)	Study population	
				184 per 1,000	179 more per 1,000 (22 fewer to 630 more)
Quality of life - not measured	-	-	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

[1] Downgraded two levels for imprecision (broad confidence interval that crossed the null)
[2] Downgraded two levels for imprecision (very broad confidence interval that crossed the null)
[3] Downgraded two levels for imprecision (very broad confidence interval)

Summary of findings 2.   Augmentation of current antidepressant (fluoxetine 20 mg/d) with mianserin (60 mg/d) compared to augmentation of current antidepressant (fluoxetine 20 mg/d) with placebo for treatment-resistant depression in adults

Augmentation of current antidepressant (fluoxetine 20 mg/d) with mianserin (60 mg/d) compared to augmentation of current antidepressant (fluoxetine 20 mg/d) with placebo for treatment-resistant depression in adults

Patient or population: treatment-resistant depression in adults
Setting: inpatient and outpatient
Intervention: augmentation of current antidepressant (fluoxetine 20 mg/d) with mianserin (60 mg/d)
Comparison: augmentation of current antidepressant (fluoxetine 20 mg/d) with placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with augmentation of current antidepressant (fluoxetine 20 mg/d) with placebo	**Risk difference with augmentation of current antidepressant (fluoxetine 20 mg/d) with mianserin (60 mg/d)**
Depressive symptoms (HAM-D) Scale from: 0 to 54 (worse) follow-up: 6 weeks	70 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	-	The mean depressive symptom score (HAM-D) was 15.6	MD 4.8 lower (8.18 lower to 1.42 lower)
Dropouts follow-up: 6 weeks	70 (1 RCT)	⊕⊕⊖⊖ LOW [2]	RR 1.02 (0.38 to 2.72)	Study population	
				184 per 1,000	4 more per 1,000 (114 fewer to 317 more)
Response (≥ 50% reduction in HAM-D score) follow-up: 6 weeks	70 (1 RCT)	⊕⊕⊖⊖ LOW [3]	RR 1.70 (1.03 to 2.78)	Study population	
				368 per 1,000	258 more per 1,000 (11 more to 656 more)

Remission (HAM-D total score ≤ 7) follow-up: 6 weeks	70 (1 RCT)	⊕⊕⊖⊖ LOW [3]	RR 2.38 (1.09 to 5.16)	Study population	
				184 per 1,000	254 more per 1,000 (17 more to 766 more)
Quality of life - not measured	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio;

__GRADE Working Group grades of evidence__
__High certainty:__ We are very confident that the true effect lies close to that of the estimate of the effect
__Moderate certainty:__ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
__Low certainty:__ Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
__Very low certainty:__ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for imprecision (broad confidence interval)
[2] Downgraded two levels for imprecision (broad confidence interval that crossed the null)
[3] Downgraded two levels for imprecision (very broad confidence interval)

__Summary of findings 3.   Augmentation of current antidepressant (SSRI/SNRI) with mirtazapine (30 mg/d) compared to augmentation of current antidepressant (SSRI/SNRI) therapy with placebo for treatment-resistant depression in adults__

__Augmentation of current antidepressant (SSRI/SNRI) with mirtazapine (30 mg/d) compared to augmentation of current antidepressant (SSRI/SNRI) therapy with placebo for treatment-resistant depression in adults__

__Patient or population:__ treatment-resistant depression in adults
__Setting:__ outpatients
__Intervention:__ augmentation of current antidepressant (SSRI/SNRI) with mirtazapine (30 mg/d)
__Comparison:__ augmentation of current antidepressant (SSRI/SNRI) therapy with placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with augmentation of current antidepressant (SSRI/SNRI) therapy with placebo	Risk difference with augmentation of current antidepressant (SSRI/SNRI) with mirtazapine (30 mg/d)
Depressive symptoms (BDI-II) Scale from: 0 to 64 (worse)	431 (1 RCT)	⊕⊕⊕⊕ HIGH	-	The mean depressive symptom score (BDI-II) was 19.7	MD 1.7 lower (4.03 lower to 0.63 higher)

follow-up: 12 weeks					
Dropouts follow-up: 12 weeks	480 (1 RCT)	⊕⊕⊕⊕ HIGH	RR 0.50 (0.15 to 1.62)	Study population	
				33 per 1,000	17 fewer per 1,000 (28 fewer to 21 more)
Response (≥ 50% improvement in BDI-II score) follow-up: 12 weeks	431 (1 RCT)	⊕⊕⊕⊕ HIGH	RR 1.22 (0.97 to 1.54)	Study population	
				359 per 1,000	79 more per 1,000 (11 fewer to 194 more)
Remission (BDI-II total score ≤ 9) follow-up: 12 weeks	431 (1 RCT)	⊕⊕⊕⊕ HIGH	RR 1.21 (0.88 to 1.65)	Study population	
				244 per 1,000	51 more per 1,000 (29 fewer to 159 more)
Quality of life (EQ-5D-5L) - 12 weeks	447 (1 RCT)	⊕⊕⊕⊕ HIGH	-	The mean quality of life (EQ-5D-5L) at 12 weeks was 0.73	MD 0.01 lower (0.06 lower to 0.04 higher)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of findings 4.   Augmentation of current antidepressant (SSRI) with busiprone (20 mg/d to 60 mg/d) compared to augmentation of current antidepressant (SSRI) with placebo for treatment-resistant depression in adults

Augmentation of current antidepressant (SSRI) with busiprone (20 mg/d to 60 mg/d) compared to augmentation of current antidepressant (SSRI) with placebo for treatment-resistant depression in adults

Patient or population: treatment-resistant depression in adults
Setting: outpatient
Intervention: augmentation of current antidepressant (SSRI) with busiprone (20 mg/d to 60 mg/d)
Comparison: augmentation of current antidepressant (SSRI) with placebo

Outcomes	№ of partici-pants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative ef-fect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with augmentation of current antidepressant (SSRI) with placebo	Risk difference with augmenta-tion of current antidepressant (SSRI) with busiprone (20 mg/d to 60 mg/d)
Depressive symptoms (MADRS) Scale from: 0 to 60 (worse) follow-up: 6 weeks	102 (1 RCT)	⊕⊕⊝⊝ LOW [1]	-	The mean depressive symptom score (MADRS) was 30.5 % reduction from baseline	MD 0.3 % reduction from baseline lower (9.48 lower to 8.88 higher)
Dropouts follow-up: 6 weeks	108 (1 RCT)	⊕⊕⊝⊝ LOW [1]	RR 0.60 (0.23 to 1.53)	Study population	
				185 per 1,000	74 fewer per 1,000 (143 fewer to 98 more)
Response to treatment - not measured	-	-	-	-	-
Remission - not measured	-	-	-	-	-
Quality of life - not measured	-	-	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
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Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded two levels for imprecision (very broad confidence interval that crossed the null)

Summary of findings 5.   Augmentation of current antidepressant (various) with cariprazine (1 mg/d to 4.5 mg/d) compared to augmentation of current antidepressant (various) with placebo for treatment-resistant depression in adults

Augmentation of current antidepressant (various) with cariprazine (1 mg/d to 4.5 mg/d) compared to augmentation of current antidepressant (various) with placebo for treatment-resistant depression in adults

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Patient or population: treatment-resistant depression in adults
Setting: outpatient
Intervention: augmentation of current antidepressant (various) with cariprazine (1 mg/d to 4.5 mg/d)
Comparison: augmentation of current antidepressant (various) with placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with augmentation of current antidepressant (various) with placebo	Risk difference with augmentation of current antidepressant (various) with cariprazine (1 mg/d to 4.5 mg/d)
Depressive symptoms (MADRS) - Any dose Scale from: 0 to 60 (worse) follow-up: 8 weeks	808 (1 RCT)	⊕⊕⊕⊕ HIGH	-	The mean depressive symptom score (MADRS) - any dose - was 16.4 points	MD 1.5 points lower (2.74 lower to 0.25 lower)
Dropouts - any dose follow-up: 8 weeks	821 (1 RCT)	⊕⊕⊕⊝ MODERATE [1]	RR 1.68 (1.16 to 2.41)	Study population	
				119 per 1,000	81 more per 1,000 (19 more to 168 more)
Response (≥ 50% improvement in MADRS score) - any dose follow-up: 8 weeks	808 (1 RCT)	⊕⊕⊕⊝ MODERATE [1]	RR 1.27 (1.07 to 1.52)	Study population	
				383 per 1,000	103 more per 1,000 (27 more to 199 more)
Remission (MADRS total score ≤ 10) - any dose follow-up: 8 weeks	808 (1 RCT)	⊕⊕⊕⊝ MODERATE [2]	RR 1.07 (0.86 to 1.33)	Study population	
				299 per 1,000	21 more per 1,000 (42 fewer to 99 more)
Quality of life - not measured	-	-	-	-	-

*The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
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Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
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Summary of findings 6. Augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with olanzapine (5 mg/d to 20 mg/d) compared to augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with placebo for treatment-resistant depression in adults

Augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with olanzapine (5 mg/d to 20 mg/d) compared to augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with placebo for treatment-resistant depression in adults

Patient or population: treatment-resistant depression in adults
Setting: outpatient
Intervention: augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with olanzapine (5 mg/d to 20 mg/d)
Comparison: augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with placebo	Risk difference with augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with olanzapine (5 mg/d to 20 mg/d)
Depressive symptoms (HAM-D) Scale from: 0 to 52 (worse) follow-up: 8 weeks	20 (1 RCT)	⊕⊕⊝⊝ LOW [1]	-	The mean depressive symptom score (HAM-D) was -3.8	MD 7.9 lower (16.76 lower to 0.96 higher)
Depressive symptoms (MADRS) Scale from: 0 to 60 (worse) follow-up: 8 weeks	20 (1 RCT)	⊕⊕⊝⊝ LOW [2]	-	The mean depressive symptom score (MADRS) was -1.2	MD 12.4 lower (22.44 lower to 2.36 lower)
Dropouts follow-up: 8 weeks	20 (1 RCT)	⊕⊕⊝⊝ LOW [1]	RR 0.33 (0.04 to 2.69)	Study population	
				300 per 1,000	201 fewer per 1,000 (288 fewer to 507 more)
Response (≥50% reduction in MADRS score) follow-up: 8 weeks	20 (1 RCT)	⊕⊕⊝⊝ LOW [2]	RR 6.00 (0.87 to 41.21)	Study population	
				100 per 1,000	500 more per 1,000 (13 fewer to 4,021 more)
Remission - not reported	-	-	-	-	-
Quality of life - not measured	-	-	-	-	-

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***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1] Downgraded two levels for imprecision (very broad confidence interval that crossed the null)
[2] Downgraded two levels for imprecision (very broad confidence interval)

Summary of findings 7.   Augmentation of current antidepressant (various) with quetiapine (150 mg/d to 300 mg/d) compared to augmentation of current antidepressant (various) with placebo for treatment-resistant depression in adults

Augmentation of current antidepressant (various) with quetiapine (150 mg/d to 300 mg/d) compared to augmentation of current antidepressant (various) with placebo for treatment-resistant depression in adults

Patient or population: treatment-resistant depression in adults
Setting: outpatient
Intervention: augmentation of current antidepressant (various) with quetiapine (150 mg/d to 300 mg/d)
Comparison: augmentation of current antidepressant (various) with placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with augmentation of current antidepressant (various) with placebo	Risk difference with augmentation of current antidepressant (various) with quetiapine (150 mg/d to 300 mg/d)
Depressive symptoms (MADRS or HAM-D) - Any dose	977 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	The mean depressive symptom score (MADRS or HAM-D) - any dose was not calculable	SMD 0.32 lower (0.46 lower to 0.18 lower)
Dropouts - Any dose	997 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]	RR 1.33 (0.90 to 1.95)	Study population	
				159 per 1,000	52 more per 1,000 (16 fewer to 151 more)

Response (≥ 50% reduction in MADRS or HAM-D score) - Any dose	977 (3 RCTs)	⊕⊕⊕⊝ MODERATE [2]	RR 1.25 (1.09 to 1.44)	Study population	
				442 per 1,000	110 more per 1,000 (40 more to 194 more)
Remission (MADRS score ≤ 8/HAM-D score ≤ 7) - Any dose	977 (3 RCTs)	⊕⊕⊕⊝ MODERATE [2]	RR 1.53 (1.23 to 1.90)	Study population	
				233 per 1,000	123 more per 1,000 (54 more to 210 more)
Quality of life (% max score of Q-LES-Q-SF) - Any dose Scale from: 0 to 100 (better) follow-up: 6 weeks	884 (2 RCTs)	⊕⊕⊕⊝ MODERATE [1]	-	The mean quality of life (% max score of Q-LES-Q-SF) - any dose was 55%	MD 0.57 higher (1.52 lower to 2.65 higher)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio;

__GRADE Working Group grades of evidence__
__High certainty:__ We are very confident that the true effect lies close to that of the estimate of the effect
__Moderate certainty:__ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
__Low certainty:__ Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
__Very low certainty:__ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for imprecision (broad confidence interval which crossed the null)
[2] Downgraded one level for imprecision (broad confidence interval)

__Summary of findings 8.__ Augmentation of current antidepressant (SSRI) with ziprasidone (40 mg/d to 160 mg/d) compared to augmentation of current antidepressant (SSRI) with placebo or continue on SSRI monotherapy for treatment-resistant depression in adults

__Augmentation of current antidepressant (SSRI) with ziprasidone (40 mg/d to 160 mg/d) compared to augmentation of current antidepressant (SSRI) with placebo or continue on SSRI monotherapy for treatment-resistant depression in adults__

__Patient or population:__ treatment-resistant depression in adults
__Setting:__ outpatient
__Intervention:__ augmentation of current antidepressant (SSRI) with ziprasidone (40 mg/d to 160 mg/d)
__Comparison:__ augmentation of current antidepressant (SSRI) with placebo or continue on SSRI monotherapy

Outcomes	№ of participants	Certainty of the evidence	Relative effect	Anticipated absolute effects* (95% CI)	

	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Risk with augmentation of current antidepressant (SSRI) with placebo or continue on SSRI monotherapy	Risk difference with Augmentation of current antidepressant (SSRI) with ziprasidone (40 mg/d to 160 mg/d)
Depressive symptoms (HAM-D) - Any dose Scale from: 0 to 54 (worse) follow-up: 6 to 8 weeks	199 (2 RCTs)	⊕⊕⊕⊝ MODERATE [1]	-	The mean depressive symptom score (HAM-D) - any dose was 14.87 points	MD 2.73 points lower (4.53 lower to 0.93 lower)
Dropouts - Any dose follow-up: 6-8	199 (2 RCTs)	⊕⊕⊕⊝ MODERATE [1]	RR 1.60 (1.01 to 2.55)	Study population	
				227 per 1,000	136 more per 1,000 (2 more to 352 more)
Response (≥ 50% reduction in MADRS/ HAM-D score) - Any dose follow-up: 6-8 weeks	199 (2 RCTs)	⊕⊕⊕⊝ MODERATE [1]	RR 1.80 (1.07 to 3.04)	Study population	
				182 per 1,000	145 more per 1,000 (13 more to 371 more)
Remission (clinician-rated) - Any dose follow-up: 6-8 weeks	199 (2 RCTs)	⊕⊕⊕⊝ MODERATE [2]	OR 1.46 (0.75 to 2.86)	Study population	
				250 per 1,000	77 more per 1,000 (50 fewer to 238 more)
Quality of life - not measured	-	-	-	-	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for imprecision (broad confidence interval)
[2] Downgraded one level for imprecision (broad confidence interval that crossed the null)

BACKGROUND

Description of the condition

Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration. By 2030, depression is predicted to be the leading cause of disability in high-income countries (Mathers 2005). Severity of depression can be classified using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria as mild (five or more symptoms with minor functional impairment), moderate (symptoms or functional impairment are between 'mild' and 'severe') and severe (most symptoms present and interfere with functioning) (NICE 2009).

Antidepressants are often prescribed as the first-line treatment for adults with moderate to severe depression (NICE 2009). In England in 2014, 57.1 million prescriptions for antidepressants were issued at a cost of GBP 265 million (NHS Digital 2015). However, two-thirds of people do not respond fully to such pharmacotherapy (Trivedi 2006). Such nonresponse may be because of intolerance to the prescribed medication or non-adherence to the treatment regimen, but may also be the result of treatment 'resistance', where an adequate dose and duration of treatment has been prescribed. The earliest definition of treatment-'resistant' depression was given by the World Psychiatric Association; it defined 'resistance' as "an absence of clinical response to treatment with a tricyclic antidepressant at a minimum dose of 150 mg per day of imipramine (or equivalent drug) for 4 to 6 weeks" (WPA 1974). Subsequently, others have suggested more complex classification systems based on nonresponse to multiple courses of treatment (Fava 2005; Fekadu 2009; Thase 1997), and used other terms such as 'treatment refractory' depression and 'antidepressant resistant' depression to describe this condition. For the purpose of this review, we will use the term 'treatment-resistant depression' as this is the descriptor that has, generally, represented the broadest definition of the condition.

Globally, the prevalence of major depressive disorder (MDD) has been estimated to be 4.7 % (Ferrari 2013), with a lifetime prevalence as high as 17% (Kessler 2013). Depression imposes an economic burden on society in terms of both the direct costs of treatment and indirectly through its effects on productivity (Wang 2003). Healthcare utilisation and related costs of TRD are higher than for MDD (Gibson 2010; Mahlich 2018). If up to one-third of patients have 'treatment-resistant' depression (TRD), it is thus clear that this condition represents a considerable burden to patients, health systems and society.

Description of the intervention

Antidepressants are commonly used as the first-line treatment for adults with moderate to severe depression (NICE 2009). There are five main types of antidepressants: tricyclic (TCAs) and related antidepressants; monoamine-oxidase inhibitors (MAOIs); selective serotonin re-uptake inhibitors (SSRIs); serotonin and noradrenaline reuptake inhibitors (SNRIs); and noradrenergic and specific serotonin antidepressants (NaSSAs). SSRIs are generally better tolerated than other classes of antidepressants and are safer with regards to overdose than TCAs. It is, therefore, not surprising that SSRIs are the most commonly prescribed antidepressants for treating depression (NHS Information Centre 2011).

There is no standard approach to the treatment of those whose depression does not respond to antidepressant medication. Guidance published by the American Psychiatric Association (APA 2010) and the National Institute for Health and Clinical Excellence (NICE 2009) suggests that the potential 'next step' may include increasing the dose of the antidepressant medication or switching to another antidepressant (within the same or a different pharmacological class) or augmentation with another pharmacological or psychological treatment. In terms of combination treatment with an additional pharmacological agent, this may comprise either: (1) another antidepressant or (2) a non-antidepressant medication, which may include (i) lithium, (ii) an antipsychotic (e.g. olanzapine), (iii) pindolol, (iv) triiodothyronine (T_3) or (v) buspirone.

How the intervention might work

Most antidepressants work by inhibiting the uptake of monoamine neurotransmitters into neurons. The SSRI group inhibit the uptake of serotonin, and many of the older tricyclics have actions on both serotonin and noradrenaline (along with other pharmacological actions not thought to be important in depression).

For those people whose depression has not responded to initial treatment with an antidepressant, increasing the dose or switching medication may improve their outcome through the associated pharmacological actions, for example, increasing levels of neurotransmitters such as serotonin and noradrenaline. Increased serotonin neurotransmission may also be expected when two serotonergic drugs with different modes of action are combined (NICE 2009). For example, mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that acts by antagonising the adrenergic alpha2-autoreceptors and alpha2-heteroreceptors as well as by blocking 5-HT2 and 5-HT3 receptors (Anttila 2001). In general, the rationale for combination therapy with two different antidepressants or augmentation with a non-antidepressant medication (such as lithium), is that such treatment broadens the pharmacological actions involved (Anderson 2008).

Why it is important to do this review

Antidepressants continue to be the first-line treatment for many people with depression. However, two-thirds of people prescribed antidepressants for depression do not respond fully to such medication (Trivedi 2006). It is, therefore, important to summarise the evidence on the effectiveness of pharmacological interventions for people with TRD in order to establish the best 'next step' treatment for this patient group.

There have been several narrative reviews of the evidence on the treatment of people whose depression has not responded to antidepressant medication alone (e.g. Carvalho 2008; Nierenberg 2007; Papakostas 2009). Systematic reviews of the effectiveness of combination treatment for people with depression have not examined the evidence for the treatment-resistant population (Friedman 2004; Pampallona 2004). Others have summarised the evidence for the effectiveness of particular treatment strategies for those who have not responded to antidepressants: (1) augmentation (Carvalho 2007) with lithium (Bauer 1999) or atypical antipsychotics (Shelton 2008); and (2) within- or between-class switches (Papakostas 2008), and one review focused on interventions for older people (≥ 55 years) (Cooper 2011). However, a number of these reviews included uncontrolled studies or non-

randomised studies or both, as well as randomised controlled trials (RCTs) (Carvalho 2007; Cooper 2011; Shelton 2008).

A previous systematic review of RCTs investigating pharmacological and psychological treatments for people with TRD failed to find strong evidence to guide the management of such people (Stimpson 2002). However this review, along with others (e.g. Bauer 1999, which summarised the evidence for lithium up to June 1997) is out-of-date and a number of relevant RCTs have been published subsequently. These include a review by Edwards 2013 that has a narrow focus both in terms of the interventions to be examined (lithium or an atypical antipsychotic) and the definition of treatment resistance. The latter is defined as "failure to respond to at least two previous antidepressants in the current episode of depression". While this definition of treatment resistance has been frequently used, we know that many people do not respond to an initial course of antidepressants and there is little evidence to inform the most appropriate 'next step' treatment for this group (NICE 2009). Therefore, given the continued reliance upon antidepressants as a first-line treatment for depression, we propose using an inclusive definition of treatment resistance (based on nonresponse to at least four weeks of antidepressant medication) in order to help establish the best 'next step' treatment for the large number of people whose depression does not respond to antidepressants. The rise in the number of prescriptions for antidepressants in recent years means that a review of the evidence for the effectiveness of pharmacological interventions for people with TRD is timely (Pincus 1998; McManus 2000; Middleton 2001).

Studies examining psychological interventions for TRD will be excluded as these are the focus of another review (Ijaz 2018). Together, the evidence from these two linked reviews will provide a comprehensive review of the main interventions for the management of TRD, which will inform clinical decision-making with regards to the best 'next step' for adults whose depression has not responded to first-line treatment with medication.

OBJECTIVES

To assess the effectiveness of pharmacological interventions for TRD in adults.

METHODS

Criteria for considering studies for this review

Types of studies

The methods used in our review were previously described in a published protocol (Williams 2013).

Randomised controlled trials (RCTs) were eligible for inclusion in the review. Trials employing a cross-over design could be included in the review, using data from the first active treatment stage only. Cluster RCTs were also eligible for inclusion.

Any other study design, including quasi-randomised studies and non-randomised studies, were excluded from this review.

Types of participants

Age range

Participants were adults aged 18 to 74 years.

If the study included some participants that were aged under 75 years and some over the age of 74 years, we excluded the study if the mean age of participants was over 74 years. Similarly, if the study included some participants that were aged under 18 years and some aged 18 years or older, we excluded the study if the mean age of participants was less than 18 years.

Definition of treatment-resistant depression

For a study to be eligible for inclusion in this review, all of the participants had to meet our criteria for treatment-resistant depression at the point at which they were randomly allocated to treatment. We included studies that began with an open-label lead-in phase to confirm treatment resistance provided that only participants meeting our definition of TRD continued into the randomised treatment phase.

We defined treatment-resistant depression as a primary diagnosis of unipolar depression that had not responded (or had only partially responded) to a minimum of four weeks of antidepressant treatment at a recommended dose (at least 150 mg/day imipramine or equivalent antidepressant (e.g. 20 mg/day citalopram)).

We excluded studies that included participants who had not responded because of intolerance to antidepressant medication.

While there have been initiatives to improve access to psychological therapies in England and elsewhere, access to psychological treatment is still limited and antidepressants are often the first-line treatment for adults with depression. Therefore, this review did not include studies of interventions intended for those who had not responded to psychological treatment.

Diagnosis

Acceptable diagnoses of unipolar depression included those based on criteria from DSM-IV-TR or earlier versions (APA 2000), International Classification of Diseases (ICD)-10 (WHO 1992), Feighner criteria (Feighner 1972) or Research Diagnostic Criteria (Spitzer 1978). Studies that had not used standardised diagnostic criteria were excluded.

Comorbidity

Studies of participants with comorbid schizophrenia or bipolar disorder were excluded.

Studies including both unipolar and bipolar participants were excluded unless data were available for the subgroup of unipolar participants.

This review included studies involving participants with comorbid physical conditions or other psychological disorders (e.g. anxiety) for whom the pharmacological therapy was not being primarily used to manage the physical illness, in other words, the focus of treatment was TRD - not the comorbidity.

Types of interventions

Experimental interventions

The experimental interventions were based on the 'next step' approach to the management of depression that had not responded to treatment with antidepressants:

- increasing the dose of antidepressant monotherapy;
- switching to a different antidepressant monotherapy;
- augmenting treatment with another antidepressant;
- augmenting treatment with a non-antidepressant.

Antidepressants can be grouped as TCAs, MAOIs, SSRIs, SNRIs and NaSSAs.

Non-antidepressant medications used as augmentors included antipsychotics (e.g. olanzapine), anxiolytics (e.g. buspirone), antimania drugs (e.g. lithium) and beta-blockers (e.g. pindolol).

Studies examining non-standard pharmacological approaches for treating TRD (e.g. sex hormones, vitamins, herbal medicines and food supplements) were excluded. Studies examining psychological interventions given in addition to antidepressant medication for individuals with TRD are included in another review (Ijaz 2018).

Comparator interventions

- The control comparison was continuing on the initial antidepressant monotherapy.

Full details of comparisons made can be found in the Data extraction and management section.

Types of outcome measures

Primary outcomes

1. Change in depressive symptoms as measured on rating scales for depression, either clinician-rated (e.g. Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960) or Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery 1979)), or self-report (e.g. Beck Depression Inventory (BDI; Beck 1961; Beck 1996) (or other validated measures)). Data on observer-rated and self-report outcomes were analysed separately.

2. Number of dropouts from study or treatment (all-cause dropout) within the trials. Where available, we extracted data on reasons for dropout and summarised these in narrative form.

Secondary outcomes

3. Response or remission rates, or both, based on changes in depression measures - either clinician-rated (e.g. HAM-D; Hamilton 1960) or self-report (e.g. BDI; Beck 1961; Beck 1996) or other validated measures. Response is frequently quantified as at least a 50% reduction in symptoms on the HAM-D or BDI but we accepted the study's original definition. Remission is based on the absolute score on the depression measure. Examples of definitions of remission include 7 or less on the HAM-D and 10 or less on BDI. Again, we accepted the study authors' original definition.

4. Improvement in social adjustment and social functioning including the Global Assessment of Function (Luborsky 1962) scores, where reported, were summarised in narrative form.

5. Improvement in quality of life as measured on the Short Form (SF)-36 (Ware 1993), Health of the Nation Outcome Scales (HoNOS) (Wing 1994), or World Health Organization Quality of Life (WHOQOL) (WHOQOL 1998) or similar scale, where reported, were summarised in narrative form.

6. Economic outcomes (e.g. days of work absence/ability to return to work, number of appointments with primary care physician, number of referrals to secondary services, use of additional treatments), where reported were summarised in narrative form.

7. Adverse effects (e.g. completed/attempted suicides), where reported, were summarised in narrative form.

Timing of outcome assessment

Outcomes at each reported follow-up point were summarised. Where appropriate and if the data allowed, outcomes were categorised as short-term (up to 12 weeks) and longer-term (longer than 12 weeks).

Search methods for identification of studies

Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)

The Cochrane Common Mental Disorders (CCMD) Group maintains an archived register of RCTs, the CCMDCTR. This register contains over 40,000 reference records (reports of RCTs) for anxiety and depressive disorders, bipolar disorder, eating disorders, self-harm and other mental disorders within the scope of this Group. The CCMDCTR is a partially studies-based register, with 50% of the reference records tagged to over 12,000 individually PICO-coded study records. Reports of trials for inclusion in the register were routinely collated from generic searches of MEDLINE (1950-), Embase (1974-) and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases (to June 2016). Reports of trials were also sourced from international trial registries, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of the CCMD Group's core search strategies (used to identify RCTs) can be found on the Group's website, with an example of the core MEDLINE search displayed in Appendix 1.

The Group's Specialised Register had fallen out of date with the Editorial Group's move from Bristol to York in the summer of 2016.

Electronic searches

We searched the CCMDCTR-Studies Register using the following terms:
Condition = ((depressi* or "affective disorder" or "mood disorder*") and ("treatment-resistant" or recurrent))

Additionally we searched the CCMDCTR-References Register using a more sensitive set of terms (keywords and subject headings) to identify additional untagged/uncoded references:

1. depressi* [Ti, Ab, KW]
2. (*refractory* or *resistan* or *recurren*) [Ti, Ab]
3. (augment* or potentiat*) [Ti, Ab]
4. (chronicity or "chronic depress*" or "chronically depress*" or "depressed chronic*" or "chronic major depressi*" or "chronic affective disorder*" or "chronic mood disorder*" or (chronic* and (relaps* or recurr*))) [Ti, Ab, KW]
5. ("persistent depress*" or "persistently depress*" or "depression persist*" or "persistent major depress*" or "persistence of depress*" or "persistence of major depress*") [Ti, Ab]

6. (nonrespon* or non-respon* or "non respon*" or "not respon*" or "no respon*" or "partial respon*" or "partially respon*" or "incomplete respon*" or "incompletely respon*" or unrespon*) [Ti, Ab]

7. ("failed to respond" or "failed to improve" or "failure to respon*" or "failure to improve" or "failed medication*" or "antidepressant fail*" or "treatment fail*") [Ti, Ab]

8. (inadequate* and respon*) [Ti, Ab]

9. "treatment-resistant depression" [KW]

10. (recurrence or "recurrent depression" or "recurrent disease") [KW]

11. "drug resistance" [KW]

12. "treatment failure" [KW]

13. "drug potentiation" [KW]

14. augmentation [KW]

15. or/2-14

16. (1 and 15)

We applied no date or language restrictions to our search. Our search of the CCMDCTR was up-to-date as of 18 March 2016.

We ran additional searches via the following biomedical databases (1 January 2016 to 31 December 2018) (Appendix 2):

1. MEDLINE/Premedline (Ovid);
2. Embase (Ovid);
3. Cochrane Central Register of Controlled Trials (CENTRAL);
4. PsycINFO (Ovid);
5. Web of Science Core Collection (Clarivate Analytics).

We used the term 'treatment-resistant' or 'treatment refractory' depression to search international trials registries, including the WHO trials portal (ICTRP) and ClinicalTrials.gov (to 31 December 2018) (Appendix 2), to identify any additional ongoing and unpublished studies. We contacted principal Investigators, when necessary, to request further details of ongoing/unpublished studies or trials reported as conference abstracts only. These searches are up-to-date as of 31 December 2018.

Searching other resources

Reference lists of all included studies and other relevant systematic reviews were searched for papers that might meet the inclusion criteria. Subject experts were also contacted to ensure that all relevant published and unpublished studies were considered for inclusion.

Data collection and analysis

Selection of studies

One review author (NW, PD or SI) examined titles and abstracts to remove obviously irrelevant reports and then screened study abstracts against inclusion criteria using a standardised abstract screening form. In any case of uncertainty, an over-inclusive approach was taken and the full paper was obtained along with those for the studies assessed as meeting the inclusion criteria. Two review authors (of CW, MT, NW, GL, DK, PD and SI) screened each paper for inclusion or exclusion from the review. If any disagreements arose, these were discussed with a third review author. If it was not possible to determine eligibility for a study, it was added to the list of those awaiting assessment and the authors were contacted for further information or clarification.

The study selection process was documented using a PRISMA study selection flow diagram.

Data extraction and management

Data regarding participants, interventions and their comparators, methodological details, and treatment effects, including dropouts and possible biases, were independently extracted by two review authors (PD and SI) using a standardised data extraction form. If any disagreements arose, these were discussed with a third review author. The data extraction form was piloted during the first phase of data extraction.

Information relating to study population, definition of TRD, sample size, interventions, comparators, potential biases in the conduct of the trial, outcomes, follow-up and methods of statistical analysis was abstracted.

Main planned comparisons

1. Increasing the dose of antidepressant monotherapy compared with continuing on an antidepressant.
2. Switching to a different antidepressant monotherapy compared with continuing on an antidepressant.
3. Augmenting treatment with another antidepressant compared with continuing on an antidepressant.
4. Augmenting treatment with a non-antidepressant compared with continuing on an antidepressant.

Within each of these strategies, where there was sufficient data, this review summarised the evidence for each drug individually. For example, taking the fourth approach of augmenting with a non-antidepressant medication, the augmentor could have been lithium, olanzapine, buspirone or pindolol. In this case, the evidence for each of these four drugs would be presented separately, rather than combined, to summarise the evidence for a particular 'treatment approach'. This was done to maximise the clinical relevance of the findings.

Given the large number of possible combinations of medications that could be evaluated, it was not possible to provide an exhaustive list of all the potential comparisons. However, one example for each of the different approaches have been given below.

1. Citalopram 40 mg/day compared with remaining on citalopram 20 mg/day.
2. Switching to mianserin compared with remaining on fluoxetine.
3. Addition of mianserin to fluoxetine compared with remaining on fluoxetine alone.
4. Nortriptyline plus lithium compared with remaining on nortriptyline alone.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each included study using Cochrane's 'Risk of bias' tool (Higgins 2011a). If any disagreements arose, these were discussed with a third review author. The following criteria were assessed:

- sequence generation: was the allocation sequence adequately generated?
- allocation concealment: was allocation adequately concealed?

- blinding of participants, study personnel and outcome assessors for each outcome: was knowledge of the allocated treatment adequately prevented during the study?
- incomplete outcome data for each main outcome or class of outcomes: were incomplete outcome data adequately addressed?
- selective outcome reporting: are reports of the study free of suggestion of selective outcome reporting?
- other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias?

A description of what was reported to have happened in each study was generated and a judgement on the risk of bias was made for each domain within and across studies, based on the following three categories: low risk of bias; unclear risk of bias; high risk of bias.

Where studies provided little or no detail about randomisation, the authors were contacted to seek clarification.

All risk of bias data were presented graphically and described in the text.

Measures of treatment effect

Continuous outcomes were analysed by calculating the mean difference (MD) between groups, where studies used the same outcome measure for comparison. Where different outcome measures were used to assess the same outcome, the standardised mean difference (SMD) and 95% confidence intervals (CI) were calculated. The SMD was interpreted as follows: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen 1988).

We calculated risk ratios (RRs) for dichotomous outcomes. When overall risks were significant, the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH) to produce one outcome was calculated by combining the overall RR with an estimate of prevalence of the event in the control group of the trials.

Unit of analysis issues

Cluster-randomised trials

We planned to incorporate results from cluster RCTs into the review using generic inverse variance methods (Higgins 2011). With cluster RCTs, it is important to ensure that the data were analysed taking into account the clustered nature of the data. The intracluster correlation coefficient (ICC) would be extracted for each trial. Where no such data were reported, this information was requested from study authors. If this was not available, in line with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we planned to use estimates from similar studies in order to 'correct' data for clustering, where this had not been done. We did not, however, identify any cluster RCTs that met the inclusion criteria for our review.

Cross-over trials

For cross-over trials, only results from the first randomised treatment period were to be included in the analysis. We did not, however, identify any cross-over trials that met the inclusion criteria for our review.

Studies with multiple treatment groups

Trials that have more than two arms (e.g. pharmacological intervention (A); pharmacological intervention (B); and control) can cause problems in pairwise meta-analysis. Where we identified studies with two or more active treatment arms, the following approach was undertaken (dependent on whether the outcome was continuous or dichotomous).

For a continuous outcome: means, standard deviations (SDs) and the number of participants for each active treatment group were pooled across treatment arms as a function of the number of participants in each arm to be compared against the control group (Higgins 2011).

For a dichotomous outcome: active treatment groups were combined into a single arm for comparison against the control group (in terms of the number of people with events and sample sizes), or the control group was split equally (Higgins 2011).

Dealing with missing data

Where there were missing data, study authors were contacted to obtain data. If an outcome was missing for more than 50% of participants, this study was excluded from the analysis. When available, we used intention-to-treat (ITT) analyses from study reports and wrote to study authors to request relevant unreported analyses.

Assessment of heterogeneity

Heterogeneity was assessed using the Chi^2 test, which provides evidence of variation in effect estimates beyond that of chance. The Chi^2 test has low power to assess heterogeneity when there are few included studies or small numbers of participants, so the P value was conservatively set at 0.1. Heterogeneity was also quantified using the I^2 statistic, which calculates the percentage of variability due to heterogeneity rather than chance. We expected, a priori, that there would be considerable clinical heterogeneity between studies, therefore I^2 values between 50% and 90% were considered to represent substantial statistical heterogeneity and were explored further. However, the importance of the observed I^2 value depended on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (Higgins 2011).

Assessment of reporting biases

Reporting bias was managed by undertaking comprehensive searches for papers that were not restricted to the English language. Outcome reporting bias was determined for all included studies and trial protocols were sought wherever possible. If outcome data were missing, these were requested from authors. We had planned to use funnel plots to help detect reporting biases if at least 10 studies were included for a comparison (Higgins 2011) and undertake formal assessment of asymmetry in the funnel plot using the Egger test (Egger 1997).

Data synthesis

Given the potential for heterogeneity in the included interventions, we used a random-effects model for all analyses. This approach incorporated the assumption that the different studies were estimating different, yet related, intervention effects and it took into account differences between studies even if there was no

statistically significant heterogeneity. Heterogeneity was tested formally using both the Chi^2 test and I^2 statistic (as outlined above). We sought clinical advice in terms of combining treatment groups in order to ensure that findings were clinically meaningful. Where studies reported both short-term and long-term outcomes, separate meta-analyses were conducted for each of these time points.

Where meta-analysis was not possible (e.g. due to insufficient data or substantial heterogeneity), a narrative assessment of the evidence was given. This assessment summarised the evidence according to intervention type.

Subgroup analysis and investigation of heterogeneity

A priori, we considered the degree of treatment resistance recorded at the point of entry to the trial as a potential effect modifier. Therefore, the following subgroup analyses were planned:

- severity of depression: classifying participants as non-responders or partial responders at baseline;
- Length of acute treatment phase (before trial entry): four weeks or longer; 12 weeks or longer and six months or longer.

Such subgroup analyses were only to be conducted when there were data from at least 10 studies to be included (Higgins 2011).

Sensitivity analysis

Sensitivity analyses were planned to explore how much of the variation between studies comparing pharmacological interventions for TRD was accounted for by between-study differences in:

- study quality: allocation concealment was used as a marker of trial quality. Studies that had not used allocation concealment were to be excluded;
- blinding: studies that were unblinded (participants, study personnel or outcome assessors) were excluded;
- attrition: studies with more than 20% dropout were excluded;
- missing data: studies that had imputed missing data were excluded;

- funding source: studies funded by pharmaceutical companies were excluded;
- publication type: studies not published in full (conference abstract/proceedings, doctoral dissertation) were excluded.

Sensitivity analysis was planned by excluding the studies above and comparing each of the results with the full analysis which included all trials.

Summary of findings tables

'Summary of findings' tables were prepared for all of the comparisons in this review for the following outcomes: depressive symptoms, dropouts, response to treatment, remission from depression and quality of life. Where studies reported outcome data based on more than one method of measurement (e.g. multiple depression severity scales) we reported the study's own choice of primary outcome in the 'Summary of findings' table. Similarly, where studies reported data for more than one time point, we chose the time point corresponding to the primary outcome to include in the summary of findings.

R E S U L T S

Description of studies

Results of the search

We identified 7969 references through our searches of bibliographic databases and trial registries and 19 references from additional sources. After removing duplicates, we screened 7342 titles and abstracts, of which we excluded 6728 as not relevant. Full-text reports of 614 references were obtained and screened against our eligibility criteria. We excluded 573 articles and provided reasons for exclusion in Figure 1. We used a hierarchy of reasons for exclusion, shown in Table 1, which also reports the number and frequency of articles excluded for each reason. The most common reasons for exclusions were: that the intervention evaluated was not a standard pharmacological treatment (n = 131, 22.9%), study participants did not meet the definition of treatment-resistant depression (n = 112, 19.5%), the comparison made in the study was not one of interest to the review (for example, there was no control group that continued on the original antidepressant therapy) (n = 100, 17.5%) or the study was not randomised (n = 106, 18.5%).

Figure 1. Flow diagram

Identification

Records identified through database searching (n = 7969)

Additional records identified through other sources (n = 19)

Screening

Records after duplicates removed (n = 7342)

Records screened (n = 7342)

Records excluded (n = 6728)

Eligibility

Full-text articles assessed for eligibility (n = 614)

Full-text articles excluded, with reasons (n = 573):
Not an RCT n = 106
Not a standard pharmacological treatment n = 131
Not TRD/at the point of randomisation n = 112
Diagnostic criteria not applied at point of randomisation n = 59
Not unipolar depression n = 27
Age n = 6
Review article (references checked) n = 31
No control group/not a comparison of interest n = 100
Study terminated n = 1

Awaiting assessment: n = 6

Included

Studies included in qualitative synthesis (n = 10; 35 references)

Studies included in quantitative synthesis (meta-analysis) (n = 10; 35 references)

Eligibility could not be determined for six references and no response was received from requests to study authors for further clarification (see Characteristics of studies awaiting classification). In total, 35 references reporting ten studies were included in this review. All studies contributed data to meta-analyses. We contacted the authors of 57 articles to clarify details of their study and received a response from 11. Full details of the study flow are given in a PRISMA flow diagram in Figure 1.

Included studies

Included studies

We identified ten studies (35 references) that were eligible for inclusion in the review (Appelberg 2001; Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); Ferreri 2001; Kessler 2018; McIntyre 2007; Papakostas 2015; Shelton 2001). Further

information on each study can be found in the Characteristics of included studies table.

Design

All of the included studies were parallel-group randomised controlled trials and the unit of allocation was the individual participant. Eight studies were multisite (number of sites ranged from two to 84). One study had a single site (McIntyre 2007). The number of study sites was not reported in Dunner 2007.

Five studies were three-arm trials (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); Ferreri 2001).

Length of follow-up was short-term (12 weeks or less) in nine studies. Only one study (Kessler 2018) reported data for longer-term outcomes (24 and 52 weeks).

Sample sizes

Sample size ranged from 20 (Shelton 2001) to 819 (Durgam 2016) with a median of 122 participants (IQR: 71, 472).

Setting and date

All studies were carried out in high-income countries. Four studies were conducted in the US (Dunner 2007; El-Khalili 2010 (PEARL); Papakostas 2015; Shelton 2001); one each in Canada (McIntyre 2007), England (Kessler 2018) Finland (Appelberg 2001) and France (Ferreri 2001); and two in multiple countries across Europe, North America and Australia (Bauer 2009 (ONYX); Durgam 2016).

Nine studies were conducted solely in outpatient medical settings and one (Ferreri 2001) included both in- and outpatients. One study (Kessler 2018) was conducted in primary care. Six studies were conducted in the decade 2000 to 2009 (Appelberg 2001; Bauer 2009 (ONYX); Dunner 2007; Shelton 2001; Ferreri 2001; McIntyre 2007) and four since 2010 (Durgam 2016; El-Khalili 2010 (PEARL); Papakostas 2015; Kessler 2018).

Participants

The mean age of participants was very similar across the included studies, ranging from 42 years (Shelton 2001) to 50.2 years (Kessler 2018). The majority of participants in the included studies were women (51.7% in Dunner 2007 to 75% in Shelton 2001).

Definition of treatment-resistant depression

Participants had a diagnosis of major depressive disorder (MDD) according to DSM III-R (Ferreri 2001), DSM-IV (Appelberg 2001; Bauer 2009 (ONYX); Dunner 2007; El-Khalili 2010 (PEARL); McIntyre 2007; Papakostas 2015; Shelton 2001) DSM-IV-TR (Durgam 2016), or ICD-10 (Kessler 2018) criteria. Participants were additionally required to have a HAM-D score of at least 18 (McIntyre 2007), 20 (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); Shelton 2001) or 25 (Ferreri 2001); a MADRS score of 22 or more (Durgam 2016); a BDI-II score of 14 or more (Kessler 2018); or a score of greater than four on the clinical global impressions (CGI) scale (Dunner 2007). MDD was recurrent for all participants in Shelton 2001.

In nine studies, participants had TRD at the time of enrolment (Appelberg 2001; Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); Ferreri 2001; McIntyre 2007; Shelton 2001; Kessler 2018). In one study (Papakostas 2015), participants were recruited with Major Depressive Disorder. Following an 8-week open-label treatment with fluoxetine (10 mg/d or greater), participants who continued to meet DSM criteria were considered to be treatment-resistant and randomised to adjunctive treatment with an antipsychotic.

In eight of the nine studies where participants had TRD at the time of enrolment, participants had had an inadequate response to at least one antidepressant at the manufacturers recommended minimum dose (or above) for a minimum of four (Bauer 2009 (ONYX); Dunner 2007) or six (Appelberg 2001; Durgam 2016; El-Khalili 2010 (PEARL); Ferreri 2001; Kessler 2018; McIntyre 2007) weeks. Two of these studies (Bauer 2009 (ONYX) and El-Khalili 2010 (PEARL)) had a further requirement of at least one dose increase as permitted by the label. In the ninth trial (Shelton 2001), participants had failed to respond to antidepressants of two different classes (each given for a minimum of four weeks).

Two of the studies in which participants had TRD at enrolment had an open-label lead-in phase in which participants had a trial of a further antidepressant at or above the recommended minimum dose for six weeks (Dunner 2007; Shelton 2001). Only participants with an inadequate response to this were then randomised into the main trial.

Two studies had exclusion criteria based on resistance to prior antidepressant treatments. Durgam 2016 and Papakostas 2015 both excluded individuals with an inadequate response to three or more antidepressants at sufficient doses during the current depressive episode.

Further details of previous antidepressant treatments can be found in the Characteristics of included studies table.

Interventions

There were no studies of increasing the dose of antidepressant monotherapy that met the inclusion criteria for the review.

One study looked at the effectiveness of switching from current antidepressant therapy (fluoxetine) to another antidepressant (mianserin, Ferreri 2001) compared with continuing on the original antidepressant therapy.

Two studies examined the effects of augmenting current antidepressant treatment with another antidepressant compared with continuing on antidepressant monotherapy. The adjunctive treatment was mianserin in one study (Ferreri 2001, a three-arm trial) and mirtazapine in the other (Kessler 2018).

Eight studies examined the effectiveness of augmenting treatment with a non-antidepressant medication compared with continuing on an antidepressant. The adjunctive treatment was an anxiolytic (buspirone) in one study (Appelberg 2001) and an antipsychotic in seven studies (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); McIntyre 2007; Papakostas 2015; Shelton 2001). Three studies examined the effectiveness of antipsychotic quetiapine (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007), two studied ziprasidone (Papakostas 2015; Dunner 2007), and there was a single study for cariprazine (Durgam 2016) and olanzapine (Shelton 2001). Four studies were three-arm trials which investigated higher and lower doses of the augmented antipsychotic (quetiapine - Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); cariprazine - Durgam 2016; ziprasidone - Dunner 2007). Length of treatment was six weeks in four studies (Appelberg 2001; Bauer 2009 (ONYX); El-Khalili 2010 (PEARL);Ferreri 2001), eight weeks in four studies (Dunner 2007; Durgam 2016; McIntyre 2007; Papakostas 2015; Shelton 2001) and up to 52 weeks in one study (Kessler 2018).

Comparisons

Participants in the comparator arm continued to receive the same dose of antidepressant monotherapy in all of the trials. In all but one trial (Dunner 2007), a placebo was given in addition to the continued antidepressant treatment.

Primary outcomes

1). Change in depressive symptoms

All studies reported one or more measures of depressive symptoms measured on a severity rating scale. Six studies used the

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Pharmacological interventions for treatment-resistant depression in adults (Review)

Montgomery-Asberg Depression Scale (Appelberg 2001; Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); Shelton 2001), six the Hamilton Depression Rating Scale (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); Ferreri 2001; McIntyre 2007; Papakostas 2015; Shelton 2001), one the Beck Depression Inventory-II (BDI-II) and Patient Health Questionnaire-9 (PHQ-9) (Kessler 2018), and one the Quick Inventory of Depressive Symptomatology - self-report version (QIDS-SR, Papakostas 2015). Five studies reported mean change from baseline in each study arm (Ferreri 2001; Kessler 2018; McIntyre 2007; Papakostas 2015; Shelton 2001), one reported mean percentage change from baseline (Appelberg 2001) and four studies reported a least squares mean change estimated from an analysis of covariance (ANCOVA) incorporating baseline depression severity as a covariate in the model (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL).

2). Number of dropouts

All studies reported the number of participants in each arm who dropped out during the treatment period for any reason.

Secondary outcomes

3). Response or remission rates

Nine studies reported a dichotomous outcome of response to treatment, defined as a reduction of 50% or more from baseline to end of treatment in score on either the MADRS (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); Shelton 2001), HAM-D (Papakostas 2015), BDI-II (Kessler 2018) or QIDS-SR (Papakostas 2015).

Eight studies reported remission from depression using a cut-off score of less than or equal to eight (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL)); or ten (Dunner 2007; Durgam 2016) on the MADRS, seven (McIntyre 2007; Papakostas 2015) or eight (Ferreri 2001) on the HAM-D, nine on the BDI-II (Kessler 2018) or five on the QIDS-SR (Papakostas 2015).

4). Social Adjustment and Social functioning scales

No studies reported data on either social adjustment or social functioning.

5). Improvement in Quality of Life Measure

Three studies reported data on quality of life. Bauer 2009 (ONYX); El-Khalili 2010 (PEARL) reported mean change from baseline in quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire short-form (Q-LES-Q-SF). Kessler 2018 reported mean scores on the five-level EQ-5D (EQ-5D-5L) scale, and the aggregate mental functioning and aggregate physical functioning scales of the SF-12 at follow-up.

6). Economic outcomes

One study (Kessler 2018) reported direct costs to health and social services, costs to patients and carers, and time off work for patients and carers.

7). Adverse Events

Eight studies reported arm-level adverse event data (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); Ferreri 2001; Kessler 2018; McIntyre 2007; Papakostas 2015). Information on adverse events was incompletely reported in two studies (Appelberg 2001; Shelton 2001).

Excluded studies

In total, we excluded 573 references at full-text screening. In accordance with the guidance in the *Cochrane Handbook*, we have provided a list of those studies that almost met our eligibility criteria and further details of their reason for exclusion (see table of Excluded studies). Of these 105 studies, the primary reasons for exclusion were as follows: 45 did not have a comparator arm where participants continued with current antidepressant medication only (with or without placebo); 33 did not meet our criteria for treatment-resistant depression at the point of randomisation and in 26 studies no formal diagnostic criteria for diagnosis of depression were applied at the point of randomisation.

The STAR*D trial (STAR*D 2004) was one of our excluded studies. This study evaluated a sequence of different treatment options for depression. Participants who failed to respond to treatment were randomised into the next level of the study. Participants enrolled in level one had MDD, not TRD (therefore, this level was not eligible for our review). Each successive level involved a switching to a different treatment strategy or augmenting current treatment with additional medication. As none of these later levels included a group that continued on current antidepressant medication alone they were also not eligible for inclusion.

Ongoing studies

We did not identify any ongoing studies.

Studies awaiting classification

There was insufficient information in the study reports for six studies (Cao 2005; Clunie 2001; Euctr-002130-11-Es 2007; Gulrez 2012; Moica 2018; Zhu 2003) to determine eligibility for inclusion in our review. Two of these reports were trial protocols (Clunie 2001; Euctr-002130-11-Es 2007) and no publications relating to the studies could be identified.

We were unable to contact the authors for further information for two of these (Euctr-002130-11-Es 2007; Zhu 2003) and did not receive a response for the remainder (Cao 2005; Clunie 2001; Gulrez 2012; Moica 2018). Further information on these studies can be found in the Characteristics of studies awaiting classification table.

Risk of bias in included studies

Full details of the risk of bias for the included studies are given in the Characteristics of included studies table. Graphical representations of the overall risk of bias in included studies are presented for each risk of bias item (Figure 2) and for each study (Figure 3). Given the small number of studies included in the various comparisons, no formal assessment of reporting bias using a funnel plot was undertaken.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
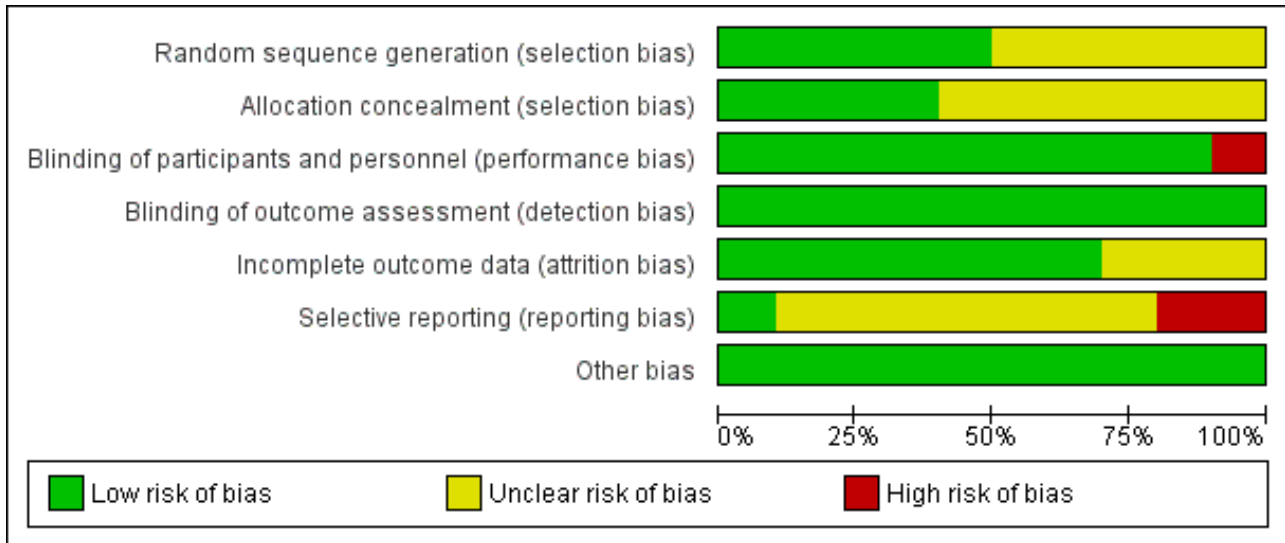
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

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Figure 3. (Continued)

Allocation

Random Sequence Generation (Selection Bias)

All included studies described themselves as randomised. Five studies did not provide any information on how the randomisation sequence was generated (Appelberg 2001; Bauer 2009 (ONYX); Dunner 2007; McIntyre 2007; Shelton 2001) and were rated as being at an unclear risk of bias. Four studies described the use of a computer or web-based software (Durgam 2016; El-Khalili 2010 (PEARL); Kessler 2018; Papakostas 2015) or a randomisation schedule (Ferreri 2001) and were judged to be at low risk.

Allocation Concealment (Selection Bias)

Allocation concealment was not described and was therefore rated as unclear in six studies (Appelberg 2001; Bauer 2009 (ONYX); Dunner 2007; Ferreri 2001; McIntyre 2007; Shelton 2001). Three studies describing a centralised allocation system (Durgam 2016; Kessler 2018; Papakostas 2015) were assessed as low risk. The final study was judged to be at low risk of bias for allocation concealment due to the use of a computer-generated randomisation sequence in combination with study treatments reported to be administered in identical packaging (El-Khalili 2010 (PEARL).

Blinding

Performance Bias (blinding of participants and those delivering the intervention)

Nine studies reported the use of a placebo intervention in the comparator arm identical in form and appearance to the active intervention and were therefore judged to be at a low risk of bias (Appelberg 2001; Bauer 2009 (ONYX); Durgam 2016; El-Khalili 2010 (PEARL); Ferreri 2001; Kessler 2018; McIntyre 2007; Papakostas 2015; Shelton 2001).One study was described as an open-label trial and therefore assigned a high risk of bias rating for this domain (Dunner 2007).

Detection Bias (blinding of outcome assessors).

All of the included studies were judged to be at a low risk of bias for this domain. Eight studies were described as double-blind and reported the use of a placebo identical in appearance to the active intervention (Appelberg 2001; Bauer 2009 (ONYX); Durgam 2016; El-Khalili 2010 (PEARL); Papakostas 2015; Shelton 2001) and we regarded this as sufficient information to conclude that outcome assessors were blinded to treatment allocation. Two studies (Dunner 2007; Kessler 2018) explicitly stated that outcome assessors were blind to treatment allocation. None of the included studies evaluated the success of blinding.

Incomplete outcome data

Overall, attrition was less than 20% in four studies (Appelberg 2001, 14.8%; Bauer 2009 (ONYX), 14%; Durgam 2016, 17.3%; Kessler 2018, 4%), between 20 and 30% in four studies (El-Khalili 2010 (PEARL), 22.9%; Ferreri 2001, 24.3%; Papakostas 2015, 26.6%; Shelton 2001,

20%) and over 40% in two studies (Dunner 2007, 40.6%; McIntyre 2007, 41.4%).

Eight studies (Appelberg 2001; Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); Ferreri 2001; McIntyre 2007; Shelton 2001) described modified intention-to-treat analyses including all participants with at least one post-baseline efficacy assessment. Last observation carried forward (LOCF) was used to account for missing data and no significant imbalances in missing data between trial arms were noted. Each of these studies, therefore, was judged to be at low risk of bias for this domain. One study (Papakostas 2015) reported an intention-to-treat analysis based on all originally randomised patients but provided no information about how missing data were handled (37 of 139 randomised participants dropped out of the study), so was judged to be at an unclear risk of bias. The primary analyses of Kessler 2018 compared the treatment groups as randomised without imputing missing values. Sensitivity analyses were conducted to investigate the influence of missing data.

Selective reporting

One study (El-Khalili 2010 (PEARL)) was judged to be at a low risk of selective outcome reporting bias as all outcomes of interest to the review that were described in the study protocol were reported. Risk of bias for this domain was rated as unclear for seven studies (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; Ferreri 2001; Kessler 2018; McIntyre 2007; Papakostas 2015). No protocol was available for two studies (Dunner 2007; Ferreri 2001) and the study protocol did not provide any details of the outcomes to be assessed in another study (McIntyre 2007). Three studies reported additional outcome data not detailed in the study protocol (Bauer 2009 (ONYX), Durgam 2016, Papakostas 2015). Kessler 2018 administered the PHQ-9 questionnaire at 12, 24 and 52 weeks but only reported data for the 12-week time point. Two studies were judged to be at a high risk of bias for selective outcome reporting. Shelton 2001 listed depression severity as measured by the HAM-D as the primary outcome measure. However, dichotomous outcomes of response and remission were determined using MADRS scores. Appelberg 2001 did not report results in full for the primary outcome of depression severity for all time points measured.

Other potential sources of bias

No other potential sources of bias were identified.

Effects of interventions

See: **Summary of findings for the main comparison** Switching to mianserin (60 mg/d) compared to continuing on current antidepressant (fluoxetine 20 mg/d) for treatment-resistant depression in adults; **Summary of findings 2** Augmentation of current antidepressant (fluoxetine 20 mg/d) with mianserin (60 mg/d) compared to augmentation of current antidepressant (fluoxetine 20 mg/d) with placebo for treatment-resistant depression in adults; **Summary of findings 3** Augmentation of current antidepressant (SSRI/SNRI) with mirtazapine (30 mg/d) compared to augmentation

of current antidepressant (SSRI/SNRI) therapy with placebo for treatment-resistant depression in adults; **Summary of findings 4** Augmentation of current antidepressant (SSRI) with busiprone (20 mg/d to 60 mg/d) compared to augmentation of current antidepressant (SSRI) with placebo for treatment-resistant depression in adults; **Summary of findings 5** Augmentation of current antidepressant (various) with cariprazine (1 mg/d to 4.5 mg/d) compared to augmentation of current antidepressant (various) with placebo for treatment-resistant depression in adults; **Summary of findings 6** Augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with olanzapine (5 mg/d to 20 mg/d) compared to augmentation of current antidepressant (fluoxetine 20 mg/d to 60 mg/d) with placebo for treatment-resistant depression in adults; **Summary of findings 7** Augmentation of current antidepressant (various) with quetiapine (150 mg/d to 300 mg/d) compared to augmentation of current antidepressant (various) with placebo for treatment-resistant depression in adults; **Summary of findings 8** Augmentation of current antidepressant (SSRI) with ziprasidone (40 mg/d to 160 mg/d) compared to augmentation of current antidepressant (SSRI) with placebo or continue on SSRI monotherapy for treatment-resistant depression in adults

Comparison 1 - Increasing the dose of antidepressant monotherapy compared with continuing on an antidepressant

None of the included studies compared increasing the dose of antidepressant monotherapy with continuing on an antidepressant.

Comparison 2 - Switching to a different antidepressant monotherapy compared with continuing on an antidepressant

One study examined the effects of switching to a different antidepressant monotherapy compared with continuing on an antidepressant (Ferreri 2001). Participants who had failed to respond to at least six weeks of treatment with fluoxetine were randomised to continue this treatment or switch to mianserin at a dose of 60 mg per day. The study was a three arm trial - in the third arm participants had their fluoxetine treatment augmented with mianserin. Participants in the two monotherapy arms (fluoxetine only or mianserin only) also received a placebo in addition to their antidepressant.

Primary Outcomes

Change in depressive symptoms

Clinician-rated measures

One study (Ferreri 2001, n = 71) found no evidence of a difference in mean change from baseline in HAM-D 17 scores when current antidepressant medication (fluoxetine) was switched to mianserin compared with continuing on current treatment (MD -1.8, 95% CI -5.23 to 1.63; low-quality evidence; Analysis 1.1).

Self-report measures

No self-report measures of depressive symptoms were made in the study.

Dropouts

There was no evidence of a difference in the numbers of participants dropping out when antidepressant medication was switched to mianserin than when current medication was

continued (one study, Ferreri 2001, n = 72; RR 2.08, 95% CI 0.94 to 4.59; low-quality evidence; Analysis 1.2)

Reasons for dropping out

Participants' reasons for discontinuation are reported in Table 2. The main reasons for dropping out were intolerance to medication or adverse events in the mianserin arm and ineffectiveness of treatment in the group that continued current antidepressant medication.

Secondary Outcomes

Response to treatment

Clinician-rated measures

One study (Ferreri 2001, n = 71) found no evidence of a difference in response to treatment between participants whose antidepressant was switched to mianserin and those who continued on their current medication (RR 1.32, 95% CI 0.76 to 2.27; low-quality evidence; Analysis 1.3).

Self-report measures

No self-report measures of response to treatment were made in the study.

Remission

Clinician-rated measures

There was no evidence of a difference in the numbers of participants experiencing remission from depression when antidepressant medication was switched to mianserin than when current medication was continued (one study, Ferreri 2001, n = 71; RR 1.97, 95% CI 0.88 to 4.42; low-quality evidence; Analysis 1.4).

Self-report measures

No self-report measures of remission from depression were made in the study.

Social adjustment and social functioning

No data on social adjustment or functioning were reported.

Quality of life

No data on quality of life were reported.

Economic outcomes

No data on any economic outcomes were reported.

Adverse effects

One study (Ferreri 2001, n = 72) reported arm-level adverse event data, including the number of participants in each arm that experienced at least one adverse event and the numbers of each type of adverse event occurring in each arm. More participants reported adverse events after switching to mianserin than continuing fluoxetine (70.5% versus 28.1%). The most commonly reported adverse events were dizziness and drowsiness in the mianserin arm and headache and asthenia in the fluoxetine arm.

Further details can be found in Table 3. The number of participants who discontinued medication due to adverse events is reported in Table 2 and described under the primary outcome of dropouts.

Comparison 3 - Augmenting treatment with another antidepressant compared with continuing on an antidepressant

Two studies examined the effects of augmenting antidepressant treatment with a second antidepressant. Augmentation was with mianserin in one study (Ferreri 2001) and mirtazapine in the other study (Kessler 2018).

Primary Outcomes

Change in depressive symptoms

Clinician-rated measures

Augmentation with mianserin

One study (Ferreri 2001, n = 70) found evidence of a difference in HAM-D scores when current antidepressant mediation was augmented with mianserin compared with placebo (MD -4.8, 95% CI -8.18 to -1.42; moderate-quality evidence; Analysis 2.1)

Augmentation with mirtazapine

No studies reported change in depressive symptoms based on clinician-rated scale.

Self-report measures

Augmentation with mianserin

No studies reported change in depressive symptoms based on a self-report scale.

Augmentation with mirtazapine

One study (Kessler 2018, n = 480) found insufficient evidence of difference in BDI-II scores between participants whose current antidepressant medication was augmented with mirtazapine and those who medication was augmented with placebo at 12 weeks (MD -1.7, 95% CI -4.03 to 0.63; high-quality evidence; Analysis 3.1), 24 weeks (MD -0.9, 95% CI -3.39 to 1.59; high-quality evidence; Analysis 3.1) or 52 weeks (MD 0.1, 95% CI -2.38 to 2.58; high-quality evidence; Analysis 3.1). There was also insufficient evidence of a difference between groups on PHQ-9 scores obtained at 12 weeks (MD -0.89, 95% CI -2.08 to 0.30; high-quality evidence; Analysis 3.2).

Dropouts

Augmentation with mianserin

The was no evidence of a difference in numbers dropping out of treatment when current antidepressant treatment was augmented with mianserin compared with placebo (one study, Ferreri 2001, n = 70; RR 1.02, 95% CI 0.38 to 2.72; low-quality evidence; Analysis 2.2).

Augmentation with mirtazapine

One study (Kessler 2018, n = 480) found no evidence of a difference in the number of participants dropping out of treatment augmented with mirtazapine compared with those who received placebo at 12, 24 or 52 weeks (12 weeks: RR 0.50, 95% CI 0.15 to 1.62; 24 weeks: RR 0.50, 95% CI 0.19 to 1.30; 52 weeks: (RR 0.46, 95% CI 0.18 to 1.18; all high-quality evidence; Analysis 3.3)

Reasons for dropping out

Participants' reasons for discontinuation are reported in Table 2.

Secondary Outcomes

Response to treatment

Clinician-rated measures

Augmentation with mianserin

One study (Ferreri 2001, n = 70) found evidence of an increased response to treatment when current antidepressant medication was augmented with mianserin compared with placebo (RR = 1.70, 95% CI 1.03 to 2.78; moderate-quality evidence; Analysis 2.3).

Augmentation with mirtazapine

No clinician-rated measures of response to treatment were made in the study.

Self-report measures

Augmentation with mianserin

No self-report measures of response to treatment were made in the study.

Augmentation with mirtazapine

The was weak evidence that participants whose current antidepressant medication was augmented with mirtazapine had an increased response to treatment compared with placebo at 12 weeks (Kessler 2018, n = 480; RR 1.22, 95% CI 0.97 to 1.54; high-quality evidence; Analysis 3.4). There was no evidence for a difference at 24 or 52 weeks (24 weeks: RR 1.01, 95% CI 0.83 to 1.23; 52 weeks: RR 1.00, 95% CI 0.82 to 1.22; high-quality evidence; Analysis 3.4).

Remission

Clinician-rated measures

Augmentation with mianserin

One study (Ferreri 2001, n = 70) found evidence of an increased likelihood of meeting criteria for remission when current antidepressant medication was augmented with mianserin compared with placebo (RR 2.38, 95% CI 1.09 to 5.16; low-quality evidence; Analysis 2.4).

Augmentation with mirtazapine

No studies reported the outcome of remission determined using a clinician-reported measure.

Self-report measures

Augmentation with mianserin

No studies reported the outcome of remission determined using a self-report measure.

Augmentation with mirtazapine

There was no evidence (Kessler 2018, n = 480) of a difference in the numbers of participants meeting the criteria for remission when current antidepressant medication was augmented with mirtazapine compared with placebo at any time point measured (12 weeks; RR 1.21, 95% CI 0.88 to 1.65; 24 weeks; RR 1.16, 95% CI

0.86 to 1.55; 52 weeks; RR 0.98, 95% CI 0.74 to 1.30; high-quality evidence; Analysis 3.4).

Social adjustment and social functioning

No data on social adjustment or functioning were reported.

Quality of life

Augmentation with mianserin

No quality of life data were reported.

Augmentation with mirtazapine

One study (Kessler 2018, n = 480) measured quality of life using the EQ-5D-5L and SF-12. There was no evidence of a difference in EQ-5D-5L scores between participants whose medication was augmented with mirtazapine compared with placebo at any of the time points measured (12 weeks; MD -0.01, 95% CI -0.06 to 0.04; 24 weeks: MD -0.02, 95% CI -0.07 to 0.03; 52 weeks: MD -0.03, 95% CI -0.08 to 0.02; all high-quality evidence; Analysis 3.6).

On the SF-12 checklist, there was evidence of an improvement on the aggregate mental functioning subscale in the mirtazapine augmentation group at 12 weeks (MD 3.61, 95% CI 1.23 to 5.99; high-quality evidence; Analysis 3.7) compared with placebo but not at 24 or 52 weeks (24 weeks: MD 1.98, 95% CI -0.64 to 4.60; 52 weeks: MD 1.29, 95% CI -1.44 to 4.02; high-quality evidence; Analysis 3.7). There was no evidence of a difference in scores on the aggregate physical functioning subscale at any of the time points measured (12 weeks: MD -1.76, 95% CI -4.20 to 0.68; 24 weeks: MD -2.49, 95% CI -5.04 to 0.06; 52 weeks: MD -0.98, 95% CI -3.61 to 1.65; all high-quality evidence; Analysis 3.8).

Economic outcomes

Augmentation with mianserin

No economic outcomes were reported.

Augmentation with mirtazapine

One study (Kessler 2018, n = 480) reported direct costs to health and social services, costs to patients and carers, and time off work for patients and carers. There was no evidence of a difference in resource use cost when current antidepressant treatment was augmented with mirtazapine compared with placebo for any of the resources considered. Cost-effectiveness analyses were also reported. No clinically important differences in quality adjusted life years (QALYs) or costs were observed between the two groups at 12 weeks follow-up (difference of 0.002, (95% CI –0.002 to 0.005) QALYs); (difference in costs £2 (95% CI –£27 to £31)) or at 52 weeks follow-up (difference of 0.009 (95% CI –0.016 to 0.035) QALYs); (difference in costs £69 (95% CI –£74 to £206)). There was, therefore, no evidence that mirtazpine was a cost-effective use of NHS resources.

Adverse effects

All of the included studies reported some information about adverse events. Further details can be found in Table 3.

Two studies of augmentation of current antidepressant therapy with an additional antidepressant reported the number of participants in each arm that experienced an adverse event. The incidence of adverse events was higher when augmenting with mianserin (44.7%, Ferreri 2001) or mirtazapine (69.3%, Kessler 2018) than placebo (28.1% and 38.1% in the respective control groups). Both studies also reported the frequency of each type of adverse event experienced. The most commonly reported adverse events were dizziness, somnolence, dry mouth, asthenia, and weight increase.

One study (Kessler 2018) reported the number of participants experiencing serious adverse events (SAEs). The overall incidence of SAEs was low and the majority were judged by the study investigators to be unrelated (or unlikely to be related) to study medication. The incidence of adverse events was 3.32% in participants whose current antidepressant therapy was augmented with mirtazapine compared with 1.25% when augmented with placebo.

The number of participants who discontinued in studies due to adverse events are reported in Table 2 and described under the primary outcome of dropouts.

Comparison 4 - Augmenting treatment with a non-antidepressant compared with continuing on an antidepressant

Eight studies examined the effects of augmenting antidepressant treatment with a non-antidepressant. Augmentation was with an anxiolytic (buspirone) in one study (Appelberg 2001) and an antipsychotic (cariprazine, olanzapine, quetiapine or ziprasidone) in seven studies (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); McIntyre 2007; Papakostas 2015; Shelton 2001).

Primary Outcomes

Change in depressive symptoms

Clinician-rated measures

Augmentation with buspirone

One study (Appelberg 2001, n = 102) found no evidence of a difference in mean change from baseline in MADRS scores when augmenting current antidepressant medication with the anxiolytic buspirone compared with placebo (MD -0.30, 95% CI -9.48 to 8.88; low-quality evidence; Analysis 4.1).

Augmentation with cariprazine

One three-arm, study (Durgam 2016, n = 808) found a reduction in MADRS scores from baseline (the primary outcome for the study) when antidepressant treatment was augmented with the antipsychotic cariprazine at a dose of 2 mg/d to 4.5 mg/d (MD -2.1, 95% CI -3.63 to -0.57; Analysis 5.1) compared with placebo, but there was only weak evidence of an effect at the lower dose of 1 mg/d to 2 mg/d (MD -0.90 , 95% CI -2.29 to 0.49; Analysis 5.1). Pooling the two active treatment arms showed an overall effect for cariprazine (MD -1.50, 95% CI -2.74 to -0.25; high-quality evidence; Analysis 5.1).

Augmentation with olanzapine

One study (Shelton 2001, n = 20) found evidence of a reduction in MADRS scores when augmenting current antidepressant treatment with the antipsychotic olanzapine compared with placebo (MD -12.4, 95% CI -22.44 to -2.36; low-quality evidence; Analysis 6.1). However, evidence of a difference between groups was weaker

based on the HAM-D rating scale, which was the primary outcome for the study (MD -7.9, 95% CI -16.76 to 0.96; low-quality evidence; Analysis 6.2).

Augmentation with quetiapine

Three studies (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007 n = 977) found evidence of a reduction in depressive symptomology (measured using MADRS - Bauer 2009 (ONYX); El-Khalili 2010 (PEARL) - or HAM-D - McIntyre 2007) when augmenting current antidepressant treatment with the antipsychotic quetiapine at a dose of 150 or 200 mg/d (SMD -0.34, 95% CI -0.53 to -0.14; I^2 = 28%; Analysis 7.1). Two of these studies (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL) also examined the effects of adjunctive quetiapine at a higher dose of 300 mg/d and found evidence of a reduction in MADRS scores compared with placebo (MD -2.85, 95% CI -4.23 to -1.47, I^2 = 0%; Analysis 7.1). Pooling across doses, there was evidence overall (three studies (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007 n = 977) of a beneficial effect for quetiapine on symptoms of depression (SMD -0.32, 95% CI -0.46 to -0.18; I^2 = 6%, high-quality evidence; Analysis 7.1).

Augmentation with ziprasidone

Two studies examined the effectiveness of augmenting current antidepressant therapy with the antipsychotic ziprasidone (Dunner 2007; Papakostas 2015, n = 199). Dunner 2007 was a three-arm study comparing two doses of ziprasidone (80 mg/d or 160 mg/d) with continuing on antidepressant monotherapy alone. Papakostas 2015 compared augmenting current antidepressant therapy with 40 mg/d to 160 mg/d of ziprasidone (mean dose 98 mg) with placebo.

Dunner 2007 found no evidence of a difference in mean change in HAM-D scores (the primary outcome of the study) for a dose of 80 mg (n = 41, mean difference -0.91, 95% CI -4.84 to 3.02; Analysis 8.1) or 160 mg per day (n = 39; MD -2.56, 95% CI -6.72 to 1.60; Analysis 8.1) but confidence intervals were wide. Papakostas 2015 found evidence of a reduction in depressive symptoms on the HAM-D (MD -3.10, 95% CI -5.19 to -1.01; Analysis 8.1) for a mean dose of 98 mg/d (range 40 mg to 160 mg) of ziprasidone daily. Pooling across doses, there was evidence overall for a greater reduction from baseline in HAM-D scores for ziprasidone compared with antidepressant monotherapy (MD -2.73, 95% CI -4.53 to -0.93; I^2 = 0, moderate-quality evidence; Analysis 8.1).

Dunner 2007 also assessed depression severity using the MADRS scale. There was no evidence of a difference in mean change in MADRS scores at any dose (80 mg/d: MD -1.53, 95% CI -6.94 to 3.88; 160 mg/d: 3.82, 95% CI -9.64 to 2.00; pooled dose: MD -2.62, 95% CI -7.47 to 2.23; low-quality evidence; Analysis 8.2).

Self-report measures

Augmentation with ziprasidone

Papakostas 2015, (n = 139) found evidence of a reduction in scores on the self-report QIDS-SR (MD -2.50, 95% CI -3.83 to -1.17; moderate-quality evidence; Analysis 8.3) for a dose of 40 mg to 160 mg of ziprasidone daily.

Dropouts

All of the included studies reported the numbers of participants who discontinued in each trial arm. Participants' reasons for discontinuation are reported in Table 2.

Augmentation with buspirone

There was no evidence of a difference in the number of participants dropping out of treatment augmented with the anxiolytic buspirone compared with those who received placebo (one study, Appelberg 2001, n = 108; RR 0.60, 95% CI 0.23 to 1.53; low-quality evidence; Analysis 4.2).

Augmentation with cariprazine

In a three-arm trial of augmentation with cariprazine (Durgam 2016, n = 821), more participants in the intervention arms dropped out than in the placebo arm (RR 1.68, 95% CI 1.16 to 2.41; moderate-quality evidence; Analysis 5.2). The evidence was weaker for the lower dose of 1 mg to 2 mg of cariprazine per day (RR 1.43, 95% CI 0.94 to 2.17; Analysis 5.2) than for the higher dose of 2 mg to 4.5 mg per day (RR 1.92, 95% CI 1.30 to 2.84; Analysis 5.2).

Augmentation with olanzapine

One study of augmentation with olanzapine (Shelton 2001, n = 20) found no evidence of a difference in numbers dropping out although the confidence interval was wide (RR 0.33, 95% CI 0.04 to 2.69; low-quality evidence; Analysis 6.3).

Augmentation with quetiapine

Three trials of augmentation with quetiapine (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007; n = 977) provided weak evidence of greater dropout in the intervention arms compared with the placebo group (RR 1.33, 95% CI 0.9 to 1.95; I^2= 1%, moderate-quality evidence; Analysis 7.2). When doses of quetiapine were considered separately, those who received the higher dose of 300 mg/d were more likely to drop out compared with the placebo group (two studies, Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); RR 1.82, 95% CI 1.29 to 2.57; I^2 = 0%; Analysis 7.2) but there was no evidence of a difference in dropouts for the lower dose of 150 mg/d or 200 mg/d of quetiapine compared with placebo (three studies, Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007; RR 1.18, 95% CI 0.86 to 1.63; I^2 = 42%; moderate-quality evidence; Analysis 7.2).

Augmentation with ziprasidone

There was evidence from two studies (Dunner 2007, Papakostas 2015, n = 199) that dropout was greater for those who received treatment augmented with ziprasidone compared with antidepressant monotherapy (RR 1.60, 95% CI 1.01 to 2.55, I^2 = 0%; moderate-quality evidence; Analysis 8.4).

Reasons for dropping out

All of the eight studies that examined the effects of augmenting antidepressant treatment with a non-antidepressant reported participants' reasons for discontinuation and these are detailed in full in Table 2. Across all of the studies, the most common reason for dropping out was due to an adverse event or an inability to tolerate the side effects of treatment (8.05% of all randomised participants). Greater numbers of participants dropped out for this reason from

active intervention arms than from placebo arms and at higher compared with lower doses (in the case of trials with more than one active intervention arm). The proportion of participants dropping out due to adverse events or intolerability was considerably higher for Dunner 2007 than any of the other included studies (n = 16, 26.67%).

Withdrawal of consent or unwillingness to continue was the second most frequently reported reason for dropping out (3.69% of all randomised participants). The proportion of participants dropping out for this reason was higher for Dunner 2007 than any of the other studies (n = 6, 10%).

In four trials, participants dropped out due to protocol violations (Appelberg 2001; Bauer 2009 (ONYX); Durgam 2016; Shelton 2001). Two trials (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL)) reported dropouts post-randomisation due to failure to fulfil eligibility criteria.

'Lost to follow-up' was cited as the reason for the dropout of 2.35% of all randomised participants. 1.15% dropped out due to the inefficacy of their treatment and 0.43% because they stopped taking their study medication or due to extreme non-compliance.

Secondary Outcomes

Response to treatment

Seven studies reported data on the dichotomous outcome of response to treatment (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); McIntyre 2007; Papakostas 2015; Shelton 2001). All measured response using an observer-rated tool (MADRS or HAM-D). One study additionally assessed response using a self-report rating scale (QIDS-SR; Papakostas 2015).

Clinician-rated measures

Augmentation with buspirone

No data were reported for the outcome of response to treatment for augmentation of current antidepressant treatment with buspirone.

Augmentation with cariprazine

One three-arm, study (Durgam 2016, n = 808) found that those whose antidepressant treatment was augmented with the antipsychotic cariprazine at a dose of 2 mg/d to 4.5 mg/d or 1 mg/d to 2 mg/d were more likely to meet criteria for response compared with the placebo group (2 mg/d to 4.5 mg/d: RR 1.29, 95% CI 1.06 to 1.57; 1 mg/d to 2 mg/d: RR 1.25, 95% CI 1.03 to 1.53; Analysis 5.3). When pooling the two active treatment arms, there was a 27% increased likelihood of response to treatment for those who received augmented treatment with cariprazine compared with placebo (RR 1.27, 95% CI 1.07 to 1.52; moderate-quality evidence; Analysis 5.3).

Augmentation with olanzapine

The single small study of augmentation with olanzapine (Shelton 2001, n = 20) found that those who received augmented treatment were more likely to meet criteria for response compared with the placebo group but the confidence interval was very wide (RR 6.00, 95% CI 0.87 to 41.21; low-quality evidence; Analysis 6.4).

Augmentation with quetiapine

There was evidence from three studies (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007; n = 977) that those whose antidepressant treatment was augmented with quetiapine (any dose) were more likely to meet criteria for response compared with those receiving placebo (RR = 1.20, 95% CI 1.02 to 1.40; I2 = 0%; moderate-quality evidence; Analysis 7.3). A benefit in terms of response to treatment was found at both higher (300 mg/d; two studies; Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); RR 1.29, 95% CI 1.10 to 1.50, I2 = 0%; Analysis 7.3) and lower doses (150 mg/d or 200 mg/d; three studies Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007; RR 1.25, 95% CI 1.09 to 1.43; I2= 0%; Analysis 7.3) compared with placebo.

Augmentation with ziprasidone

In a three-arm trial, Dunner 2007 found no evidence of a difference in response (based on scores on the MADRS) for augmenting with ziprasidone at a daily dose of either 80 mg (RR 1.90, 95% CI 0.39 to 9.28; Analysis 8.5) or 160 mg (RR 3.16, 95% CI 0.72 to 13.76; Analysis 8.5) compared with continuing with antidepressant therapy alone. Papakostas 2015 found weak evidence (RR 1.71, 95% CI 0.97 to 3.00; Analysis 8.5) that those whose antidepressant treatment was augmented with ziprasidone (mean dose: 98 mg/d, range 40 mg to 160 mg) were more likely to meet criteria for response (based on scores of the HAM-D; with response being the primary outcome for this study) than those who received placebo. Pooling across studies and doses, there was evidence that those whose current antidepressant therapy was augmented with ziprasidone were more likely to meet criteria for response (RR 1.80, 95% CI 1.07 to 3.04; moderate-quality evidence; Analysis 8.5).

Self-report measures

Augmentation with ziprasidone

Papakostas 2015 also measured response to treatment on the self-report SIDS-SR scale and found evidence that those who received augmentation with ziprasidone were more likely to meet criteria for response to treatment in the ziprasidone augmentation arm compared with the placebo group (n = 139, RR = 2.34, 95% CI 1.16 to 4.72; moderate-quality evidence; Analysis 8.6).

Remission

Six studies reported the outcome of remission from depression at the end of the treatment period (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); McIntyre 2007; Papakostas 2015). All six studies defined remission based on a cut-off on an observer-rated depression scale (MADRS or HAM-D). One study additionally assessed remission using a self-report rating scale (QIDS-SR; Papakostas 2015).

Clinician-rated measures

No data were reported for the outcome of remission for augmentation of current antidepressant treatment with either the anxiolytic buspirone or with the antipsychotic olanzapine.

Augmentation with cariprazine

One three-arm, study (Durgam 2016, n = 808) found no evidence of a difference in the number meeting criteria for remission amongst participants whose current antidepressant was augmented with either 1 mg/d to 2 mg/d (RR 1.06, 95% CI 0.83 to 1.37; Analysis 5.4) or 4 mg/d to 5 mg/d (RR 1.07, 95% CI 0.83 to 1.38; Analysis 5.4) of

cariprazine compared with placebo. Pooling across the cariprazine arms showed no evidence of a difference between groups (RR 1.07, 95% CI 0.86 to 1.33; moderate-quality evidence; Analysis 5.4).

Augmentation with quetiapine

There was evidence of an increased likelihood of meeting criteria for remission in those who received augmentation of current antidepressant therapy with quetiapine at a higher dose (300 mg/d, two studies, Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); RR 1.53, 95% CI 1.13 to 2.07; I2 = 32%; Analysis 7.5) or lower dose (150 mg/d or 200 mg/d, three studies, Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007; RR 1.51, 95% CI 1.19 to 1.93; I2 = 0%; Analysis 7.5) than those receiving a placebo.

Pooling across the quetiapine doses showed that those who received quetiapine (any dose) in addition to their antidepressant medication had a 50% increased likelihood of meeting criteria for remission compared with those who received placebo (three studies, Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007; RR 1.53, 95% CI 1.22 to 1.90; I2 = 0%; moderate-quality evidence; Analysis 7.5).

Augmentation with ziprasidone

There was little evidence of a difference in remission outcomes based on clinician-rated scales for those who received ziprasidone in addition to antidepressant medication compared with those who continued on antidepressant monotherapy (Dunner 2007, Papakostas 2015, n = 199; RR 1.27, 95% CI 0.81 to 2.00, I2 = 0%; moderate-quality evidence; Analysis 8.7).

Self-report measures

Augmentation with ziprasidone

Papakostas 2015 (n = 139) found evidence that those whose antidepressant treatment was augmented with ziprasidone were more likely to meet criteria for remission when this was determined using a self-report instrument (RR 2.33, 95% CI 1.03 to 5.25; moderate-quality evidence; Analysis 8.8).

Social adjustment and social functioning

No studies reported data on social adjustment or functioning.

Quality of life

No quality of life data were reported in studies that examined augmentation with buspirone, cariprazine, olanzapine or ziprasidone.

Augmentation with quetiapine

Two three-arm trials (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL), n = 884) found no evidence of a difference in terms of quality of life for those whose antidepressant treatment was augmented with the antipsychotic quetiapine compared with placebo (dose 150 mg/d: MD 0.70, 95% CI -2.31 to 3.71, I2= 36%; 300 mg/d: MD 0.35, 95% CI -2.06 to 2.77, I2= 0; pooled across arms: mean difference 0.57, 95% CI -1.52 to 2.65, I2= 0%; Analysis 7.4).

Economic outcomes

No studies reported data on any economic outcomes.

Adverse effects

All of the included studies reported some information about adverse events. Further details can be found in Table 3.

In the study of augmentation of current antidepressant therapy with the anxiolytic busiprone, Appelberg 2001 reported no serious adverse events and that there were "no statistically significant differences" (p.450) in scores on the Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale (Lingjaerde 1987) between treatment groups during the study.

Six studies of augmentation of current antidepressant therapy with an antipsychotic reported arm-level adverse event data (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); McIntyre 2007; Papakostas 2015). Four of these studies reported the number of participants in each arm that experienced at least one adverse event (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL)). The incidence of adverse events ranged from 40% to 66.9% in the control arms and from 65% to 100% in the intervention arms. All six of the studies reported the frequency of each type of adverse event. A seventh study (Shelton 2001) described the most commonly occurring events across all treatment groups but did not report the numbers experiencing each type of event. Across all six studies, the most commonly reported adverse events were somnolence, dry mouth, akathisia, asthenia, dizziness, headache, nausea, constipation, diarrhoea and changes in appetite or weight.

Six studies of augmentation with an antipsychotic reported the numbers of participants experiencing serious adverse events (SAEs) (Bauer 2009 (ONYX); Dunner 2007; Durgam 2016; El-Khalili 2010 (PEARL); McIntyre 2007; Papakostas 2015). Overall, the number of serious adverse events reported was low. Further details of the events reported are provided in Table 3.

The number of participants who discontinued in studies due to adverse events are reported in Table 2 and described under the primary outcome of dropouts.

Subgroup analyses

No subgroup analyses were undertaken to explore potential sources of heterogeneity because there were fewer than ten studies available in any comparison.

Sensitivity analysis

There were too few studies to enable pre-planned sensitivity analyses to be conducted.

DISCUSSION

This review focused on pharmacological approaches for adults with treatment-resistant depression (TRD). We identified one randomised controlled trial that examined switching current antidepressant treatment to another antidepressant and two trials that augmented current antidepressant therapy with a second antidepressant. We identified eight randomised controlled trials that examined augmentation of current antidepressant therapy with a non-antidepressant. Augmentation was with an anxiolytic (busiprone) in one study and with an antipsychotic (cariprazine, olanzapine, quetiapine or ziprasidone) in seven studies. We did not identify any studies meeting our eligibility criteria that examined increasing the dose of current antidepressant monotherapy.

Summary of main results

The main findings of the review are summarised in eight key tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8).

The single study that examined switching from current antidepressant treatment to another antidepressant found no evidence of a difference in depressive symptoms, response to treatment, remission rates or numbers dropping out (all moderate-quality estimates). The sample size was small (n = 72 for this comparison) and there was imprecision in the estimates, therefore our confidence in these findings is limited.

Evidence for the effectiveness of augmenting current antidepressant treatment with another antidepressant was mixed. There was moderate-quality evidence from one study that augmenting with mianserin was associated with a greater reduction in depression severity scores from baseline, an increased response to treatment and increased remission of depressive symptoms. There was no evidence of a difference in numbers dropping out of treatment (moderate-quality) but there was considerable imprecision in this estimate. A second study, of augmentation of current antidepressant treatment with mirtazapine, found no evidence of a difference in depressive symptoms or other outcomes (remission, quality of life, numbers dropping out of treatment; all estimates high-quality) at any time point, although there was weak evidence of an increased response to treatment at 12 weeks (but not at later follow-up). There were also no differences in resource use costs between treatment groups or evidence that augmenting current treatment with mirtazapine was cost-effective compared with continuing on antidepressant monotherapy.

The single study (n = 102) that focused on augmentation of current antidepressant therapy with the anxiolytic busiprone found no evidence of a difference in depressive symptoms (low-quality) or numbers dropping out (moderate-quality). No data were reported for response to treatment or remission rates. There was considerable imprecision (very wide confidence intervals) in the estimates of effect for the depression outcomes and therefore our confidence in these findings is limited.

Seven studies examined the effectiveness of augmenting current antidepressant therapy with an antipsychotic (cariprazine, olanzapine, quetiapine or ziprasidone). All found evidence of a greater reduction in depression severity scores from baseline in the augmentation group compared with the control group. For cariprazine (moderate-quality), quetiapine (high-quality) and ziprasidone (moderate-quality), this difference was modest, corresponding to an average difference of between 1.5 and 2.7 points on the depression severity scale used that equate to an effect size of approximately 0.18 to 0.42 SD. The NICE guidelines group (NICE 2004) previously suggested that a difference of around 0.33 SD equated to a minimum clinically important difference (MCID) and, therefore, the effects seen here may be clinically relevant. However, there is some evidence that patients with TRD require larger improvements in their symptoms to report feeling better (Button 2015). A larger effect was observed in the study of augmentation with olanzapine (n = 20) but certainty in this estimate was judged to be low due to imprecision.

We also found evidence to support a beneficial effect of adjunctive treatment with an antipsychotic for the dichotomous outcome of response to treatment. The effect was largest for olanzapine, but this estimate was judged to be of low quality due to considerable imprecision. The evidence for all other antipsychotics was judged to be of moderate quality.

Findings for the more stringent outcome of remission of depressive symptoms (where measured) were mixed. There was moderate-quality evidence that augmentation with quetiapine was associated with an increased likelihood of remission of depressive symptoms compared with continuing on an existing antidepressant treatment alone. There was no evidence of a difference for cariprazine (moderate-quality). For ziprasidone, there was no evidence of a difference when remission was determined using an observer-rated measure (HAM-D), but increased likelihood of remission when depressive symptoms were self-reported (QIDS-SR) (both estimates, moderate-quality). Remission rates were not reported for olanzapine.

There was moderate-quality evidence of a differential dropout rate when current antidepressant therapy was augmented with cariprazine, quetiapine or ziprasidone, with those who received an antipsychotic drug being more likely to drop out. There was no evidence of a difference in dropout rates when current therapy was augmented with olanzapine but the quality of this estimate was low. The most common reason for dropping out was an adverse event. Definitions of adverse events varied between included studies but reports of adverse events were higher in the groups who received augmented treatment with an antipsychotic compared with those who continued antidepressant therapy alone or augmented with a placebo.

Data for all other outcomes were limited. Two trials found no evidence of a difference in quality of life for participants whose current treatment was augmented with quetiapine compared with placebo (moderate-quality). One trial found no evidence of a difference in resource use costs (to health and social services, patients and carers) when current antidepressant treatment was augmented with mirtazapine compared with placebo.

None of the studies we identified reported data on social adjustment or functioning.

Due to the small number of studies identified, we were unable to conduct any subgroup analyses or explore the robustness of the findings through sensitivity analyses. Our confidence in the majority of the effect estimates obtained in this review was lowered by the imprecision of these estimates.

In summary, there is a small body of evidence on the effectiveness of augmenting current antidepressant therapy with a second pharmacological treatment. There is currently insufficient evidence to support the addition of busiprone to current antidepressant treatment but further trials may change this conclusion. There is evidence of a benefit for augmenting antidepressant therapy with the antidepressant mianserin (based on a single study) or with an antipsychotic, but this needs to be balanced against the increased likelihood of dropping out of treatment or experiencing an adverse event as a side effect of treatment. There is currently insufficient evidence to support switching existing antidepressant treatment to another antidepressant but further trials may change this conclusion.

Overall completeness and applicability of evidence

Our search was comprehensive; we utilised the CMDCTR's trial reference and studies registers, which were collated from searches (from inception) of multiple databases, and also included assessment of unpublished literature accessed by contacting study authors. In addition, we screened reference lists of included studies and contacted study authors for any unpublished or ongoing studies.

Despite this, we identified only a small body of evidence. Individual comparisons were supported by only one, two or three studies. Importantly, we identified a number of gaps in the literature. There were no trials of increasing the dose of existing antidepressant medication and only one of switching to another antidepressant treatment that were eligible for inclusion in our review. Only two trials assessed efficacy outcomes (depressive symptoms, response to treatment and remission) using a self-report tool. Only three studies reported quality of life data, none reported on social adjustment/functioning and only one study reported economic outcomes. Only one study (Kessler 2018) assessed outcomes beyond the short term (duration of studies ranged between six and eight weeks) so long-term outcomes of treatment of most treatment strategies are unknown.

Findings from this review are applicable to adults with TRD defined as "depression (meeting diagnostic criteria) that has not responded to at least 4 weeks treatment with a therapeutic dose of antidepressant medication". Definitions of TRD varied between studies ranging from between one and three previous failed treatments. Duration of treatment in most trials was six to eight weeks which is comparable with other pharmacological intervention trials in depressed patients. The age and gender distribution of participants recruited in the included studies reflect the average age/gender profile of depressed patients - women in their 40s. In terms of the severity of depression, mean depression scores on the HAM-D/MADRS equated to moderate/severe depression. Nine trials recruited outpatients from hospital (secondary care) outpatient clinics. Only one trial recruited participants from primary care. Whilst we know that many patients with TRD will be seen in primary care settings (Thomas 2013), similarities in terms of age, gender and severity of depression increase the generalisability of review findings. Four studies were conducted in the US, one each in Canada, England, Finland and France, and two in multiple countries across Europe, North America and Australia. As such, findings may have limited generalisability to other countries where the system for delivering mental health care is substantially different from those described in the included studies.

Quality of the evidence

We assessed the quality of the evidence using the GRADE approach for each of the outcomes presented in the summary of findings tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8).

Study limitations

All studies were judged to be at a low or unclear (due to insufficient reporting) risk of selection bias. Outcome assessors were blinded in all included studies and a placebo intervention was administered in the comparator arm of all but one study to protect against performance and detection bias. We had no concerns in relation to completeness of outcome data. Although we had some concerns with regards to the possibility of selective outcome reporting in some of the studies, we did not consider that these would reduce the confidence in the estimates of effect as none of the issues identified directly related to the outcomes of interest. Overall, we did not consider any of the included studies to be at a sufficient risk of bias to warrant downgrading the evidence for any outcome.

Consistency of effect

For each of the majority of comparisons made in this review, only one study provided data. For two of the treatment strategies considered (augmenting with quetiapine and augmenting with ziprasidone), data were provided from two or more studies. No significant heterogeneity was observed for any outcome for augmentation of current treatment with ziprasidone. An I^2 value of 42% was observed for the numbers of participants dropping out when current antidepressant treatment was augmented with quetiapine compared to placebo. The confidence intervals for three studies contributing to this estimate overlapped and a statistical test for heterogeneity was not significant (P = 0.18). No significant heterogeneity was observed for any other outcomes for these comparisons. We did not therefore downgrade any of the evidence included in the review for inconsistency.

Imprecision

Imprecision is the key issue affecting our confidence in the body of evidence identified in this review. For each of many of the comparisons examined, only one study contributed data. Some of the included studies had very small sample sizes (e.g. Dunner 2007; Shelton 2001) and were arguably underpowered to detect a difference between treatment groups. Many of the effect estimates obtained had wide confidence intervals. For augmentation with the anxiolytic buspirone, the estimates of treatment effects (mean change in depression severity, response to treatment and numbers dropping out) were judged to have very serious imprecision and are therefore of low quality. Estimates of treatment effectiveness and numbers dropping out for augmentation with olanzapine also exhibited very serious imprecision, as did those for switching to or augmenting current treatment with mianserin. For each of these treatment strategies, the true effect may be substantially different from the estimate of the effect obtained in this review.

Indirectness

The studies included in this review were free from indirectness in terms of the comparisons of interest (all direct comparisons) as well as the target population, types of intervention, comparator and methods of outcome determination.

Publication bias

We minimised the likelihood of publication bias by searching for and including unpublished and ongoing studies. However, due to the small numbers of studies available for each comparison of interest, we were unable to perform a formal test of small-study bias (Eggers test) and are therefore unable to reach any formal conclusion regarding the absence of publication bias for this review.

Potential biases in the review process

We attempted to contact authors of included studies in order to resolve any queries related to their study and/or to obtain missing information relevant to this review. This, combined with a very comprehensive search strategy, including searching trial registers for unpublished literature along with the inclusion of non-English language papers, minimised the likelihood of publication bias, although the small number of included studies precluded the use of a funnel plot to formally test for such bias. Moreover, our attempts to obtain missing information addressed the potential for selective outcome reporting.

We judged two studies to be at high risk of bias for selective outcome reporting although these issues did not relate directly to the outcomes of interest and therefore we judged these as unlikely to bias the findings of this review. All but one study included a placebo group, minimising the potential for detection and performance bias. All but one (Kessler 2018) of the included studies were industry sponsored and, as shown by previous reviews (e.g. Lundh 2017), may be more likely to give a favourable view of the drug trialled.

The small number of included studies precluded us from undertaking prespecified subgroup analyses and we were therefore unable to determine whether severity of depression and length of the acute treatment phase were potential effect modifiers.

Agreements and disagreements with other studies or reviews

We identified seven previous systematic reviews of pharmacological interventions for treatment-resistant depression. The majority restricted their inclusion to randomised controlled trials. Most looked at the effectiveness of augmentation strategies (with an antipsychotic or other pharmacological agent, Edwards 2013; Liu 2015; Zhou 2015; Zhou 2015a). Two reviews examined the effectiveness of switching to another antidepressant (Bschor 2010; Ruhe 2006) and one looked at increasing the dose of existing antidepressant treatment (Ruhe 2006a). The definition of treatment-resistant depression was not always clear within the reviews' eligibility criteria and some also considered non-standard pharmacological treatments. Consequently, other reviews have included a somewhat different set of trials.

Zhou 2015 conducted a systematic review and network meta-analysis of augmenting antidepressant treatment with an atypical antipsychotic. Whilst their definition of TRD was similar to ours (current episode of major depressive disorder diagnosed according to standard diagnostic interview and an inadequate response to at least one course of conventional antidepressant treatment), they did not specify the length of the initial treatment trial. RCTs of augmentation with an atypical antipsychotic compared with either augmentation with another atypical antipsychotic or with placebo were suitable for inclusion. Several of their included studies were excluded from our review as formal diagnostic criteria were not applied at the point of randomisation or because the length of prior antidepressant treatment was less than four weeks. The review included studies examining the atypical antipsychotics risperidone and aripiprazole, whereas these studies did not meet our inclusion criteria. Conversely, Zhou 2015 did not include any evidence for ziprasidone or cariprazine (the one study of cariprazine included in our review was published beyond the search dates of Zhou 2015).

Nonetheless, Zhou's findings are broadly consistent with ours - atypical antipsychotics were more efficacious than placebo (SMDs ranged from -0.27 to -0.43). All, apart from risperidone, had more side effect discontinuations than placebo (ORs ranged from 2.72 to 6.40), but only quetiapine (mean 250 mg to 350 mg daily) had more all-cause dropouts than placebo (OR = 1.89).

Zhou 2015a also published a systematic review and network meta-analysis of all pharmacological augmentation agents (evidence was identified for aripiprazole, bupropion, buspirone, lamotrigine, lithium, methylphenidate, olanzpine, pindolol, quetiapine, risperidone, thyroid hormone). TRD was defined as in Zhou 2015. The authors identified one small trial of the anxiolytic buspirone (Appelberg 2001, also included in our review). None of the nine trials of augmentation with lithium compared with placebo met the inclusion criteria for this review (as formal diagnostic criteria were not applied at the point of randomisation or because the length of prior antidepressant treatment was less than four weeks). Four included RCTs of augmentation with pindolol compared with placebo also failed to meet our inclusion criteria.

Edwards 2013 examined the effectiveness of augmenting an SSRI with either lithium or an antipsychotic. TRD was defined as failure to respond to at least two previous antidepressants in the current episode of depression. No continuous outcome of depression severity was reported. Edwards identified evidence for aripiprazole, olanzapine, quetiapine and lithium. We excluded all three aripiprazole studies included in the Edwards review as none applied formal diagnostic criteria at the point of randomisation. Five of six olanzapine studies were excluded from our review for the same reason (Shelton 2005a being the exception). The review found evidence that augmenting current antidepressant therapy with olanzapine increased response rates (OR = 1.60, 95% CI 1.01 to 2.53). This estimate, based on five studies, was more precise than ours. None of the quetiapine studies included in our review (Bauer 2009 (ONYX); El-Khalili 2010 (PEARL); McIntyre 2007) met the inclusion criteria for Edwards 2013 as only one treatment failure was required for entry in these trials and that treatment did not have to be an SSRI. No studies of ziprasidone were included. Dunner 2007 was excluded by Edwards 2013 as the dosages were high and not used in the UK. Papakostas 2015 was published beyond the dates of their search as was the cariprazine study included in our review (Durgam 2016).

Liu 2015 carried out a systematic review of the effectiveness of augmenting current antidepressant therapy with the beta-blocker pindolol in participants with a primary diagnosis of unipolar TRD who failed to respond to at least one SSRI compared with continuing on antidepressant therapy (with or without placebo). None of the five trials identified met the inclusion criteria for our review (three did not meet our criteria for TRD, one included bipolar patients, and the mean age of participants was greater than 74 years in the fifth study).

Two systematic reviews examined the effectiveness of switching to another antidepressant. Bschor 2010 defined TRD as depression determined using formal diagnostic criteria and a failure to respond to four weeks or more of antidepressant treatment at standard or higher dose. In addition to the one study included in our review (Ferreri 2001), the authors included two further studies that did not meet our inclusion criteria (both examined a switch to fluoxetine and neither employed formal diagnostic criteria to diagnose depression at the point of randomisation to

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treatment). Bschor 2010 found no evidence a difference in response to treatment or remission from depression when switching to another antidepressant compared with continuing on current antidepressant treatment (no continuous measure of depression symptoms was considered in the review). Ruhe 2006 examined switching antidepressants after an insufficient response to an SSRI and included six RCTs in their review. One of these was the STAR*D study, from which three levels met the criteria for inclusion in the review. Thus, there were eight randomised comparisons in total. Only one (Ferreri 2001) met our inclusion criteria (seven did not include a comparator arm that continued on current antidepressant therapy alone or with placebo). The review authors' definition of TRD was not described in the paper.

Finally, Ruhe 2006a examined the effectiveness of dose escalating in participants who had failed to respond to a minimum of three weeks of treatment with an SSRI. They identified seven randomised studies, none which met the inclusion criteria for our review (four did not meet our definition of TRD as participants had only had three weeks of prior SSRI treatment, two had no comparator group that continued on the same dose of the SSRI, and one did not apply diagnostic criteria at point of randomisation).

AUTHORS' CONCLUSIONS

Implications for practice

This review found moderate- to high-quality evidence that augmenting antidepressant treatment with an antipsychotic – cariprazine (moderate), quetiapine (high) or ziprasidone (moderate) - for individuals with treatment-resistant depression reduced depressive symptoms over the short term (8 to 12 weeks). Findings from a small study of the antipsychotic olanzapine also suggested augmenting current antidepressant treatment with this drug may reduce symptoms of depression but this study was of low quality. However, those who received adjunctive antipsychotic treatment were more likely to experience adverse events or not tolerate treatment compared with those who received placebo. As such, adjunctive treatment with an antipsychotic may be less acceptable.

There was no evidence that augmenting antidepressant treatment with an anxiolytic, buspirone, reduced symptoms of depression compared with placebo. However, this evidence was judged to be low-quality.

There was some evidence that augmenting existing antidepressant treatment with a second antidepressant may be beneficial but this was not consistent across different drugs. There was moderate-quality evidence that adjunctive treatment with mianserin reduced depressive symptoms over the short term (six weeks). However, there was no evidence of improvements in depressive symptoms when existing antidepressant treatment was augmented with mirtazapine compared with placebo.

There was no evidence that switching to a different antidepressant treatment (mianserin) was beneficial compared with placebo. This evidence was judged to be moderate quality due to imprecision in the results.

No evidence was identified for other treatment strategies, such as increasing the dose of existing antidepressant treatment or augmenting with other medications (e.g. lithium or beta-blockers).

Implications for research

Only a small number of studies were included in our review and most of these examined the effectiveness of a single treatment strategy - augmenting antidepressant treatment with a non-antidepressant medication - most commonly, an antipsychotic medication. Evidence is therefore needed on the effectiveness of other pharmacological approaches to the management of treatment-resistant depression in adults in order to improve outcomes for the large group of patients who do not respond to antidepressant treatment. Future trials need to examine strategies such as switching to a different antidepressant, increasing the dose of antidepressant monotherapy, combining two antidepressant treatments, as well as evidence on other augmentation strategies.

Future trials in this area need to give careful consideration to their design. Many of the trials that were excluded from this review did not apply diagnostic criteria for depression at the point of randomisation. We also excluded a large number of trials as they lacked a suitable comparator. In order to make a meaningful comparison that will inform clinical practice, studies need to include a 'control' group that continues on existing antidepressant monotherapy. In addition, it is important that future trials are independent of the pharmaceutical industry to minimise the potential for bias.

Future studies also need to ensure that they include outcomes that are important to patients (and caregivers), such as quality of life, which were rarely measured in studies included this review. Most of the existing evidence only relates to outcomes over the short term. It is important that future research evaluates longer-term outcomes and gathers data about resource use in order to inform discussions about allocation of resources based on evidence of both clinical and cost-effectiveness. Moreover, it is important that adverse effects are consistently recorded in future studies in order to enable patients and clinicians to have an informed discussion about the potential benefits of treatment in light of possible adverse events.

As the evidence base in this area increases, it will be important that researchers compare the effectiveness of different pharmacological interventions with each other, and with psychological interventions. Advances in the development of methods for network meta-analysis that enable multiple treatment options to be compared simultaneously will provide evidence to further inform policy and practice.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Appelberg 2001

Methods	Parallel group RCT
Participants	Country: Finland
	Setting: Outpatient care
	N randomised: 108 (n = 64 (62.7%) female (of 102 participants included in analyses))
	Age: Mean 44 years (SD not reported; range 18 - 61)
	Inclusion: Patients being treated or seeking treatment for depression, 18 years of age or older, meeting DSM-IV criteria for a major depressive episode
	Exclusion: Psychotic or bipolar depression, being regarded by the clinician in charge of treatment to be seriously suicidal, severe neurologic or somatic disease, mental disorder due to a general medical condition, substance-induced disorders, and other psychiatric disorders (except generalised anxiety disorder and specific phobias)
Interventions	Group 1: Augmentation of current SSRI with buspirone (20 mg/d - 60 mg/d) for six weeks
	Group 2: Augmentation of current SSRI with placebo for six weeks
Outcomes	Post-treatment assessment (6 weeks):
	1. Depressive symptoms, continuous (MADRS)
	2. Dropouts
Definition of TRD	Had received fluoxetine or citalopram for at least 6 weeks without showing an antidepressant response according to the psychiatrist in charge of treatment. For at least the last 4 weeks before inclusion, their daily fluoxetine dose was at least 30 mg or their daily citalopram dose at least 40 mg
Notes	Funding: Supported by a grant from Bristol-Myers Quibb, Finland. Respone to treatment (defined as an improvement in CGI-S score ≥ 2 points; data not included in this review as the CGI-S is a generic measure of illness severity rather than specifically measuring depression symptomology)

Risk of bias

Bias	Authors' judgement	Support for judgement

Appelberg 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as randomised but no information given about how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information about how allocation was concealed. "After a single-blind placebo wash-in period of 2 weeks while continuing their SSRI, the patients were randomly assigned to adjunctive treatment with buspirone … or placebo".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study was designed as a placebo-controlled, double-blind ….. Buspirone and placebo were administered as tablets that were identical in appearance".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigators, but not the patients, were aware of the placebo wash-in period. The double-blind phase began immediately after baseline and lasted for 6 weeks … Buspirone and placebo were administered as tablets that were identical in appearance".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF used to account for missing data. Six participants (3 from each arm) were excluded from the analyses as no observations available. "The primary assessment was based on last observation carried forward (LOCF) according to the principle of intention to treat …. One hundred and thirteen patients were enrolled in the study … Five patients were removed from the study during the placebo wash-in phase … Six more patients (3 in the buspirone and 3 in the placebo group) were removed from the study because of a protocol violation before week 1 … One hundred and two patients had at least 1 evaluation after placebo wash-in phase and were included in the final analysis."
Selective reporting (reporting bias)	High risk	No protocol available. MADRS scores reported as percentage mean change and reported for weeks 1 and 6 only. Mean scores for all time points are shown on a graph (with no measure of precision).
Other bias	Low risk	No other concerns identified

Bauer 2009 (ONYX)

Methods	Parallel group RCT
Participants	Country: Australia, Canada, Europe, South Africa
	Setting: Outpatient care
	N randomised: (n = 329 (67.6%) female (of 487 included in analyses))
	Age: Mean 45.44 years (SD 10.53).
	Inclusion: Patients aged 18 to 65 years with a documented DSM-IV-TR diagnosis of MDD (single episode [296.2x] or recurrent [296.3x]). Diagnoses confirmed by the Mini-International Neuropsychiatric Interview. HAM-D-17 total score > 20 and HAM-D item 1 (depressed mood) score ≥ 2 at enrolment and randomisation.
	Exclusion: Any DSM-IV Axis I disorder other than MDD within 6 months prior to enrolment; any DSM-IV Axis II disorder significantly impacting the patient's current psychiatric status; duration of current MDD episode > 12 months or < 4 weeks from enrolment; substance or alcohol abuse or dependence, as defined by DSM-IV criteria, within 6 months prior to enrolment; any clinically significant medical illness, such as renal or hepatic impairment, or coronary artery disease; conditions that could affect absorption or metabolism of study medication risk of suicide or homicide; HAM-D item 3 score of ≥ 3; or suicide attempt within the past 6 months. Patients requiring psychotherapy (other than supportive thera-

Bauer 2009 (ONYX) *(Continued)*

py), unless psychotherapy had been ongoing for ≥ 3 months before randomisation. Drugs that induce or inhibit the hepatic metabolising cytochrome P450 3A4 enzymes within 2 weeks prior to randomisation. Quetiapine > 25 mg/d for insomnia within 7 days before randomisation, known lack of response following 4 weeks' treatment with quetiapine ≥ 50 mg/d for depression or were receiving quetiapine ≥ 50 mg/d at enrolment

Interventions	Group 1: Augmentation of current antidepressant with quetiapine XR (150 mg/d) for six weeks
	Group 2: Augmentation of current antidepressant with quetiapine XR (300 mg/d) for six weeks
	Group 3: Augmentation of current antidepressant with placebo for six weeks
Outcomes	Post-treatment assessment (6 weeks):
	1. Depressive symptoms, continuous (MADRS, HAM-D)
	2. Dropouts
	3. Response, dichotomous (≥ 50% reduction in MADRS total score from randomisation)
	4. Remission, dichotomous (MADRAS total score ≤ 8)
	5. Quality of life, continuous (Q-LES-Q-SF)
	6. Adverse events
Definition of TRD	Inadequate response during the current episode to amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine given for ≥ 6 weeks at adequate doses (minimum effective dose according to label and including at least 1 dose increase as permitted by label)
Notes	Funding: Study funded by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no information given about how the randomisation sequence was generated. "eligible patients … were randomly assigned (1:1:1 ratio) to receive 6 weeks of double-blind treatment with 1 of 3 treatment regimens".
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to enable a judgment ''eligible patients … were randomly assigned ..''.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind and placebo given to control group so unlikely that either participants or study personnel would have been aware of treatment allocation. "This was a 6-week, randomized, double-blind, parallel-group, placebo-controlled, phase III, double-dummy study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specifically stated that outcome assessors were blind to treatment allocation but study described as double-blind and interventions that were identical in appearance."'This was a 6-week, randomized, double-blind, parallel-group, placebo-controlled, phase III, double-dummy study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF used to account for missing data. MITT analysis carried out. Six randomised participants could not be included in it. Missing data balanced across groups. "Efficacy analyses were based on the MITT [modified intention to treat] population; a last-observation-carried-forward (LOCF) approach was used for missing data … modified intent-to-treat (MITT) population (all patients assigned to randomized treatment who took study medication and who

Bauer 2009 (ONYX) *(Continued)*

		had a MADRS assessment at randomization and at least 1 valid MADRS assessment after randomization)."
Selective reporting (reporting bias)	Unclear risk	Very limited information in the protocol about which outcomes will be assessed but all those mentioned were reported in the paper. Additional outcomes reported that did not appear in the protocol (e.g. adverse events)
Other bias	Low risk	No other concerns identified

Dunner 2007

Methods	Parallel group RCT
Participants	<u>Country:</u> US <u>Setting:</u> Outpatients <u>N randomised:</u> 64 (n = 31 (50.8%) female (of 61 included in analyses)) <u>Age:</u> Mean 44 years (SD 11) <u>Inclusion:</u> Adult outpatients aged 21 to 65 years meeting DSM-IV criteria for MDD and MADRS total score ≥ 20 <u>Exclusion:</u> Current DSM-IV diagnosis of any psychotic disorder, post-traumatic stress disorder, panic disorder, or obsessive-compulsive disorder; DSM-IV substance abuse or dependence disorder in the past 3 months; history of treatment with an atypical antipsychotic agent; treatment with fluoxetine, a monoamine oxidase inhibitor, or electroconvulsive therapy during the 6 weeks prior to study entry; any clinically significant abnormality on electrocardiogram (ECG); current therapy with medications known to prolong the corrected QT interval; any acute or unstable medical illness; pregnancy or breast feeding
Interventions	Group 1: Augmentation of sertraline with ziprasidone (160 mg) for eight weeks Group 2: Augmentation of sertraline with ziprasidone (80 mg) for eight weeks Group 3: Sertraline for eight weeks
Outcomes	Post-treatment assessment (8 weeks): 1. Depressive symptoms, continuous (MADRS, HAM-D) 2. Dropouts 3. Response, dichotomous (≥ 50% decrease from baseline MADRS score) 4. Remission, dichotomous (MADRS score ≤ 10) 5. Adverse events
Definition of TRD	Nonresponse to at least 1 course of treatment of at least 4 weeks' duration with a clinically appropriate dose of an SSRI or non-SSRI antidepressant. Also confirmed prospectively by a failure to achieve at least a 30% decrease in MADRS score and a CGI-S score ≥ 4 following a 6-week open-label sertraline (100 to 200 mg/d) treatment period
Notes	Funding: Study funded by Pfizer Inc

Risk of bias

Bias	Authors' judgement	Support for judgement

Dunner 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as randomised but no information given about how the randomisation sequence was generated. "Subjects who continued to meet TRD criteria at the conclusion of the 6-week sertraline lead-in period were randomly assigned, in a 1:1:1 ratio".
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make a judgment. "Subjects who continued to meet TRD criteria at the conclusion of the 6-week sertraline lead-in period were randomly assigned, in a 1:1:1 ratio".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial so likely that participants and those delivering the intervention knew their treatment allocation. "After completion of the 6-week lead-in study, nonresponders were randomized to open-label treatment with 8 weeks of …"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to participants' treatment assignment. ''The clinician who rated efficacy was blind to the subject's treatment assignment, and, whenever possible, the rater who conducted a subject's baseline assessments rated that subject at end point."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three randomised participants discontinued prior to taking the study drug and were not included in the analyses. LOCF used to account for missing data for the remaining participants. Minor discrepancy between the text and the table with regards to numbers of participants (text stated 61 but table reported data for 60 participants)
Selective reporting (reporting bias)	Unclear risk	No study protocol available. All outcomes detailed in the methods are reported in the study results.
Other bias	Low risk	No other concerns identified

Durgam 2016

Methods	Parallel group RCT
Participants	Country: USA, Estonia, Finland, Slovakia, Sweden, Ukraine
	Setting: Outpatients
	N randomised: 819 (n = 578 (71.2%) female (of 812 included in the safety population))
	Age: 45.7 years (mean 11.6)
	Inclusion: Outpatients, aged 18-65 years, meeting DSM-IV-TR criteria for MDD without psychotic features and had a current depressive episode (duration ≥ 8 weeks to ≤ 24 months). MADRS total score ≥ 22, BMI between 18 and 40, normal results from physical examinations, laboratory tests and electrocardiogram or abnormal results that were not considered clinically significant
	Exclusion: Principal Axis I disorder other than MDD, or any Axis I disorder other than MDD that was the primary focus of treatment within 6 months of screening; and Axis II disorder that might interfere with participation and judged by the investigator; alcohol/substance abuse or dependence within 6 months of screening; or lifetime history of depressive episodes with psychotic or catatonic features, bipolar disorder, schizophrenia or other psychotic disorder, panic disorder, obsessive-compulsive disorder, anorexia or bulimia, and dementia or other cognitive disorder, suicide risk. Refractory depression (inadequate response ≥ 3 antidepressants at sufficient dosages and duration for the current episode); antidepressant augmentation with any medication within 1 week of baseline (up to 4 weeks for some medications) or 5 half-lives of the medication concomitant use of antipsychotics, anxiolytics, or stimulants; or psychotherapy for depression within 3 months of screening.

Durgam 2016 *(Continued)*

Interventions	Group 1: Augmentation of current antidepressant with cariprazine (1 mg/d to 2 mg/d) for eight weeks
	Group 2: Augmentation of current antidepressant with cariprazine (2 mg/d to 4.5 mg/d) for eight weeks
	Group 3: Augmentation of current antidepressant with placebo for eight weeks
Outcomes	Post-treatment assessment (8 weeks):
	1. Depressive symptoms, continuous (MADRS)
	2. Dropouts
	3. Response, dichotomous (≥ 50% decrease from baseline MADRS score)
	4. Remission, dichotomous (MADRS score ≤ 10)
	5. Adverse events
Definition of TRD	Ongoing inadequate response during the current episode to antidepressant treatment for ≥ 6 weeks at recommended doses per label guidelines
Notes	Funding: Supported by funding from Forest Laboratories, LLC (Jersey City, New Jersey), an Allergan affiliate and Gedeon Richter Plc (Budapest, Hungary)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated by web based software. "Patient identification and randomization codes were generated by an interactive voice/web system".
Allocation concealment (selection bias)	Low risk	Centralised allocation using a web-based system. "Patient identification and randomization codes were generated by an interactive voice/web system, and study medication was identical in appearance".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-administered. Study participants reported to be blind to treatment allocation. "Patients and study staff were blinded throughout treatment … and study medication was identical in appearance. Breaking the blind resulted in discontinuation from the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo-administered. Study staff reported to be blind to treatment allocation. "Patients and study staff were blinded throughout treatment … and study medication was identical in appearance. Breaking the blind resulted in discontinuation from the study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT population included all those with at least one post-baseline assessment. LOCF used. 11 randomised participants not included in the ITT population. 1 and 5 from the cariprazine 1 mg/d to 2 mg/d and 2 mg/d to 4.5 mg/d groups, and 5 from the placebo group. No significant imbalance between arms. "The safety population included all patients who received ≥ 1 dose of double-blind study drug. The intent-to-treat population included all patients in the safety population who had ≥ 1 post-baseline MADRS total score assessment." "The safety population included 812 patients 4 of whom (2 each for placebo and cariprazine 2 mg/d to 4.5 mg/d) did not have a post-baseline MADRS assessment and were excluded from efficacy analyses".
Selective reporting (reporting bias)	Unclear risk	Very limited information in the protocol about which outcomes would be assessed but all those mentioned were reported in the paper. Additional outcomes reported that did not appear in the protocol (e.g. adverse events, response/remission)

Durgam 2016 *(Continued)*

Other bias	Low risk	No other concerns identified

El-Khalili 2010 (PEARL)

Methods	Parallel group RCT
Participants	<u>Country:</u> US
	<u>Setting:</u> Outpatients
	<u>N randomised:</u> 446 (n = 313 (72.5%) female (of 432 included in the analyses))
	<u>Age:</u> Mean 44.5 years (SD 12.8)
	<u>Inclusion:</u> Patients aged 18 to 65 years with a documented DSM-IV-TR diagnosis of MDD (single episode [296.2x] or recurrent [296.3x], confirmed by the Mini-International Neuropsychiatric Interview). HAM-D-17 total score > 20 and HAM-D item 1 (depressed mood) score ≥ 2 at enrolment and randomisation
	<u>Exclusion:</u> Any DSM-IV Axis I disorder other than MDD within 6 months prior to enrolment; any DSM-IV Axis II disorder significantly impacting the patient's current psychiatric status; duration of current MDD episode > 12 months or < 4 weeks from enrolment; history of substance or alcohol abuse or dependence, as defined by DSM-IV criteria, within 6 months prior to enrolment; clinically significant medical illness; risk of suicide or homicide; HAM-D item 3 score of ≥ 3; or suicide attempt within the past 6 months; requiring psychotherapy (other than supportive therapy), unless psychotherapy had been ongoing for ≥ 3 months before randomisation
Interventions	Group 1: Augmentation of current antidepressant with quetiapine XR (150 mg/d) for six weeks
	Group 2: Augmentation of current antidepressant with quetiapine XR (300 mg/d) for six weeks
	Group 3: Augmentation of current antidepressant with placebo for six weeks
Outcomes	Post-treatment assessment (6 weeks):
	1. Depressive symptoms, continuous (MADRS, HAM-D)
	2. Dropouts
	3. Response, dichotomous (≥ 50% reduction in MADRS total score from randomisation)
	4. Remission, dichotomous (MADRS total score <= 8)
	5. Quality of life, continuous (Q-LES-Q-SF)
	6. Adverse events
Definition of TRD	Inadequate response during the current episode to amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine given for ≥ 6 weeks at adequate doses (minimum effective dose according to label and including at least 1 dose increase as permitted by label)
Notes	Funding: Study funded by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement

El-Khalili 2010 (PEARL) *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence used. "Patients were randomized (in a 1:1:1 ratio) in a non-centre-specific manner using a computer-based system".
Allocation concealment (selection bias)	Low risk	Sequence generation done by computer so would not have been possible to anticipate. Study treatments administered in identical packaging. "Patients were randomized (in a 1:1:1 ratio) in a non-centre-specific manner using a computer-based system … Quetiapine XR 50 mg and 300 mg tablets were identical in appearance, smell, and taste to their respective placebo tablets".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind. Identical interventions administered to participants. Not specifically stated that study personnel were blind to treatment but likely due to the use of interventions that were identical in appearance. "Quetiapine XR 50 mg and 300 mg tablets were identical in appearance, smell, and taste to their respective placebo tablets".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study described as double-blind. Not specifically stated that outcome assessors were blind to treatment but likely due to the use of interventions that were identical in appearance. "Quetiapine XR 50 mg and 300 mg tablets were identical in appearance, smell, and taste to their respective placebo tablets".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF used to account for missing data for all but 14 participants. Slightly larger number missing from the quetiapine 300 mg/d group. "The modified intent-to-treat (MITT) population (randomized patients who received study drug, and had randomization and ≥ 1 post-randomization MADRS total scores) was used for analysis of primary and secondary variables. For all efficacy analyses, missing data were handled using a last observation carried forward (LOCF) approach. 446 patients were randomised …. and 432 were analysed for efficacy (MITT population) after 13 patients were excluded due to missing/invalid randomization or post-randomization MADRS scores."
Selective reporting (reporting bias)	Low risk	All outcomes listed in the protocol were reported. Missing standard deviations for mean change from baseline in depression symptoms (but these could be calculated from other information provided)
Other bias	Low risk	No other concerns identified

Ferreri 2001

Methods	Parallel group RCT
Participants	<u>Country:</u> France <u>Setting:</u> Inpatients and outpatients <u>N randomised:</u> 104 <u>Age:</u> Mean 46.6 years (SD 12.6) <u>Inclusion:</u> Diagnosis of major depression according to DSM-III-R and have scores ≥ 25 on the Hamilton Depression Rating Scale 17 items (HAM-D) and scores ≥ 28 on the HARD diagram scale [Mood-Anxiety-Retardation-Danger (Humeur-Angoisse-Ralentissement-Danger)], after at least 6 weeks of treatment with 20 mg/day of fluoxetine. Both in- and outpatients were included. <u>Exclusion:</u> Pregnant or lactating women, women without contraception at childbearing age, somatic disease condition that could interfere with everyday life activities, psychiatric disorders with psychotic features (with the exception of psychotic mood disorder), unreliable patients, in particular drug and alcohol abuse and dependence, treatment with psychotropic drugs other than fluoxetine, with the ex-

Ferreri 2001 *(Continued)*

	ception of benzodiazepines if benzodiazepine equivalent dosage was equal to or lower than 15 mg/day of diazepam
Interventions	Group 1: Augmentation of current antidepressant (fluoxetine 20 mg/d) with mianserin (60 mg/d) for six weeks
	Group 2: Switched treatment to Mianserin (60 mg/d) given with placebo for six weeks
	Group 3: Augmentation of current antidepressant (fluoxetine 20 mg/d) with placebo for six weeks
Outcomes	Post-treatment assessment (6 weeks):
	1. Depressive symptoms, continuous (HAM-D-17)
	2. Dropouts
	3. Response, dichotomous (≥ 50% reduction in HAM-D score from baseline)
	4. Remission, dichotomous (HAM-D total score ≤ 8)
	5. Adverse events
Definition of TRD	Inadequate response after at least 6 weeks of treatment with 20 mg/d of fluoxetine
Notes	Funding: Study funded by Organon Pharmaceuticals, France

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Limited information about how sequence was generated but likely random. "Patients were randomized according to a randomization schedule by blocks of four up to 120."
Allocation concealment (selection bias)	Unclear risk	No information about how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind and placebo given to control group so unlikely that either participants or study personnel would have been aware of treatment allocation. "Placebo of fluoxetine was provided in the form of identical capsules and, similarly, placebo of mianserin and mianserin were also indistinguishable."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specifically stated that outcome assessors were blind to treatment allocation but study described as double-blind and interventions were identical in appearance. "Placebo of fluoxetine was provided in the form of identical capsules and, similarly, placebo of mianserin and mianserin were also indistinguishable."
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT population included all participants who had taken at least one dose of the study drug. LOCF used to account for missing data. "For missing data the method of Last Observation Carried Forward was used … The intent-to-treat population consisted of all randomized patients who took at least one dose of a study drug … One patient was lost at day 0; thus, the intent-to-treat population consisted of 103 patients treated."
Selective reporting (reporting bias)	Unclear risk	No study protocol available. All outcomes detailed in the methods were reported in the study results.
Other bias	Low risk	No other concerns identified

Kessler 2018

Methods	Parallel group RCT
Participants	<u>Country:</u> UK
	<u>Setting:</u> Primary care
	<u>N randomised:</u> 480
	<u>Age:</u> 50.15 years (SD 13.16)
	<u>Inclusion:</u> Aged 18-75 years. Treated for depression with any of the following SSRI or SNRI antidepressants for at least 6 weeks at recommended (British National Formulary, BNF) doses: fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine, paroxetine, duloxetine or venlafaxine; scored 14 or more on the Beck Depression Inventory (BDI) and have adhered to their medication and meet ICD-10 criteria for depression (assessed using the Computerised Interview Schedule – Revised version (CIS-R).
	<u>Exclusion:</u> Currently taking combined or augmented antidepressant treatment, having their medication managed by a psychiatrist, dementia (formal diagnosis), bipolar disorder, psychosis or alcohol or substance abuse/dependence, pregnant, planning a pregnancy or breastfeeding, unable to complete the study questionnaires, previous adverse reaction to mirtazapine, currently being treated with a monoamine oxidase inhibitor (MAOI), including moclobemide, or with other medical contraindications to mirtazapine
Interventions	Group 1: Augmentation of current antidepressant with mirtazapine (30 mg/d) for up to 52 weeks
	Group 2: Augmentation of current antidepressant with placebo for up to 52 weeks
Outcomes	Assessed at 12, 24 and 52 weeks (unless specified):
	1. Depressive symptoms, continuous (BDI-II, PHQ-9)
	2. Dropouts
	3. Response, dichotomous (≥ 50% reduction in BDI-II total score from baseline)
	4. Remission, dichotomous (BDI-II < 10)
	5. Social functioning (SF-12 aggregate mental functioning, SF-12 aggregate physical functioning)
	6. Quality of life, continuous (EQ-5D-5L)
	7. Economic outcomes (health and social care use, costs to patients/carers, time off work)
	8. Adverse events (12 and 52 weeks)
Definition of TRD	Inadequate response to fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine, paroxetine, duloxetine or venlafaxine given for at least six weeks at BNF recommended dose and adherent to antidepressant treatment
Notes	Funding: National Institute for Health Research (NIHR) Health Technology Assessment programme, UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence generated by a computer. "Participants were randomised using the automated randomisation service provided by the Bristol Randomised Trials Collaboration (BRTC). Randomisation was carried out by means of a computer-generated code to ensure concealment of allocation."

Kessler 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	Centralised allocation provided by an independent organisation using a computer-generated code. "Participants were randomised using the automated randomisation service provided by the Bristol Randomised Trials Collaboration (BRTC). Randomisation was carried out by means of a computer-generated code to ensure concealment of allocation".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-administered. Study participants reported to be blind to treatment allocation. "Participants were randomly assigned to one of two treatments: (1) 1 × 15 mg encapsulated mirtazapine tablet daily for 2 weeks followed by 2 × 15 mg encapsulated mirtazapine tablets for up to 50 weeks or (2) identical placebo tablets…. Participants, clinicians, outcome assessors and the research team were blinded to allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo-administered. Study staff reported to be blind to treatment allocation. "Participants were randomly assigned to one of two treatments: (1) 1 × 15 mg encapsulated mirtazapine tablet daily for 2 weeks followed by 2 × 15 mg encapsulated mirtazapine tablets for up to 50 weeks or (2) identical placebo tablets…. Participants, clinicians, outcome assessors and the research team were blinded to allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analyses carried out. "The primary comparative analyses of clinical effectiveness were conducted according to the principle of intention to treat (ITT) …. A number of sensitivity analyses were conducted to assess the impact of missing primary outcome data on the main findings."
Selective reporting (reporting bias)	Unclear risk	PHQ-9 measured at 12, 24 and 52 weeks but only data for 12 weeks was reported.
Other bias	Low risk	No other concerns identified

McIntyre 2007

Methods	Parallel group RCT
Participants	<u>Country:</u> Canada <u>Setting:</u> Outpatient <u>N randomised:</u> 58 <u>Age:</u> 44.5 years (SD 11) <u>Inclusion:</u> Adults (18–65 years of age) with a DSM-IV diagnosis of major depression; a 17-item Hamilton Depression Scale (HAM-D) score of ≥ 18; a Clinical Global Impression of Severity (CGI-S) score of ≥ 4 (moderately ill); and a 14-item Hamilton Anxiety Scale (HAM-A) score of ≥ 14. These criteria had to be met both at screening and baseline. In addition, all patients had been treated for their current episode of major depressive disorder with a single SSRI/venlafaxine tablet at a therapeutic dose for at least 6 weeks. <u>Exclusion:</u> Exclusion criteria included: a DSM-IV diagnosis of substance abuse or dependence within 6 months of screening, and patients who received an antipsychotic or benzodiazepine 7 days prior to entering the study, or a potent cytochrome P450 inhibitor or inducer 14 days prior to entering the study. Patients who were pregnant, breastfeeding, or at risk of suicide in the investigator's opinion were also excluded.
Interventions	Group 1: Augmentation of SSRI/venlafaxine with quetiapine (mean 182 mg/d) for 8 weeks

McIntyre 2007 *(Continued)*

	Group 2: Augmentation of SSRI/venlafaxine with placebo for 8 weeks
Outcomes	Post-treatment assessment (8 weeks):
	1. Depressive symptoms, continuous (HAM-D-17)
	2. Dropouts
	3. Response, dichotomous (≥ 50% reduction in HAM-D score from baseline)
	4. Remission, dichotomous (HAM-D total score ≤ 7)
	5. Adverse events
Definition of TRD	Inadequate response to at least six weeks of a single SSRI or venlafaxine at an acceptable therapeutic dose
Notes	Funding: Study funded by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no information given about how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information about how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind and placebo given to control group so unlikely that either participants or study personnel would have been aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specifically stated that outcome assessors were blind to treatment allocation but study described as double-blind and placebo given to control group
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses. "The intent-to-treat (ITT) population (any randomized patient who received at least one dose of study medication) was used in all statistical analyses... LOCF analyses are reported for the above measures".
Selective reporting (reporting bias)	Unclear risk	Study protocol did not provide details of the outcomes to be assessed. All outcomes and time points described in the methods were reported in the results.
Other bias	Low risk	No other concerns identified

Papakostas 2015

Methods	Parallel group RCT
Participants	<u>Country:</u> US
	<u>Setting:</u> Outpatient
	<u>N randomised:</u> 139 (n = 98 (70.5%) female))

Papakostas 2015 *(Continued)*

Age: Mean 44.5 years (SD 12.8)

Inclusion: men and women 18–65 years of age with a primary diagnosis of current major depressive disorder according to DSM-IV criteria and confirmed with the Structured Clinical Interview for DSM-IV and a score >= 10 on the 16-item Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR) at screening

Exclusion: Patients were considered ineligible for participation in the study if they were pregnant, breastfeeding, or lactating or if they were women of childbearing potential who were not using a medically accepted means of contraception; high risk of suicide or homicide or other reasons the investigator might deem a patient unsafe to enrol in the study; an unstable medical illness or an uncontrolled seizure disorder; a history of multiple adverse reactions or an allergy to the study drug; and a DSM-IV diagnosis of a substance use disorder (including alcohol) active within the past 6 months, bipolar disorder (current or past), or any psychotic disorder or psychotic symptoms (current or past). Patients who had received an adequate trial of escitalopram during the current major depressive episode (prior to study entry) or any lifetime trial of ziprasidone were also excluded, as were patients who had received an investigational psychotropic drug within 3 months of their screening visit. In addition, patients who had failed to benefit after more than three antidepressant trials of adequate dose and duration during the current major depressive episode were excluded.

Interventions	Group 1: Augmentation of escitalopram with ziprasidone (40 mg/d to 160 mg/d) for eight weeks
	Group 2: Augmentation of escitalopram with placebo for eight weeks
Outcomes	Post-treatment assessment (8 weeks):
	1. Depressive symptoms, continuous (HAM-D, QIDS-SR)
	2. Dropouts
	3. Response, dichotomous (≥ 50% reduction in MADRS total score from randomisation; ≥ 50% reduction in QIDS-SR score from randomisation)
	4. Remission, dichotomous (HAM-D score ≤ 7; QIDS-SR score ≤ 5)
	5. Adverse events
Definition of TRD	Confirmed prospectively by failure to respond to an 8-week open-label trial of escitalopram (10 mg/d to 30 mg/d). Continuing to meet DSM-IV criteria for MDD and had a QIDS-SR score ≥10
Notes	Funding: Supported by a National Institute of Mental Health (NIMH) grant, Pfizer (which supplied blinded ziprasidone and placebo pills), and Forest Laboratories (which supplied escitalopram)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence. "Patients were randomly assigned to receive adjunctive ziprasidone or placebo, in a 1:1 ratio, throughout the remainder of the study. A central randomization center used a computer-generated list of random numbers to allocate treatments."
Allocation concealment (selection bias)	Low risk	Centralised allocation, adequately concealed. "A central randomization center used a computer-generated list of random numbers to allocate treatments. None of the investigators, study clinicians, clinical raters, or participants at any of the study sites had access to the randomization list".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and study personnel were blind to treatment allocation due to the use of a placebo. "Ziprasidone (20 mg per capsule) and placebo were in capsule form and identical in appearance. Independent pharmacists prepared ziprasidone and placebo capsules. Study drugs were prepackaged in bottles

Papakostas 2015 *(Continued)*

and consecutively numbered for each patient according to the randomization schedule."

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were kept blind to treatment allocation. "None of the investigators, study clinicians, clinical raters, or participants at any of the study sites had access to the randomization list. Ziprasidone (20 mg per capsule) and placebo were in capsule form and identical in appearance. Independent pharmacists prepared ziprasidone and placebo capsules. Study drugs were prepackaged in bottles and consecutively numbered for each patient according to the randomization schedule."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	37 participants reported as having dropped out. ITT analyses carried out (including all 139 randomised participants). No information about how any missing data was handled. "All analyses used the intent-to-treat data set (including all randomized patients)."
Selective reporting (reporting bias)	Unclear risk	All outcomes listed in the clinical trial registry entry were reported in the paper. Authors reported carrying out additional analyses; they reported an additional measure QIDS-SR for secondary outcomes compared with what was listed in the protocol.
Other bias	Low risk	No other concerns identified

Shelton 2001

Methods	Parallel group RCT
Participants	Country: US
	Setting: Outpatients
	N randomised: 28 (8 of whom randomised to a treatment arm not included in this review) (n = 21 (75%) female (of 28 included in whole study))
	Age: Mean 42 years (SD 11)
	Inclusion: Outpatients who met DSM-IV criteria for recurrent major depression without psychotic features and were resistant to conventional antidepressant pharmacotherapy
	Exclusion: History of psychosis, dysthymic disorder, or bipolar disorder
Interventions	Group 1: Augmentation of fluoxetine with olanzapine (5 mg/d to 20 mg/d) for eight weeks
	Group 2: Augmentation of fluoxetine with placebo for eight weeks
	(Other arms not relevant to this review: olanzapine (5 mg/d to 20 mg/d) plus placebo for eight weeks)
Outcomes	Post-treatment assessment (8 weeks):
	1. Depressive symptoms, continuous (MADRS, HAM-D)
	2. Dropouts
	3. Response, dichotomous (≥ 50% reduction in MADRS total score from randomisation)
	4. Adverse events
Definition of TRD	History of failure to respond to antidepressants of two different classes, one of which was not an SSRI, after at least 4 weeks of therapy at an acceptable therapeutic dose. Failure to respond was confirmed

Shelton 2001 *(Continued)*

prospectively during a six-week screening period in which fluoxetine (20 mg/d to 60 mg/d) was given. At entry, patients were required to score ≥ 20 on the 21-item Hamilton Depression Rating Scale and still meet DSM-IV criteria (confirmed by study author).

Notes	Funding: Supported in part by Eli Lilly and Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated randomised but sequence generation not described. "Non-responders to fluoxetine were randomly assigned in a 1:1:1 ratio".
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to enable a judgment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind. Placebo used in the arm that did not receive augmentation with antipsychotic. "The second phase was an 8-week double-blind trial in which non-responders to fluoxetine were randomly assigned in a 1:1:1 ratio to receive … fluoxetine plus placebo ('fluoxetine') or olanzapine plus fluoxetine ('combination')".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind. Placebo used in the arm that did not receive augmentation with antipsychotic
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were analysed in the group to which they were randomised with LOCF used to account for missing data. 'Analyses were performed on an intent-to-treat basis…. The last observation carried forward was used to analyse weekly visits".
Selective reporting (reporting bias)	High risk	HAM-D reported to be the primary outcome in the published paper. Dichotomous data not given for HAM-D but were for MADRS. FDA documentation suggested that MADRS was a post hoc analysis and that the 'response' outcome was originally based on reduction in HAM-D score.
Other bias	Low risk	No other concerns identified

BDI and BDI-II: Beck Depression Inventory
BMI: body mass index
BNF: British National Formulary
BRTC: Bristol Randomised Trials Collaboration
CGI-S: Clinical Global Impressions - Severity
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders (version 3, revised).
DSM-IV and DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders (version 4, text revision).
ECG: electrocardiogram
EQ-5D-5L: EuroQoL 5 level version
FDA: Food and Drug Administration
HAM-A: Hamilton Anxiety Rating Scale
HAM-D and HAM-D-17: Hamilton Depression Rating Scale
HARD: Humeur-Angoisse-Ralentissement-Danger diagramme [Mood-Anxiety-Retardation-Danger depression scale]
ICD-10: International Classification of Diseases
ITT: intention-to-treat
LOCF: last observation carried forward
MADRS: Montgomery Asberg Depression Rating Scale
MAOI: monoamine oxidase inhibitor
MDD: major depressive disorder

MITT: modified intention-to treat

PHQ-9: Patient Health Questionnaire

QIDS-SR: Quick Inventory of Depressive Symptomatology - Self Report

Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form

RCT: randomised controlled trial

SD: standard deviation

SF-12: Short-Form

SNRI: serotonin-norepinephrine reuptake inhibitor

SSRI: selective serotonin reuptake inhibitor

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aarnell 2002	Not TRD (no duration criteria defined for prior antidepressant treatment)
ADAPT-A 2012	Diagnostic criteria not applied at point of randomisation
Baca 2005	Not TRD (included participants that were intolerant to AD)
Barbee 2011	Diagnostic criteria not applied at point of randomisation
Bares 2013	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy
Bauer 2013 (RUBY)	Compared switching to an antipsychotic (not a treatment strategy covered by the review) with augmenting with quetiapine or augmenting with lithium. No control comparison of continuing on initial antidepressant monotherapy
Bauer 2018	Diagnostic criteria not applied at point of randomisation
Benkert 1997	Not TRD (prior antidepressant therapy for 3 weeks only). Not MDD (included patients with minor depression)
Berman 2007	Diagnostic criteria not applied at point of randomisation
Berman 2009	Diagnostic criteria not applied at point of randomisation
Birkenhager 2004	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy.
Bose 2012	Compared dose increase with switch. No control comparison of continuing on initial antidepressant monotherapy
Brecht 2011	Not TRD (MDD only were randomised, non-responders during trial all got a dose increase)
Chaput 2004	Not a comparison of interest. Compared switch to cognitive behavioural therapy plus quetiapine augmentation to CBT plus placebo. No control comparison of continuing on initial antidepressant monotherapy
Cheon 2017	Compared two augmentation strategies. No control comparison of continuing on initial antidepressant monotherapy
Cipriani 2013	Not TRD (dose and duration of prior antidepressant treatment not specified)
Corya 2006	Diagnostic criteria not applied at point of randomisation

Study	Reason for exclusion
Doree 2007	Compared augmentation with lithium with augmentation with quetiapine. No control comparison of continuing on initial antidepressant monotherapy
e-Therapeutics 2013	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy.
Earley 2018	Diagnostic criteria not applied at point of randomisation
Edwards 1998	Not TRD (dose and duration of prior antidepressant not defined)
Fang 2010	Diagnostic criteria not applied at point of randomisation
Fang 2011	Not TRD (medical history-based definition of TRD, no dose or duration for prior AD defined)
Fava 1994	Three-arm trial that compared increasing dose of current antidepressant with two augmentation strategies (desipramine or lithium). No control comparison of continuing on initial antidepressant monotherapy
Fava 2001	Not TRD (included patients who were intolerant as well as resistant)
Fava 2002	Three-arm trial that compared increasing dose of current antidepressant with two augmentation strategies (desipramine or lithium). No control comparison of continuing on initial antidepressant monotherapy
Fava 2018	Diagnostic criteria not applied at point of randomisation
Fornaro 2014	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy
Franco-Chaves 2013	Compared two switching strategies and combination treatment. No control comparison of continuing on initial antidepressant monotherapy
Furukawa 2011	Not TRD (3 weeks duration of prior AD treatment)
Garry 1963	Not TRD (all treatments for depression were discontinued for two weeks prior to randomisation into the trial)
Gonul 1999	Compared two augmentation strategies. No control comparison of continuing on initial antidepressant monotherapy
Grant 2017	Compared dose escalation with a switching strategy. No control comparison of continuing on initial antidepressant monotherapy
Han 2015	Compared augmenting current antidepressant treatment with an antipsychotic and switching to another antidepressant. No control comparison of continuing on initial antidepressant monotherapy
Hides 2006	Not TRD (participants had major depression which had not responded to CBT, participants had no prior antidepressant treatment)
Hobart 2018	Diagnostic criteria not applied at point of randomisation
Horikoshi 2017	Compared two augmentation strategies. No control comparison of continuing on initial antidepressant monotherapy
Joffe 1993	Diagnostic criteria not applied at point of randomisation

Study	Reason for exclusion
Joffe 2006	Not TRD (range of doses reported for previous antidepressant use included subtherapeutic dose)
Kamijima 2013	Diagnostic criteria not applied at point of randomisation
Kamijima 2018	Diagnostic criteria not applied at point of randomisation
Keitner 2009	Not TRD (only three weeks of prior antidepressant treatment)
Kennedy 2003	Compared cognitive therapy and lithium augmentation of current antidepressant treatment. No control comparison of continuing on initial antidepressant monotherapy
Kocsis 1988	Not TRD (participants had chronic depression and had failed to respond to two weeks treatment with imipramine)
Lejoyeux 2015	Not a comparison of interest. Compared three tapering strategies. No control comparison of continuing on initial antidepressant monotherapy
Lenox-Smith 2008	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy
Lenze 2015 (IRL GREY)	Diagnostic criteria not applied at point of randomisation
Li 2006	Compared augmentation of current antidepressant therapy with lithium and switching to another antidepressant. No control comparison of continuing on initial antidepressant monotherapy
Li 2013	Compared two switching strategies. No control comparison of continuing on antidepressant monotherapy
Licht 2002	Diagnostic criteria not applied at point of randomisation
Maes 1996	Not TRD at the point of randomisation. Participants who had not responded to previous antidepressant medication underwent a ten-day washout followed by a week of trazadone. Participants who then had HAM-D ≥ 14 were randomised to augment with pindolol, fluoxetine or placebo.
Maes 1999	Not TRD (no dose or duration criteria defined)
Marcus 2008	Diagnostic criteria not applied at point of randomisation
Marwood 2017	Compared two augmentation strategies. No control comparison of continuing on initial antidepressant monotherapy
Mattingly 2006	Not TRD (dosage criteria for prior antidepressant treatment not defined)
Medhus 1994	Not TRD (no dosage criteria defined, "presumed adequate dosage")
Mohamed 2017 (VAST-D)	Compared switching to another antidepressant with augmenting with an antidepressant. No control comparison of continuing on initial antidepressant monotherapy
Montgomery 2014 (REVIVE)	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy
Moreno 1997	Not all participants had received an antidepressant at the manufacturer's minimum recommended therapeutic dose.
Nakajima 2011	Not TRD (run-in phase with antidepressant was two weeks duration at which point non-responders were randomised)

Study	Reason for exclusion
NCT00273624	Study terminated early. No results available. TRD defined as two courses of antidepressants from different classes for at least three weeks at an adequate dose
NCT00296517	Not a comparison of interest. Nonresponders to paroxetine had their dose tapered down and augmented with either bupropion or placebo.
NCT01052077	Diagnostic criteria not applied at point of randomisation
NCT02272517	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy
NCT02960763	Compared an augmentation strategy with switching to another antidepressant. No control comparison of continuing on initial antidepressant monotherapy
NCT02977299	Compared augmentation with aripiprazole with augmentation with rTMS. No control comparison of continuing on initial antidepressant monotherapy
Nierenberg 2003	Diagnostic criteria not applied at point of randomisation
Nolen 1993	Not TRD (only three weeks of prior antidepressant treatment)
Perahia 2008	Compared two switching strategies (immediate switch versus immediate switch with tapering down of original antidepressant). No control comparison of continuing on initial antidepressant monotherapy
Perez 1999	TRD defined as failure to respond to a minimum of six weeks of antidepressant treatment, however dose was only required to have been fixed at a therapeutic level for the final two weeks.
Petrescu 2014	Compared dose escalation with switching to another antidepressant. No control comparison of continuing on initial antidepressant monotherapy
Poirier 1999	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy
Rapaport 2006 (ARISe-RD)	Diagnostic criteria not applied at point of randomisation
Ravindran 2006	Compared adjunctive olanzapine with adjunctive risperidone. No control comparison of continuing on initial antidepressant monotherapy
Rele 2015	Compared three switching strategies. No control comparison of continuing on initial antidepressant monotherapy
Romera 2010	Compared two switching strategies (early or delayed switch). No control comparison of continuing on initial antidepressant monotherapy
Ruhe 2009	Diagnostic criteria not applied at point of randomisation
Russell 1995	Not treatment-resistant depression. Participants with chronic depression (with or without dysthymia, 'double depression') were randomised to sertraline or imipramine (i.e. not TRD). In a second part of the study, those who did not respond were crossed over to the other treatment (i.e. not randomised). Responders continued in a maintenance study.
Rybakowski 1999	Compared augmentation with lithium to augmentation with carbamazine. No control comparison of continuing on initial antidepressant monotherapy

Study	Reason for exclusion
Santos 2008	Participants had a history of TRD. Study did not state that treatment resistance had to be in the current episode. TRD defined as failure to respond to a minimum of two antidepressants of different classes at the maximum-tolerated dose for at least six weeks
Schindler 2007	Compared two augmentation strategies. No control comparison of continuing on initial antidepressant monotherapy
Schweizer 1990	TRD defined as failure to respond to fluoxetine 20 mg/day for 3 weeks
Schweizer 2001	TRD defined as failure to respond to three weeks of antidepressant therapy
Shelton 2005a	Compared two augmentation strategies. No control comparison of continuing on initial antidepressant monotherapy
Shelton 2005b	Diagnostic criteria not applied at point of randomisation
Small 1981	Not TRD. Included participants who had received lower than recommended tricyclic antidepressant dose who had been unable to tolerate side effects
Song 2007	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy
Souche 1991	Diagnostic criteria not applied at point of randomisation
Souery 2011	Phase 1: compared two switching strategies (no control group). Phase 2: not randomised
STAR*D 2004	Evaluated a sequence of different treatment options for depression. Participants who failed to respond to treatment were randomised into the next phase of the study. Continuation of current antidepressant therapy was not a treatment option at any phase of the study. There was, therefore, no control comparison of continuing on initial antidepressant monotherapy.
Stein 1993	Not TRD (only three weeks of prior antidepressant treatment)
Sun 2004	Described as 'refractory depression' but participants had not received prior treatment for their depression
Sunderland 1994	Not TRD (patients were drug-free for three weeks before randomisation)
Tanghe 1997	Not TRD (no dose or duration criteria for prior AD treatment)
Thase 2000	Compared switching to mirtazapine with switching to sertraline. No control comparison of continuing on initial antidepressant monotherapy
Thase 2006	Not TRD (included participants intolerant to medication)
Thase 2007	Diagnostic criteria not applied at point of randomisation
Thase 2011	Diagnostic criteria not applied at point of randomisation
Thase 2015 (PYXIS)	Diagnostic criteria not applied at point of randomisation
Thase 2015a (POLARIS)	Diagnostic criteria not applied at point of randomisation
Yang 2005	Compared two switching therapies. No control comparison of continuing on initial antidepressant monotherapy

Study	Reason for exclusion
Yoshimura 2012	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy
Yoshimura 2014	Compared three augmentation strategies. No control comparison of continuing on initial antidepressant monotherapy
Zhao 2003	Compared two switching strategies. No control comparison of continuing on initial antidepressant monotherapy
Zusky 1988	Not TRD. Included participants unable to tolerate manufacturer's recommended dose

AD: Antidepressant
CBT: Cognitive behavioural therapy
MDD: Major depressive disorder
rTMS: Repetitive transcranial magnetic stimulation
TRD: Treatment-resistant depression

Characteristics of studies awaiting assessment *[ordered by study ID]*

Cao 2005

Methods	Randomised controlled trial
Participants	Chinese depression diagnosis. Failure to respond to two antidepressants for at least six weeks
Interventions	1. Venlafaxine 2. Venlafaxine and quetiapine
Outcomes	Measured at 1, 2, 4 and 6 weeks. 1. Depression severity HAM-D 2. Treatment-emergent symptom scales (TESS) 3. Treatment efficacy (dichotomous outcome)
Notes	No information about the dose of prior antidepressants reported and no response received from study authors. Unclear whether there was a control group that continued on current antidepressant therapy

Clunie 2001

Methods	Randomised controlled trial
Participants	Depressed patients (no information about method of diagnosis) who failed to respond to clomipramine
Interventions	1. Phenelzine 2. Moclobemide
Outcomes	Not reported

Clunie 2001 *(Continued)*

Notes	Trial protocol from National Institute for Health Research Research Registry. No publications relating to the study identified. No information about method of diagnosis or duration and dose of prior treatment. Unclear whether there was a control group that continued on current antidepressant therapy. No response from contact person listed.

Euctr-002130-11-Es 2007

Methods	Randomised controlled trial
Participants	Diagnosis of depression according to DSM-IV-TR criteria, failure to respond to SSRI at correct dose for a minimum of 6 weeks, score of >= 14 of HAM-D-17
Interventions	1. Venlafaxine 75 mg to 150 mg 2. Lithium carbonate 400 mg 3. Nortriptyline 25 mg 4. Control group
Outcomes	Primary outcome measure: HAM-D-17
Notes	Trial registry entry. No publications relating to the study identified. Study authors could not be identified to enable requests for further information. Unclear whether interventions were given as monotherapy or in addition to current antidepressant treatment. Details of control condition also unclear

Gulrez 2012

Methods	Randomised controlled trial
Participants	Diagnosis of MDD according to DSM-IV-TR criteria, HAM-D score of >= 16 after 4 weeks of treatment with an SSRI
Interventions	1. Bupropion, starting at 150 mg/d and increasing to 300 mg/d after 1 week, in addition to SSRI 2. Placebo in addition to SSRI
Outcomes	Change in HAM-D and MADRS scores Remission: HAM-D score <= 7 or MADRS score <= 12 Spontaneously reported adverse events
Notes	Dose of previous SSRI treatment could not be determined from the paper and no response received from corresponding study author.

Moica 2018

Methods	Randomised controlled trial
Participants	Major depressive disorder, single or recurrent, without psychotic symptoms and an inadequate response to the antidepressant therapy (the use of minimal doses accepted as effective for a period

Moica 2018 *(Continued)*

	of at least 4 to 6 weeks). At the time of the enrolment, all participants were treated with duloxetine 60 mg per day.
Interventions	1. Current antidepressant treatment (duloxetine 60 mg/d) augmented with quetiapine (150 mg/d)
	2. Continue on duloxetine (60 mg/d) monotherapy
Outcomes	Change in HAM-D score
Notes	Unclear how long participants had been receiving current antidepressant (duloxetine) treatment. Also unclear if/when formal diagnostic criteria applied. No response received from corresponding study author

Zhu 2003

Methods	Randomised controlled trial
Participants	Diagnosis of depression according to CCMD-3 (Chinese Classification of Mental Disorders). Failure to respond to 6 weeks of treatment with an SSRI. HAM-D score >= 18
Interventions	1. Mirtazapine (30 mg/d to 45 mg/d) for 6 weeks
	2. Continue on original antidepressant therapy for 6 weeks
Outcomes	Measured at 1, 2, 4 and 6 weeks
	1. Depression severity (HAM-D)
	2. Treatment-emergent symptom scales (TESS)
Notes	Details of treatment resistance could not be determined. Unable to contact study author

CCMD-3: Chinese Classification of Mental Disorders version 3
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders
HAM-D: Hamilton Depression Rating Scale
HAM-D-17: Hamilton Depression Rating Scale-17
MADRS: Montgomery Asberg Depression Rating Scale
SSRI: selective serotonin reuptake inhibitor
TESS: Treatment Emergent Symptoms Scale

DATA AND ANALYSES

Comparison 1. Switch to mianserin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Depressive symptoms (HAM-D)	1	71	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-5.23, 1.63]
2 Dropouts	1	72	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [0.94, 4.59]

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
3 Response (≥ 50% improvement in HAM-D score)	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.76, 2.27]
4 Remission (HAM-D total score ≤ 8)	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.88, 4.42]

Analysis 1.1. Comparison 1 Switch to mianserin, Outcome 1 Depressive symptoms (HAM-D).

Study or subgroup	Switch to mianserin		Fluoxetine monotherapy		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Ferreri 2001	33	-13.1 (7.3)	38	-11.3 (7.4)		100%	-1.8[-5.23,1.63]
Total ***	33		38			100%	-1.8[-5.23,1.63]

Heterogeneity: Not applicable

Test for overall effect: Z=1.03(P=0.3)

Favours mianserin switch   -10 -5 0 5 10   Favours control
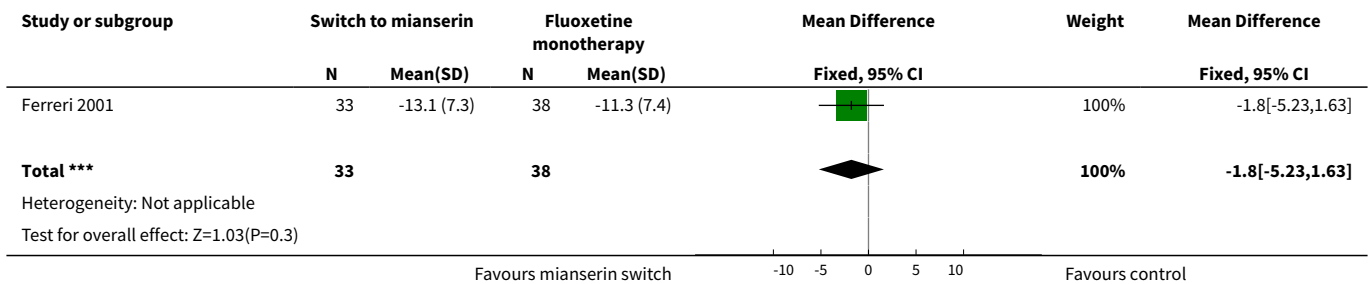
Analysis 1.2.   Comparison 1 Switch to mianserin, Outcome 2 Dropouts.

Study or subgroup	Switch to mianserin	Fluoxetine monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Ferreri 2001	13/34	7/38		100%	2.08[0.94,4.59]
Total (95% CI)	34	38		100%	2.08[0.94,4.59]

Total events: 13 (Switch to mianserin), 7 (Fluoxetine monotherapy)

Heterogeneity: Not applicable

Test for overall effect: Z=1.8(P=0.07)

Favours mianserin switch   0.01 0.1 1 10 100   Favours control
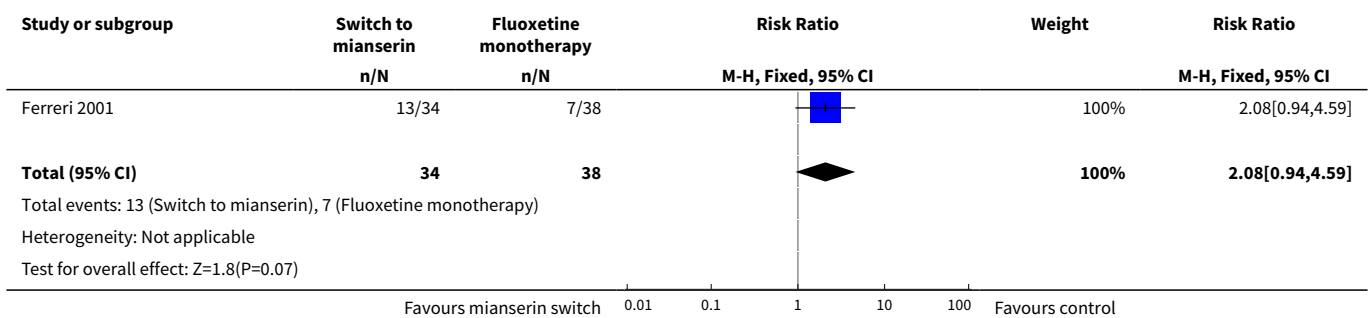
Analysis 1.3.   Comparison 1 Switch to mianserin, Outcome 3 Response (≥ 50% improvement in HAM-D score).

Study or subgroup	Switch to mianserin	Fluoxetine monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Ferreri 2001	16/33	14/38		100%	1.32[0.76,2.27]
Total (95% CI)	33	38		100%	1.32[0.76,2.27]

Total events: 16 (Switch to mianserin), 14 (Fluoxetine monotherapy)

Heterogeneity: Not applicable

Test for overall effect: Z=0.99(P=0.32)

Favours control   0.01 0.1 1 10 100   Favours mianserin switch
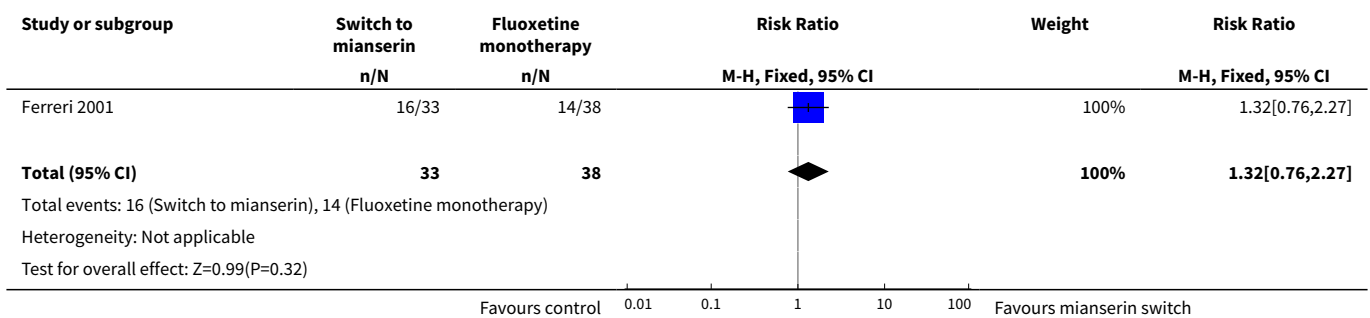
Analysis 1.4.   Comparison 1 Switch to mianserin, Outcome 4 Remission (HAM-D total score ≤ 8).
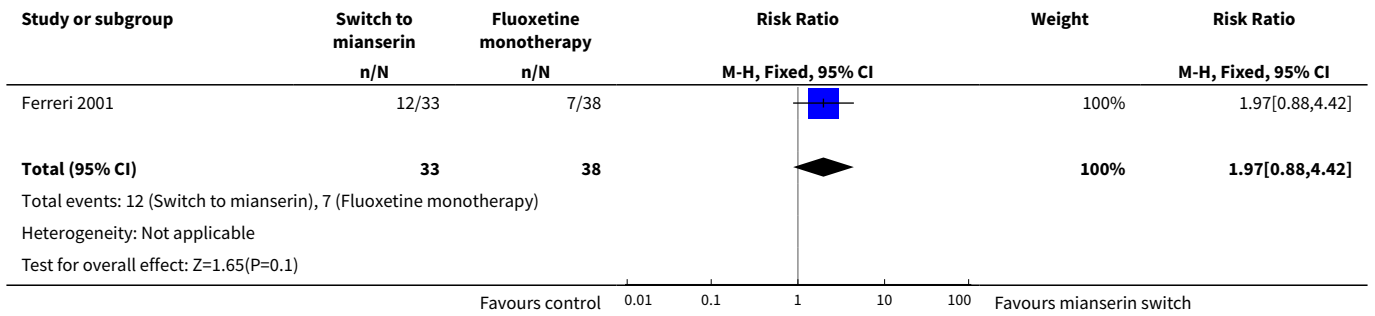
Study or subgroup	Switch to mianserin	Fluoxetine monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Ferreri 2001	12/33	7/38		100%	1.97[0.88,4.42]
Total (95% CI)	**33**	**38**		**100%**	**1.97[0.88,4.42]**
Total events: 12 (Switch to mianserin), 7 (Fluoxetine monotherapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.65(P=0.1)					

Favours control   0.01 0.1 1 10 100   Favours mianserin switch

Comparison 2.   Augment current antidepressant with mianserin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Depressive symptoms (HAM-D)	1	70	Mean Difference (IV, Fixed, 95% CI)	-4.80 [-8.18, -1.42]
2 Dropouts	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.38, 2.72]
3 Response (≥ 50% reduction in HAM-D score)	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.03, 2.78]
4 Remission (HAM-D total score ≤ 7)	1	70	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [1.09, 5.16]

Analysis 2.1.   Comparison 2 Augment current antidepressant with mianserin, Outcome 1 Depressive symptoms (HAM-D).

Study or subgroup	Mianserin		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Ferreri 2001	32	-16.1 (7)	38	-11.3 (7.4)		100%	-4.8[-8.18,-1.42]
Total *	32		38			100%	-4.8[-8.18,-1.42]
Heterogeneity: Not applicable							
Test for overall effect: Z=2.78(P=0.01)							

Favours mianserin   -50 -25 0 25 50   Favours control
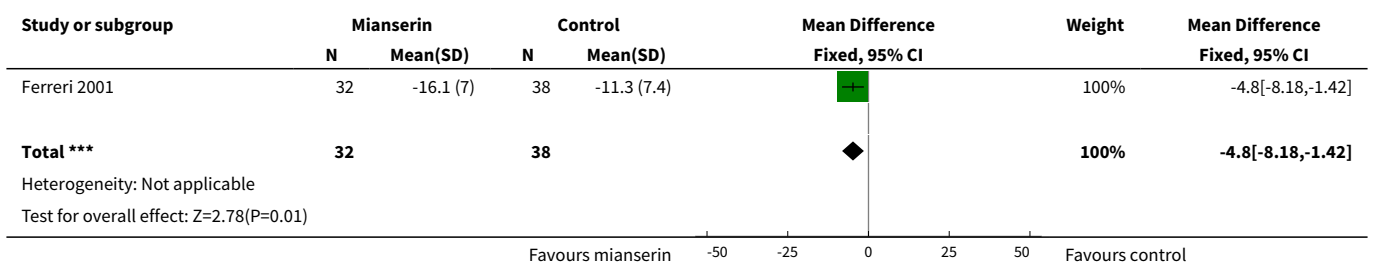
Analysis 2.2.   Comparison 2 Augment current antidepressant with mianserin, Outcome 2 Dropouts.

Study or subgroup	Mianserin	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Ferreri 2001	6/32	7/38		100%	1.02[0.38,2.72]

Favours mianserin   0.01 0.1 1 10 100   Favours control

Study or subgroup	Mianserin n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	32	38		100%	1.02[0.38,2.72]
Total events: 6 (Mianserin), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					

Favours mianserin 0.01 0.1 1 10 100 Favours control

Analysis 2.3. Comparison 2 Augment current antidepressant with mianserin, Outcome 3 Response (≥ 50% reduction in HAM-D score).

Study or subgroup	Mianserin n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ferreri 2001	20/32	14/38		100%	1.7[1.03,2.78]
Total (95% CI)	32	38		100%	1.7[1.03,2.78]
Total events: 20 (Mianserin), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.09(P=0.04)					

Favours control 0.01 0.1 1 10 100 Favours mianserin
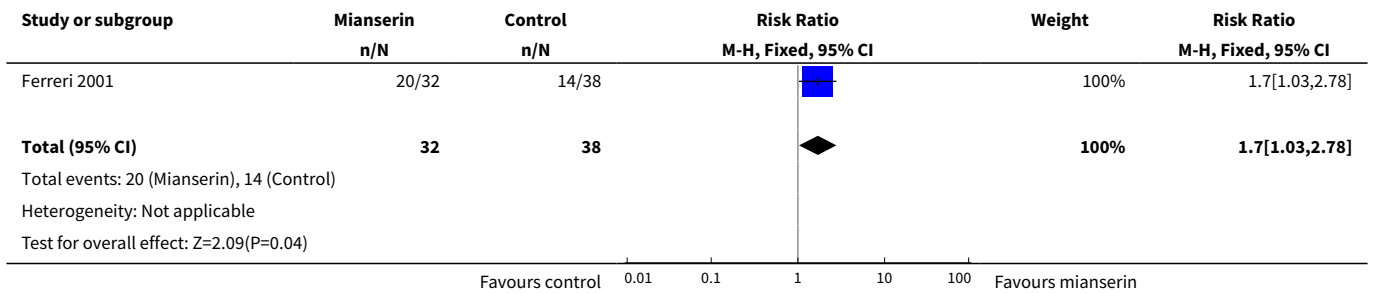
Analysis 2.4. Comparison 2 Augment current antidepressant with mianserin, Outcome 4 Remission (HAM-D total score ≤ 7).

Study or subgroup	Mianserin n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ferreri 2001	14/32	7/38		100%	2.38[1.09,5.16]
Total (95% CI)	32	38		100%	2.38[1.09,5.16]
Total events: 14 (Mianserin), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.19(P=0.03)					

Favours control 0.01 0.1 1 10 100 Favours mianserin
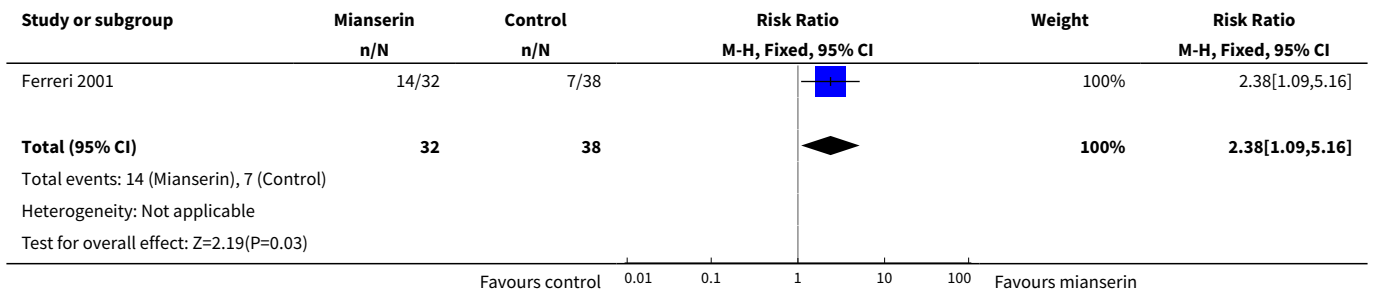
Comparison 3. Augment current antidepressant with mirtazapine

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Depressive symptoms (BDI-II)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 12 weeks	1	431	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-4.03, 0.63]
1.2 24 weeks	1	402	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-3.39, 1.59]
1.3 52 weeks	1	388	Mean Difference (IV, Fixed, 95% CI)	0.10 [-2.38, 2.58]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Depressive symptoms (PHQ-9, 12 weeks)	1	429	Mean Difference (IV, Fixed, 95% CI)	-0.89 [-2.08, 0.30]
3 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 12 weeks	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.15, 1.62]
3.2 24 weeks	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.19, 1.30]
3.3 52 weeks	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.18, 1.18]
4 Response (≥ 50% improve-ment in BDI-II score)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 12 weeks	1	431	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.97, 1.54]
4.2 24 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.83, 1.23]
4.3 52 weeks	1	388	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.82, 1.22]
5 Remission (BDI-II total score ≤ 9)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 12 weeks	1	431	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.88, 1.65]
5.2 24 weeks	1	402	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.86, 1.55]
5.3 52 weeks	1	388	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.74, 1.30]
6 Quality of life (EQ-5D-5L)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 12 weeks	1	447	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
6.2 24 weeks	1	403	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.07, 0.03]
6.3 52 weeks	1	388	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.08, 0.02]
7 Quality of life (SF-12 - aggre-gate mental functioning)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 12 weeks	1	418	Mean Difference (IV, Fixed, 95% CI)	3.61 [1.23, 5.99]
7.2 24 weeks	1	392	Mean Difference (IV, Fixed, 95% CI)	1.98 [-0.64, 4.60]
7.3 52 weeks	1	373	Mean Difference (IV, Fixed, 95% CI)	1.29 [-1.44, 4.02]
8 Quality of life (SF-12 - aggre-gate physical functioning)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 12 weeks	1	418	Mean Difference (IV, Fixed, 95% CI)	-1.76 [-4.20, 0.68]
8.2 24 weeks	1	392	Mean Difference (IV, Fixed, 95% CI)	-2.49 [-5.04, 0.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.3 52 weeks	1	373	Mean Difference (IV, Fixed, 95% CI)	-0.98 [-3.61, 1.65]

Analysis 3.1. Comparison 3 Augment current antidepressant with mirtazapine, Outcome 1 Depressive symptoms (BDI-II).

Study or subgroup	Mirtazapine		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
3.1.1 12 weeks							
Kessler 2018	214	18 (12.3)	217	19.7 (12.4)		100%	-1.7[-4.03,0.63]
Subtotal ***	214		217			100%	**-1.7[-4.03,0.63]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.43(P=0.15)							
3.1.2 24 weeks							
Kessler 2018	196	17.3 (12.9)	206	18.2 (12.6)		100%	-0.9[-3.39,1.59]
Subtotal ***	196		206			100%	**-0.9[-3.39,1.59]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.71(P=0.48)							
3.1.3 52 weeks							
Kessler 2018	190	16.8 (12.7)	198	16.7 (12.2)		100%	0.1[-2.38,2.58]
Subtotal ***	190		198			100%	**0.1[-2.38,2.58]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.08(P=0.94)							

Favours mitrazapine -10 -5 0 5 10 Favours control

Analysis 3.2. Comparison 3 Augment current antidepressant with mirtazapine, Outcome 2 Depressive symptoms (PHQ-9, 12 weeks).

Study or subgroup	Mirtazapine		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Kessler 2018	212	9.7 (6.4)	217	10.6 (6.2)		100%	-0.89[-2.08,0.3]
Total ***	212		217			100%	**-0.89[-2.08,0.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.47(P=0.14)							

Favours mitrazapine -10 -5 0 5 10 Favours control

Analysis 3.3. Comparison 3 Augment current antidepressant with mirtazapine, Outcome 3 Dropouts.

Study or subgroup	Mirtazapine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 12 weeks					
Kessler 2018	4/241	8/239		100%	0.5[0.15,1.62]
Subtotal (95% CI)	**241**	**239**		**100%**	**0.5[0.15,1.62]**
Total events: 4 (Mirtazapine), 8 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.16(P=0.25)					
3.3.2 24 weeks					
Kessler 2018	6/241	12/239		100%	0.5[0.19,1.3]
Subtotal (95% CI)	**241**	**239**		**100%**	**0.5[0.19,1.3]**
Total events: 6 (Mirtazapine), 12 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.43(P=0.15)					
3.3.3 52 weeks					
Kessler 2018	6/241	13/239		100%	0.46[0.18,1.18]
Subtotal (95% CI)	**241**	**239**		**100%**	**0.46[0.18,1.18]**
Total events: 6 (Mirtazapine), 13 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.61(P=0.11)					

Favours mirtazapine 0.01 0.1 1 10 100 Favours control

Analysis 3.4. Comparison 3 Augment current antidepressant with mirtazapine, Outcome 4 Response (≥ 50% improvement in BDI-II score).

Study or subgroup	Mirtazapine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 12 weeks					
Kessler 2018	94/214	78/217		100%	1.22[0.97,1.54]
Subtotal (95% CI)	**214**	**217**		**100%**	**1.22[0.97,1.54]**
Total events: 94 (Mirtazapine), 78 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.68(P=0.09)					
3.4.2 24 weeks					
Kessler 2018	96/196	100/206		100%	1.01[0.83,1.23]
Subtotal (95% CI)	**196**	**206**		**100%**	**1.01[0.83,1.23]**
Total events: 96 (Mirtazapine), 100 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.09(P=0.93)					
3.4.3 52 weeks					
Kessler 2018	97/190	101/198		100%	1[0.82,1.22]
Subtotal (95% CI)	**190**	**198**		**100%**	**1[0.82,1.22]**
Total events: 97 (Mirtazapine), 101 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					

Favours control 0.05 0.2 1 5 20 Favours mirtazapine

Analysis 3.5. Comparison 3 Augment current antidepressant with mirtazapine, Outcome 5 Remission (BDI-II total score ≤ 9).

Study or subgroup	Mirtazapine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 12 weeks					
Kessler 2018	63/214	53/217		100%	1.21[0.88,1.65]
Subtotal (95% CI)	**214**	**217**		**100%**	**1.21[0.88,1.65]**
Total events: 63 (Mirtazapine), 53 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.17(P=0.24)					
3.5.2 24 weeks					
Kessler 2018	65/196	59/206		100%	1.16[0.86,1.55]
Subtotal (95% CI)	**196**	**206**		**100%**	**1.16[0.86,1.55]**
Total events: 65 (Mirtazapine), 59 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.98(P=0.33)					
3.5.3 52 weeks					
Kessler 2018	63/190	67/198		100%	0.98[0.74,1.3]
Subtotal (95% CI)	**190**	**198**		**100%**	**0.98[0.74,1.3]**
Total events: 63 (Mirtazapine), 67 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.14(P=0.89)					

Favours control 0.01 0.1 1 10 100 Favours mirtazapine

Analysis 3.6. Comparison 3 Augment current antidepressant with mirtazapine, Outcome 6 Quality of life (EQ-5D-5L).

Study or subgroup	Mirtazapine N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.6.1 12 weeks							
Kessler 2018	231	0.7 (0.3)	216	0.7 (0.3)		100%	-0.01[-0.06,0.04]
Subtotal ***	**231**		**216**			**100%**	**-0.01[-0.06,0.04]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.41(P=0.68)							
3.6.2 24 weeks							
Kessler 2018	196	0.7 (0.3)	207	0.7 (0.3)		100%	-0.02[-0.07,0.03]
Subtotal ***	**196**		**207**			**100%**	**-0.02[-0.07,0.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.8(P=0.42)							
3.6.3 52 weeks							
Kessler 2018	189	0.7 (0.3)	199	0.8 (0.3)		100%	-0.03[-0.08,0.02]
Subtotal ***	**189**		**199**			**100%**	**-0.03[-0.08,0.02]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.11(P=0.27)							

Favours mirtazapine -0.2 -0.1 0 0.1 0.2 Favours control

Analysis 3.7. Comparison 3 Augment current antidepressant with mirtazapine, Outcome 7 Quality of life (SF-12 - aggregate mental functioning).

Study or subgroup	Mirtazapine N	Mirtazapine Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.7.1 12 weeks							
Kessler 2018	208	39.9 (12.3)	210	36.3 (12.5)		100%	3.61[1.23,5.99]
Subtotal ***	**208**		**210**			**100%**	**3.61[1.23,5.99]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.98(P=0)							
3.7.2 24 weeks							
Kessler 2018	191	39.9 (13.9)	201	37.9 (12.4)		100%	1.98[-0.64,4.6]
Subtotal ***	**191**		**201**			**100%**	**1.98[-0.64,4.6]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.48(P=0.14)							
3.7.3 52 weeks							
Kessler 2018	182	40.5 (13.8)	191	39.3 (13.1)		100%	1.29[-1.44,4.02]
Subtotal ***	**182**		**191**			**100%**	**1.29[-1.44,4.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.93(P=0.35)							

Favours mirtazapine -10 -5 0 5 10 Favours control

Analysis 3.8. Comparison 3 Augment current antidepressant with mirtazapine, Outcome 8 Quality of life (SF-12 - aggregate physical functioning).

Study or subgroup	Mirtazapine N	Mirtazapine Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.8.1 12 weeks							
Kessler 2018	208	44.1 (12.9)	210	45.9 (12.5)		100%	-1.76[-4.2,0.68]
Subtotal ***	**208**		**210**			**100%**	**-1.76[-4.2,0.68]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.42(P=0.16)							
3.8.2 24 weeks							
Kessler 2018	191	42.9 (13)	201	45.4 (12.8)		100%	-2.49[-5.04,0.06]
Subtotal ***	**191**		**201**			**100%**	**-2.49[-5.04,0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.91(P=0.06)							
3.8.3 52 weeks							
Kessler 2018	182	43.3 (13.4)	191	44.3 (12.5)		100%	-0.98[-3.61,1.65]
Subtotal ***	**182**		**191**			**100%**	**-0.98[-3.61,1.65]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.73(P=0.47)							

Favours mirtazapine -10 -5 0 5 10 Favours control

Comparison 4. Augment current antidepressant with buspirone (anxiolytic)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depressive symptoms (MADRS)	1	102	Mean Difference (IV, Random, 95% CI)	-0.30 [-9.48, 8.88]
2 Dropouts	1	108	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.23, 1.53]

Analysis 4.1. Comparison 4 Augment current antidepressant with buspirone (anxiolytic), Outcome 1 Depressive symptoms (MADRS).

Study or subgroup	Augmentation of AD		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Appelberg 2001	51	30.5 (23.8)	51	30.8 (23.5)		100%	-0.3[-9.48,8.88]
Total ***	**51**		**51**			**100%**	**-0.3[-9.48,8.88]**

Heterogeneity: Not applicable
Test for overall effect: Z=0.06(P=0.95)

Favours augmentation   -10 -5 0 5 10   Favours control
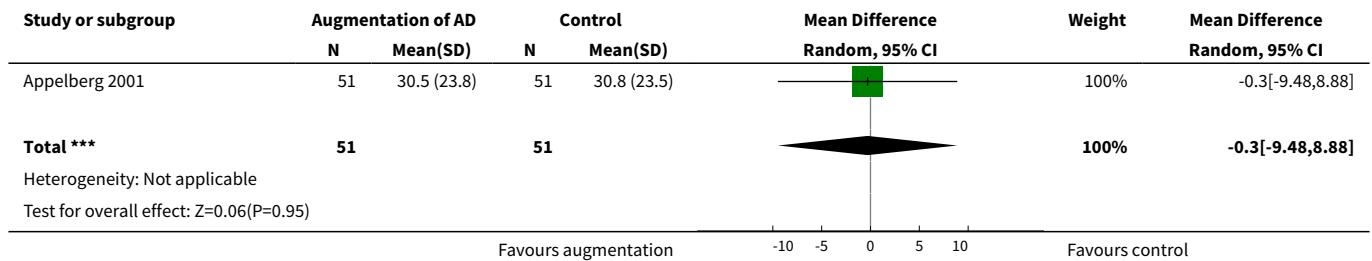
Analysis 4.2. Comparison 4 Augment current antidepressant with buspirone (anxiolytic), Outcome 2 Dropouts.
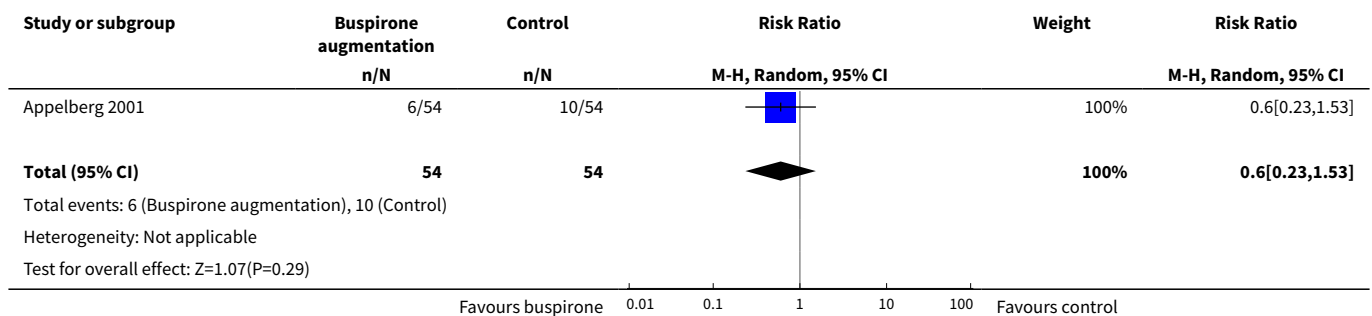
Study or subgroup	Buspirone augmentation	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Appelberg 2001	6/54	10/54		100%	0.6[0.23,1.53]
Total (95% CI)	**54**	**54**		**100%**	**0.6[0.23,1.53]**

Total events: 6 (Buspirone augmentation), 10 (Control)
Heterogeneity: Not applicable
Test for overall effect: Z=1.07(P=0.29)

Favours buspirone   0.01 0.1 1 10 100   Favours control

Comparison 5. Augment current antidepressant with cariprazine (antipsychotic)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depressive symptoms (MADRS)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 1-2 mg/d	1	537	Mean Difference (Fixed, 95% CI)	-0.9 [-2.29, 0.49]
1.2 2-4.5mg/d	1	535	Mean Difference (Fixed, 95% CI)	-2.1 [-3.63, -0.57]
1.3 Any dose	1	808	Mean Difference (Fixed, 95% CI)	-1.50 [-2.74, -0.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 1-2 mg/d	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.94, 2.17]
2.2 2-4.5mg/d	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.30, 2.84]
2.3 Pooled dose	1	821	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [1.16, 2.41]
3 Response (≥ 50% improvement in MADRS score)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 1-2 mg/d	1	537	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.03, 1.53]
3.2 2-4.5mg/d	1	535	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.06, 1.57]
3.3 Pooled dose	1	808	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.07, 1.52]
4 Remission (MADRS total score ≤ 10)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 1-2mg/d	1	537	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.83, 1.37]
4.2 2-4.5mg/d	1	535	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.83, 1.38]
4.3 Pooled data	1	808	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.86, 1.33]

Analysis 5.1. Comparison 5 Augment current antidepressant with cariprazine (antipsychotic), Outcome 1 Depressive symptoms (MADRS).

Study or subgroup	Cariprazine N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
5.1.1 1-2 mg/d						
Durgam 2016	273	264	-0.9 (0.707)		100%	-0.9[-2.29,0.49]
Subtotal (95% CI)					**100%**	**-0.9[-2.29,0.49]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.27(P=0.2)						
5.1.2 2-4.5mg/d						
Durgam 2016	271	264	-2.1 (0.781)		100%	-2.1[-3.63,-0.57]
Subtotal (95% CI)					**100%**	**-2.1[-3.63,-0.57]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.69(P=0.01)						
5.1.3 Any dose						
Durgam 2016	544	264	-1.5 (0.635)		100%	-1.5[-2.74,-0.25]
Subtotal (95% CI)					**100%**	**-1.5[-2.74,-0.25]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.36(P=0.02)						

Favours cariprazine   -5 -2.5 0 2.5 5   Favours control

Analysis 5.2. Comparison 5 Augment current antidepressant with cariprazine (antipsychotic), Outcome 2 Dropouts.

Study or subgroup	Cariprazine augmentation n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 1-2 mg/d					
Durgam 2016	47/276	32/269		100%	1.43[0.94,2.17]
Subtotal (95% CI)	**276**	**269**		**100%**	**1.43[0.94,2.17]**
Total events: 47 (Cariprazine augmentation), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.69(P=0.09)					
5.2.2 2-4.5mg/d					
Durgam 2016	63/276	32/269		100%	1.92[1.3,2.84]
Subtotal (95% CI)	**276**	**269**		**100%**	**1.92[1.3,2.84]**
Total events: 63 (Cariprazine augmentation), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.27(P=0)					
5.2.3 Pooled dose					
Durgam 2016	110/552	32/269		100%	1.68[1.16,2.41]
Subtotal (95% CI)	**552**	**269**		**100%**	**1.68[1.16,2.41]**
Total events: 110 (Cariprazine augmentation), 32 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=2.77(P=0.01)					

Favours cariprazine 0.01 0.1 1 10 100 Favours control

Analysis 5.3. Comparison 5 Augment current antidepressant with cariprazine (antipsychotic), Outcome 3 Response (≥ 50% improvement in MADRS score).

Study or subgroup	Cariprazine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.3.1 1-2 mg/d					
Durgam 2016	131/273	101/264		100%	1.25[1.03,1.53]
Subtotal (95% CI)	**273**	**264**		**100%**	**1.25[1.03,1.53]**
Total events: 131 (Cariprazine), 101 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=2.26(P=0.02)					
5.3.2 2-4.5mg/d					
Durgam 2016	134/271	101/264		100%	1.29[1.06,1.57]
Subtotal (95% CI)	**271**	**264**		**100%**	**1.29[1.06,1.57]**
Total events: 134 (Cariprazine), 101 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.58(P=0.01)					
5.3.3 Pooled dose					
Durgam 2016	265/544	101/264		100%	1.27[1.07,1.52]
Subtotal (95% CI)	**544**	**264**		**100%**	**1.27[1.07,1.52]**
Total events: 265 (Cariprazine), 101 (Control)					

Favours control 0.01 0.1 1 10 100 Favours cariprazine

Study or subgroup	Cariprazine	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=2.69(P=0.01)					

Favours control 0.01 0.1 1 10 100 Favours cariprazine

Analysis 5.4. Comparison 5 Augment current antidepressant with cariprazine (antipsychotic), Outcome 4 Remission (MADRS total score ≤ 10).

Study or subgroup	Cariprazine	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
5.4.1 1-2mg/d					
Durgam 2016	87/273	79/264		100%	1.06[0.83,1.37]
Subtotal (95% CI)	**273**	**264**		**100%**	**1.06[0.83,1.37]**
Total events: 87 (Cariprazine), 79 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.63)					
5.4.2 2-4.5mg/d					
Durgam 2016	87/271	79/264		100%	1.07[0.83,1.38]
Subtotal (95% CI)	**271**	**264**		**100%**	**1.07[0.83,1.38]**
Total events: 87 (Cariprazine), 79 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
5.4.3 Pooled data					
Durgam 2016	174/544	79/264		100%	1.07[0.86,1.33]
Subtotal (95% CI)	**544**	**264**		**100%**	**1.07[0.86,1.33]**
Total events: 174 (Cariprazine), 79 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					

Favours control 0.01 0.1 1 10 100 Favours cariprazine

Comparison 6. Augment current antidepressant with olanzapine (antipsychotic)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Depressive symptoms (MADRS)	1	20	Mean Difference (IV, Fixed, 95% CI)	-12.4 [-22.44, -2.36]
2 Depressive symptoms (HAM-D)	1	20	Mean Difference (IV, Random, 95% CI)	-7.90 [-16.76, 0.96]
3 Dropouts	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.69]
4 Response (≥ 50% reduction in MADRS score)	1	20	Risk Ratio (M-H, Random, 95% CI)	6.0 [0.87, 41.21]

Analysis 6.1.   Comparison 6 Augment current antidepressant with olanzapine (antipsychotic), Outcome 1 Depressive symptoms (MADRS).

Study or subgroup	Olanzapine		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Shelton 2001	10	-13.6 (11.9)	10	-1.2 (11)		100%	-12.4[-22.44,-2.36]
Total ***	**10**		**10**			**100%**	**-12.4[-22.44,-2.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.42(P=0.02)							

Favours olanzapine   -100   -50   0   50   100   Favours control
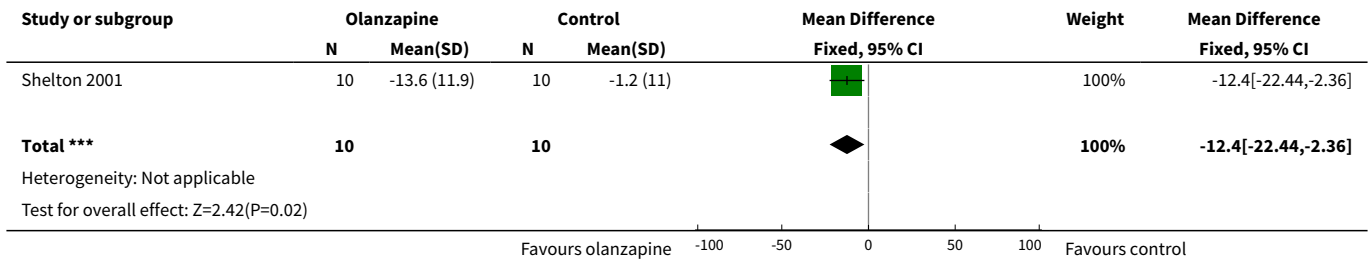
Analysis 6.2.   Comparison 6 Augment current antidepressant with olanzapine (antipsychotic), Outcome 2 Depressive symptoms (HAM-D).

Study or subgroup	Olanzapine		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Shelton 2001	10	-11.7 (10.6)	10	-3.8 (9.6)		100%	-7.9[-16.76,0.96]
Total ***	**10**		**10**			**100%**	**-7.9[-16.76,0.96]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.75(P=0.08)							

Favours olanzapine   -100   -50   0   50   100   Favours control

Analysis 6.3.   Comparison 6 Augment current antidepressant with olanzapine (antipsychotic), Outcome 3 Dropouts.

Study or subgroup	Olanzapine augmentation	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Shelton 2001	1/10	3/10		100%	0.33[0.04,2.69]
Total (95% CI)	**10**	**10**		**100%**	**0.33[0.04,2.69]**
Total events: 1 (Olanzapine augmentation), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.03(P=0.3)					

Favours olanzapine   0.01   0.1   1   10   100   Favours control

Analysis 6.4.   Comparison 6 Augment current antidepressant with olanzapine (antipsychotic), Outcome 4 Response (≥ 50% reduction in MADRS score).

Study or subgroup	Olanzapine augmentation	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Shelton 2001	6/10	1/10		100%	6[0.87,41.21]

Favours control   0.01   0.1   1   10   100   Favours olanzapine

Study or subgroup	Olanzapine augmentation	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Total (95% CI)	10	10		100%	6[0.87,41.21]
Total events: 6 (Olanzapine augmentation), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.82(P=0.07)					

Favours control 0.01 0.1 1 10 100 Favours olanzapine

Comparison 7. Augment current antidepressant with quetiapine (antipsychotic)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depressive symptoms (MADRS or HAM-D)	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
1.1 150 -200 mg/d	3	670	Std. Mean Difference (Random, 95% CI)	-0.34 [-0.53, -0.14]
1.2 300mg/d	2	610	Std. Mean Difference (Random, 95% CI)	-0.33 [-0.49, -0.17]
1.3 Any dose	3	977	Std. Mean Difference (Random, 95% CI)	-0.32 [-0.46, -0.18]
2 Dropouts	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 150 - 200 mg/d	3	684	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.86, 1.63]
2.2 300 mg/d	2	624	Risk Ratio (M-H, Random, 95% CI)	1.82 [1.29, 2.57]
2.3 Any dose	3	997	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.90, 1.95]
3 Response (≥ 50% reduction in MADRS or HAM-D score)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 150 -200 mg/d	3	673	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.02, 1.40]
3.2 300 mg/d	2	610	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.10, 1.50]
3.3 Any dose	3	977	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.09, 1.43]
4 Quality of life (% max score of Q-LES-Q-SF)	2		Mean Difference (Random, 95% CI)	Subtotals only
4.1 150 mg/d	2	591	Mean Difference (Random, 95% CI)	0.70 [-2.31, 3.71]
4.2 300 mg/d	2	589	Mean Difference (Random, 95% CI)	0.35 [-2.06, 2.77]
4.3 Any dose	2	884	Mean Difference (Random, 95% CI)	0.57 [-1.52, 2.65]
5 Remission (MADRS score ≤ 8/ HAM-D score ≤ 7)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 150 - 200 mg/d	3	673	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.18, 1.92]
5.2 300 mg/d	2	610	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.13, 2.07]
5.3 Any dose	3	977	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.22, 1.90]

Analysis 7.1. Comparison 7 Augment current antidepressant with quetiapine (antipsychotic), Outcome 1 Depressive symptoms (MADRS or HAM-D).

Study or subgroup	Quetiap-ine aug-mentation	Control	Std. Mean Difference	Std. Mean Difference	Weight	Std. Mean Difference
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
7.1.1 150 -200 mg/d						
Bauer 2009 (ONYX)	166	160	-0.4 (0.112)		45.78%	-0.35[-0.57,-0.13]
El-Khalili 2010 (PEARL)	143	143	-0.2 (0.119)		42.54%	-0.22[-0.45,0.02]
McIntyre 2007	29	29	-0.7 (0.271)		11.68%	-0.7[-1.23,-0.17]
Subtotal (95% CI)					100%	-0.34[-0.53,-0.14]
Heterogeneity: Tau²=0.01; Chi²=2.79, df=2(P=0.25); I²=28.32%						
Test for overall effect: Z=3.43(P=0)						
7.1.2 300mg/d						
Bauer 2009 (ONYX)	161	160	-0.3 (0.112)		52.68%	-0.32[-0.54,-0.1]
El-Khalili 2010 (PEARL)	143	146	-0.3 (0.119)		47.32%	-0.34[-0.57,-0.11]
Subtotal (95% CI)					100%	-0.33[-0.49,-0.17]
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.89); I²=0%						
Test for overall effect: Z=4(P<0.0001)						
7.1.3 Any dose						
Bauer 2009 (ONYX)	327	160	-0.3 (0.097)		48.92%	-0.3[-0.49,-0.11]
El-Khalili 2010 (PEARL)	289	143	-0.3 (0.103)		44.16%	-0.28[-0.48,-0.08]
McIntyre 2007	29	29	-0.7 (0.271)		6.92%	-0.7[-1.23,-0.17]
Subtotal (95% CI)					100%	-0.32[-0.46,-0.18]
Heterogeneity: Tau²=0; Chi²=2.14, df=2(P=0.34); I²=6.37%						
Test for overall effect: Z=4.43(P<0.0001)						

Favours quetiapine -2 -1 0 1 2 Favours control

Analysis 7.2. Comparison 7 Augment current antidepressant with quetiapine (antipsychotic), Outcome 2 Dropouts.

Study or subgroup	quetiapine augmentation	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
7.2.1 150 - 200 mg/d					
Bauer 2009 (ONYX)	21/167	18/163		28.99%	1.14[0.63,2.06]
El-Khalili 2010 (PEARL)	34/148	23/148		44.3%	1.48[0.92,2.38]
McIntyre 2007	11/29	13/29		26.71%	0.85[0.46,1.57]

Favours quetiapine 0.01 0.1 1 10 100 Favours control

Study or subgroup	quetiapine augmentation	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Subtotal (95% CI)	344	340		100%	1.18[0.86,1.63]
Total events: 66 (quetiapine augmentation), 54 (Control)					
Heterogeneity: Tau²=0; Chi²=2.01, df=2(P=0.37); I²=0.69%					
Test for overall effect: Z=1.02(P=0.31)					
7.2.2 300 mg/d					
Bauer 2009 (ONYX)	30/163	18/163		40.56%	1.67[0.97,2.87]
El-Khalili 2010 (PEARL)	45/150	23/148		59.44%	1.93[1.23,3.02]
Subtotal (95% CI)	313	311		100%	1.82[1.29,2.57]
Total events: 75 (quetiapine augmentation), 41 (Control)					
Heterogeneity: Tau²=0; Chi²=0.17, df=1(P=0.68); I²=0%					
Test for overall effect: Z=3.39(P=0)					
7.2.3 Any dose					
Bauer 2009 (ONYX)	51/330	18/163		33.47%	1.4[0.85,2.32]
El-Khalili 2010 (PEARL)	79/298	23/148		40.48%	1.71[1.12,2.6]
McIntyre 2007	11/29	13/29		26.05%	0.85[0.46,1.57]
Subtotal (95% CI)	657	340		100%	1.33[0.9,1.95]
Total events: 141 (quetiapine augmentation), 54 (Control)					
Heterogeneity: Tau²=0.05; Chi²=3.47, df=2(P=0.18); I²=42.43%					
Test for overall effect: Z=1.45(P=0.15)					
Test for subgroup differences: Chi²=3.36, df=1 (P=0.19), I²=40.45%					

Favours quetiapine 0.01 0.1 1 10 100 Favours control

Analysis 7.3. Comparison 7 Augment current antidepressant with quetiapine (antipsychotic), Outcome 3 Response (≥ 50% reduction in MADRS or HAM-D score).

Study or subgroup	Quetiapine	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
7.3.1 150 -200 mg/d					
Bauer 2009 (ONYX)	92/166	74/160		52.3%	1.2[0.97,1.49]
El-Khalili 2010 (PEARL)	74/143	66/146		42.73%	1.14[0.9,1.45]
McIntyre 2007	14/29	8/29		4.97%	1.75[0.87,3.52]
Subtotal (95% CI)	338	335		100%	1.2[1.02,1.4]
Total events: 180 (Quetiapine), 148 (Control)					
Heterogeneity: Tau²=0; Chi²=1.27, df=2(P=0.53); I²=0%					
Test for overall effect: Z=2.26(P=0.02)					
7.3.2 300 mg/d					
Bauer 2009 (ONYX)	93/161	74/160		52.29%	1.25[1.01,1.55]
El-Khalili 2010 (PEARL)	86/143	66/146		47.71%	1.33[1.06,1.66]
Subtotal (95% CI)	304	306		100%	1.29[1.1,1.5]
Total events: 179 (Quetiapine), 140 (Control)					
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%					
Test for overall effect: Z=3.21(P=0)					
7.3.3 Any dose					
Bauer 2009 (ONYX)	185/327	74/160		51.42%	1.22[1.01,1.48]

Favours control 0.5 0.7 1 1.5 2 Favours quetiapine

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Study or subgroup	Quetiapine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
El-Khalili 2010 (PEARL)	160/286	66/146		44.7%	1.24[1.01,1.52]
McIntyre 2007	14/29	8/29		3.88%	1.75[0.87,3.52]
Subtotal (95% CI)	**642**	**335**		**100%**	**1.25[1.09,1.43]**
Total events: 359 (Quetiapine), 148 (Control)					
Heterogeneity: Tau²=0; Chi²=0.95, df=2(P=0.62); I²=0%					
Test for overall effect: Z=3.14(P=0)					
Test for subgroup differences: Chi²=0.42, df=1 (P=0.81), I²=0%					

Favours control 0.5 0.7 1 1.5 2 Favours quetiapine

Analysis 7.4. Comparison 7 Augment current antidepressant with quetiapine (antipsychotic), Outcome 4 Quality of life (% max score of Q-LES-Q-SF).

Study or subgroup	Quetiapine N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
7.4.1 150 mg/d						
Bauer 2009 (ONYX)	160	160	2.1 (1.638)		53.94%	2.12[-1.09,5.33]
El-Khalili 2010 (PEARL)	135	136	-1 (1.852)		46.06%	-0.96[-4.59,2.67]
Subtotal (95% CI)					**100%**	**0.7[-2.31,3.71]**
Heterogeneity: Tau²=1.69; Chi²=1.55, df=1(P=0.21); I²=35.56%						
Test for overall effect: Z=0.46(P=0.65)						
7.4.2 300 mg/d						
Bauer 2009 (ONYX)	157	160	0.2 (1.643)		56.23%	0.24[-2.98,3.46]
El-Khalili 2010 (PEARL)	136	136	0.5 (1.862)		43.77%	0.5[-3.15,4.15]
Subtotal (95% CI)					**100%**	**0.35[-2.06,2.77]**
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.92); I²=0%						
Test for overall effect: Z=0.29(P=0.77)						
7.4.3 Any dose						
Bauer 2009 (ONYX)	317	160	1.2 (1.423)		56.07%	1.18[-1.61,3.97]
El-Khalili 2010 (PEARL)	271	136	-0.2 (1.608)		43.93%	-0.22[-3.37,2.93]
Subtotal (95% CI)					**100%**	**0.57[-1.52,2.65]**
Heterogeneity: Tau²=0; Chi²=0.43, df=1(P=0.51); I²=0%						
Test for overall effect: Z=0.53(P=0.6)						
Test for subgroup differences: Chi²=0.03, df=1 (P=0.98), I²=0%						

Favours control -10 -5 0 5 10 Favours quetiapine

Analysis 7.5. Comparison 7 Augment current antidepressant with quetiapine (antipsychotic), Outcome 5 Remission (MADRS score ≤ 8/HAM-D score ≤ 7).

Study or subgroup	Quetiapine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.5.1 150 - 200 mg/d					
Bauer 2009 (ONYX)	60/166	38/160		49.73%	1.52[1.08,2.15]
El-Khalili 2010 (PEARL)	50/143	35/146		43.97%	1.46[1.01,2.1]
McIntyre 2007	9/29	5/29		6.31%	1.8[0.69,4.72]

Favours control 0.01 0.1 1 10 100 Favours quetiapine

Study or subgroup	Quetiapine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	338	335	◆	100%	1.51[1.18,1.92]
Total events: 119 (Quetiapine), 78 (Control)					
Heterogeneity: Tau²=0; Chi²=0.16, df=2(P=0.92); I²=0%					
Test for overall effect: Z=3.33(P=0)					
7.5.2 300 mg/d					
Bauer 2009 (ONYX)	50/161	38/160	■	48.56%	1.31[0.91,1.88]
El-Khalili 2010 (PEARL)	61/143	35/146	■	51.44%	1.78[1.26,2.51]
Subtotal (95% CI)	304	306	◆	100%	1.53[1.13,2.07]
Total events: 111 (Quetiapine), 73 (Control)					
Heterogeneity: Tau²=0.01; Chi²=1.46, df=1(P=0.23); I²=31.55%					
Test for overall effect: Z=2.77(P=0.01)					
7.5.3 Any dose					
Bauer 2009 (ONYX)	110/327	38/160	■	48.4%	1.42[1.03,1.94]
El-Khalili 2010 (PEARL)	111/286	35/146	■	46.38%	1.62[1.17,2.24]
McIntyre 2007	9/29	5/29	—	5.22%	1.8[0.69,4.72]
Subtotal (95% CI)	642	335	◆	100%	1.53[1.22,1.9]
Total events: 230 (Quetiapine), 78 (Control)					
Heterogeneity: Tau²=0; Chi²=0.45, df=2(P=0.8); I²=0%					
Test for overall effect: Z=3.76(P=0)					
Test for subgroup differences: Chi²=0.01, df=1 (P=1), I²=0%					

Favours control 0.01 0.1 1 10 100 Favours quetiapine

Comparison 8.   Augment current antidepressant with ziprasidone (antipsychotic)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Depressive symptoms (HAM-D)	2		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 80 mg/d	1	41	Mean Difference (Fixed, 95% CI)	-0.91 [-4.84, 3.02]
1.2 40 - 160 mg/d (mean 98 mg/d)	1	139	Mean Difference (Fixed, 95% CI)	-3.1 [-5.19, -1.01]
1.3 160 mg/d	1	39	Mean Difference (Fixed, 95% CI)	-2.56 [-6.72, 1.60]
1.4 Any dose	2	199	Mean Difference (Fixed, 95% CI)	-2.73 [-4.53, -0.93]
2 Depressive symptoms (MADRS)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 80 mg/d	1	41	Mean Difference (Fixed, 95% CI)	-1.53 [-6.94, 3.88]
2.2 160 mg/d	1	39	Mean Difference (Fixed, 95% CI)	-3.82 [-9.64, 2.00]
2.3 Any dose	1	60	Mean Difference (Fixed, 95% CI)	-2.62 [-7.47, 2.23]
3 Depressive symptoms (QIDS-SR)	1	139	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-3.83, -1.17]

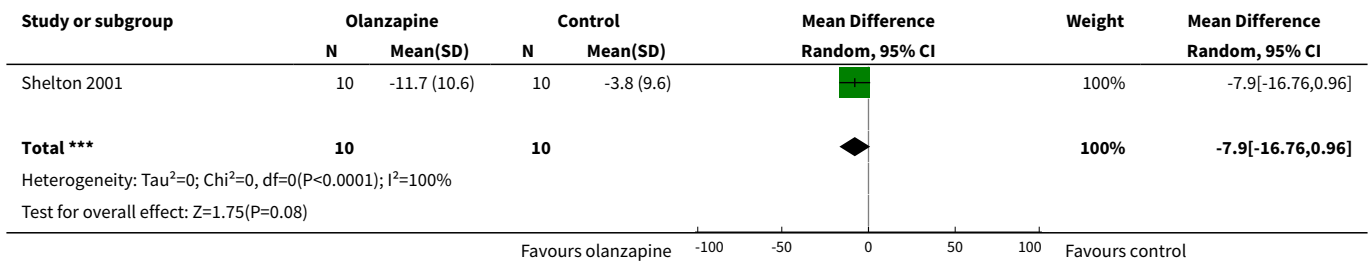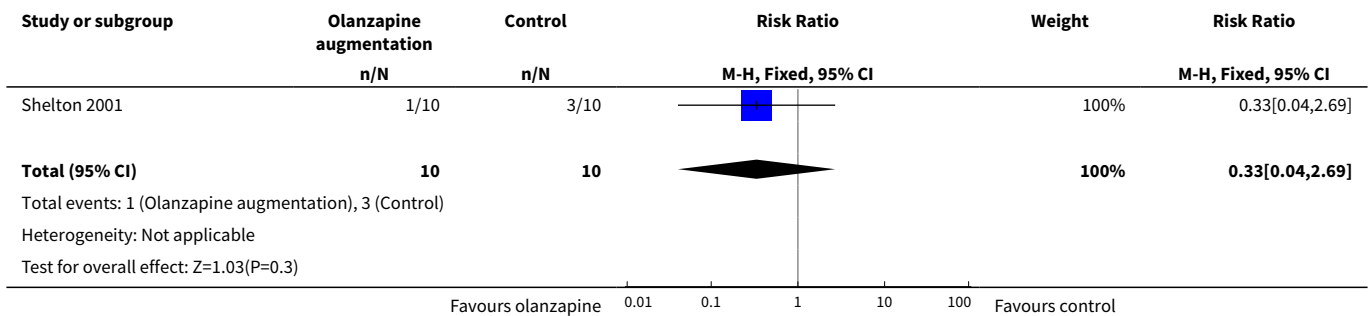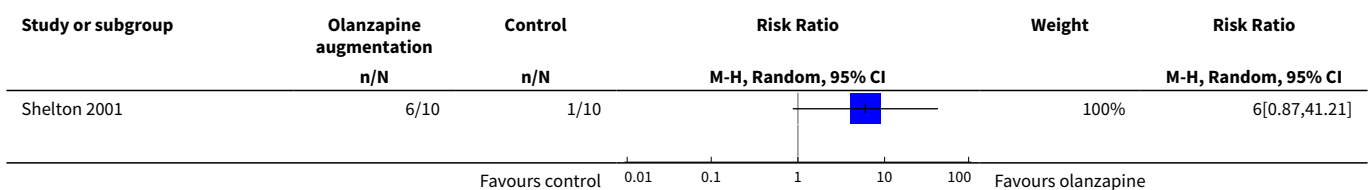| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 40 - 160 mg/d (mean 98 mg/d)	1	139	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-3.83, -1.17]
4 Dropouts	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 80 mg/d	1	41	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.89, 4.96]
4.2 160 mg/d	1	39	Risk Ratio (M-H, Random, 95% CI)	2.11 [0.88, 5.03]
4.3 40 - 160 mg/d (mean 98 mg/d)	1	139	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.80, 2.47]
4.4 Any dose	2	199	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.01, 2.55]
5 Response (≥ 50% reduction in MADRS/HAM-D score)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 80 mg/d (MADRS)	1	41	Risk Ratio (M-H, Random, 95% CI)	1.90 [0.39, 9.28]
5.2 160 mg/d (MADRS)	1	39	Risk Ratio (M-H, Random, 95% CI)	3.16 [0.72, 13.76]
5.3 40 - 160 mg/d (mean 98 mg/d) (HAM-D)	1	139	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.97, 3.00]
5.4 Any dose	2	199	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.07, 3.04]
6 Response (≥ 50% reduction in QIDS-SR)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 40 - 160 mg/d (mean 98 mg/d)	1	139	Risk Ratio (M-H, Random, 95% CI)	2.34 [1.16, 4.72]
7 Remission (MADRS/HAM-D)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 80 mg/d	1	41	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.06, 14.22]
7.2 160 mg/d	1	39	Risk Ratio (M-H, Random, 95% CI)	4.21 [0.52, 34.36]
7.3 40 - 160 mg/d (mean 98 mg/d)	1	139	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.77, 1.96]
7.4 Any dose	2	199	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.81, 2.00]
8 Remission (QIDS-SR)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 40 - 160 mg/d (mean 98 mg/d)	1	139	Risk Ratio (M-H, Random, 95% CI)	2.33 [1.03, 5.25]

Analysis 8.1. Comparison 8 Augment current antidepressant with ziprasidone (antipsychotic), Outcome 1 Depressive symptoms (HAM-D).
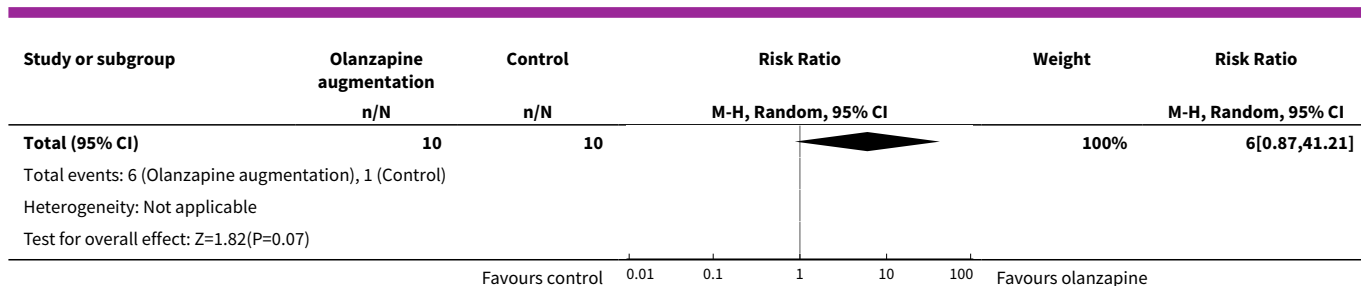
Study or subgroup	Ziprasidone	Control	Mean Difference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
8.1.1 80 mg/d						
Dunner 2007	21	20	-0.9 (2.003)		100%	-0.91[-4.84,3.02]
Subtotal (95% CI)					100%	**-0.91[-4.84,3.02]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.45(P=0.65)						
8.1.2 40 - 160 mg/d (mean 98 mg/d)						
Papakostas 2015	71	68	-3.1 (1.069)		100%	-3.1[-5.19,-1.01]
Subtotal (95% CI)					100%	**-3.1[-5.19,-1.01]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.9(P=0)						
8.1.3 160 mg/d						
Dunner 2007	19	20	-2.6 (2.122)		100%	-2.56[-6.72,1.6]
Subtotal (95% CI)					100%	**-2.56[-6.72,1.6]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.21(P=0.23)						
8.1.4 Any dose						
Dunner 2007	40	20	-1.7 (1.786)		26.37%	-1.69[-5.19,1.81]
Papakostas 2015	71	68	-3.1 (1.069)		73.63%	-3.1[-5.19,-1.01]
Subtotal (95% CI)					100%	**-2.73[-4.53,-0.93]**
Heterogeneity: Tau²=0; Chi²=0.46, df=1(P=0.5); I²=0%						
Test for overall effect: Z=2.98(P=0)						
Test for subgroup differences: Chi²=0.94, df=1 (P=0.82), I²=0%						

Favours ziprasidone   -10 -5 0 5 10   Favours control

Analysis 8.2. Comparison 8 Augment current antidepressant with ziprasidone (antipsychotic), Outcome 2 Depressive symptoms (MADRS).

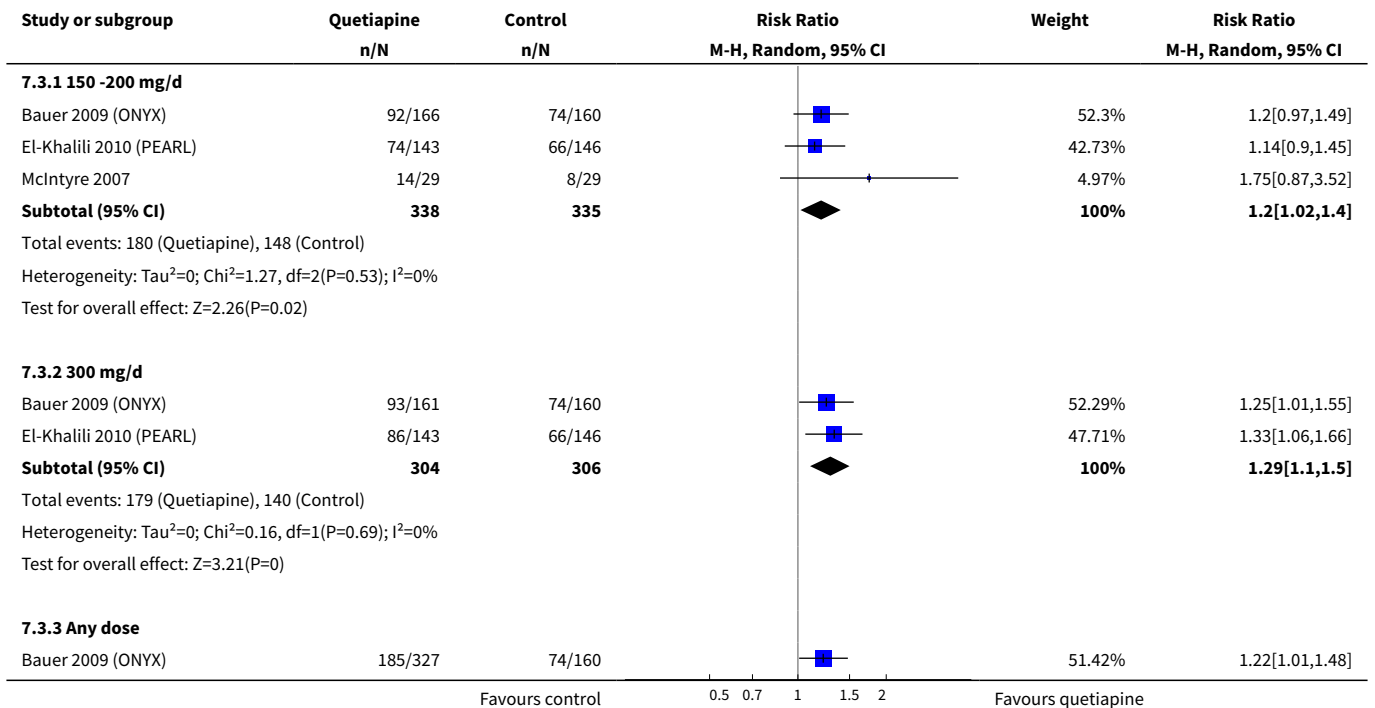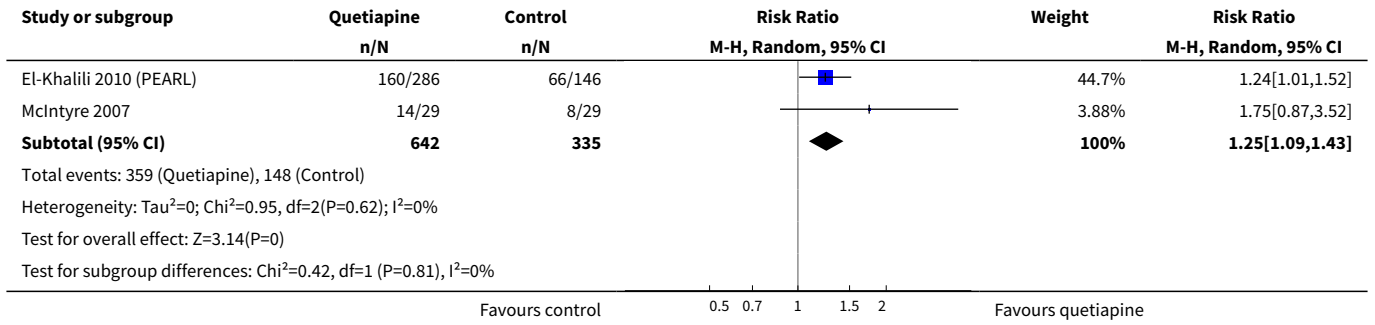| Study or subgroup	Ziprasidone	Control	Mean Difference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
8.2.1 80 mg/d						
Dunner 2007	21	20	-1.5 (2.76)		100%	-1.53[-6.94,3.88]
Subtotal (95% CI)					100%	**-1.53[-6.94,3.88]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.55(P=0.58)						
8.2.2 160 mg/d						
Dunner 2007	19	20	-3.8 (2.972)		100%	-3.82[-9.64,2]
Subtotal (95% CI)					100%	**-3.82[-9.64,2]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.29(P=0.2)						
8.2.3 Any dose						

Favours ziprasidone   -20 -10 0 10 20   Favours control

Study or subgroup	Ziprasidone	Control	Mean Difference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Dunner 2007	40	20	-2.6 (2.476)		100%	-2.62[-7.47,2.23]
Subtotal (95% CI)					100%	**-2.62[-7.47,2.23]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.06(P=0.29)						
Test for subgroup differences: Chi²=0.32, df=1 (P=0.85), I²=0%						

Favours ziprasidone -20 -10 0 10 20 Favours control

Analysis 8.3. Comparison 8 Augment current antidepressant with ziprasidone (antipsychotic), Outcome 3 Depressive symptoms (QIDS-SR).

Study or subgroup	Ziprasidone		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.3.1 40 - 160 mg/d (mean 98 mg/d)							
Papakostas 2015	71	-4.5 (4.7)	68	-2 (3.2)		100%	-2.5[-3.83,-1.17]
Subtotal ***	71		68			100%	**-2.5[-3.83,-1.17]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.68(P=0)							
Total ***	71		68			100%	**-2.5[-3.83,-1.17]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.68(P=0)							

Favours ziprasidone -20 -10 0 10 20 Favours control

Analysis 8.4. Comparison 8 Augment current antidepressant with ziprasidone (antipsychotic), Outcome 4 Dropouts.

Study or subgroup	Ziprasidone	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
8.4.1 80 mg/d					
Dunner 2007	11/21	5/20		100%	2.1[0.89,4.96]
Subtotal (95% CI)	21	20		100%	**2.1[0.89,4.96]**
Total events: 11 (Ziprasidone), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.68(P=0.09)					
8.4.2 160 mg/d					
Dunner 2007	10/19	5/20		100%	2.11[0.88,5.03]
Subtotal (95% CI)	19	20		100%	**2.11[0.88,5.03]**
Total events: 10 (Ziprasidone), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.68(P=0.09)					
8.4.3 40 - 160 mg/d (mean 98 mg/d)					
Papakostas 2015	22/71	15/68		100%	1.4[0.8,2.47]
Subtotal (95% CI)	71	68		100%	**1.4[0.8,2.47]**
Total events: 22 (Ziprasidone), 15 (Control)					
Heterogeneity: Not applicable					

Favours ziprasidone 0.01 0.1 1 10 100 Favours control

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Study or subgroup	Ziprasidone	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for overall effect: Z=1.18(P=0.24)					
8.4.4 Any dose					
Dunner 2007	21/40	5/20		32.56%	2.1[0.93,4.74]
Papakostas 2015	22/71	15/68		67.44%	1.4[0.8,2.47]
Subtotal (95% CI)	**111**	**88**		**100%**	**1.6[1.01,2.55]**
Total events: 43 (Ziprasidone), 20 (Control)					
Heterogeneity: Tau²=0; Chi²=0.63, df=1(P=0.43); I²=0%					
Test for overall effect: Z=1.99(P=0.05)					
Test for subgroup differences: Chi²=0.92, df=1 (P=0.82), I²=0%					

Favours ziprasidone 0.01 0.1 1 10 100 Favours control

Analysis 8.5. Comparison 8 Augment current antidepressant with ziprasidone (antipsychotic), Outcome 5 Response (≥ 50% reduction in MADRS/HAM-D score).

Study or subgroup	Ziprasidone	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
8.5.1 80 mg/d (MADRS)					
Dunner 2007	4/21	2/20		100%	1.9[0.39,9.28]
Subtotal (95% CI)	**21**	**20**		**100%**	**1.9[0.39,9.28]**
Total events: 4 (Ziprasidone), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.43)					
8.5.2 160 mg/d (MADRS)					
Dunner 2007	6/19	2/20		100%	3.16[0.72,13.76]
Subtotal (95% CI)	**19**	**20**		**100%**	**3.16[0.72,13.76]**
Total events: 6 (Ziprasidone), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.53(P=0.13)					
8.5.3 40 - 160 mg/d (mean 98 mg/d) (HAM-D)					
Papakostas 2015	25/71	14/68		100%	1.71[0.97,3]
Subtotal (95% CI)	**71**	**68**		**100%**	**1.71[0.97,3]**
Total events: 25 (Ziprasidone), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.87(P=0.06)					
8.5.4 Any dose					
Dunner 2007	10/40	2/20		13.6%	2.5[0.6,10.34]
Papakostas 2015	25/71	14/68		86.4%	1.71[0.97,3]
Subtotal (95% CI)	**111**	**88**		**100%**	**1.8[1.07,3.04]**
Total events: 35 (Ziprasidone), 16 (Control)					
Heterogeneity: Tau²=0; Chi²=0.24, df=1(P=0.62); I²=0%					
Test for overall effect: Z=2.2(P=0.03)					

Favours control 0.01 0.1 1 10 100 Favours ziprasidone

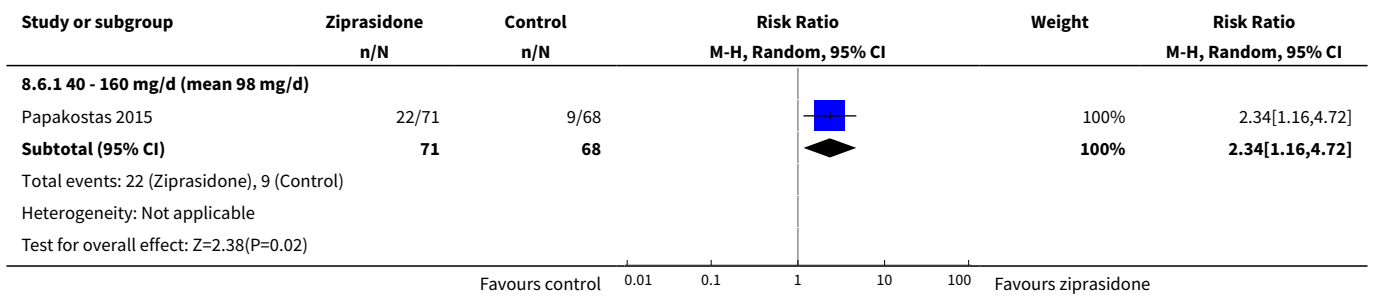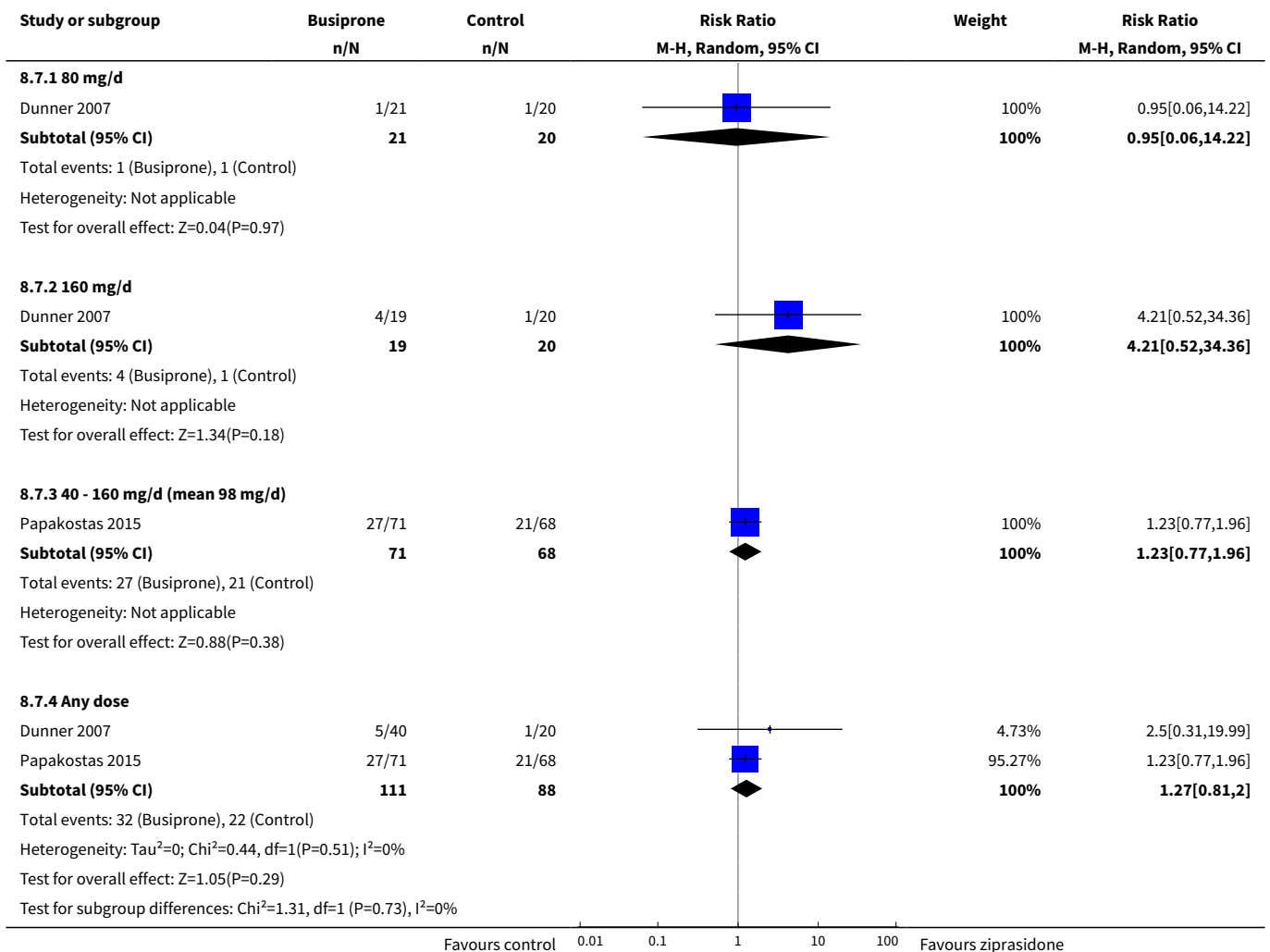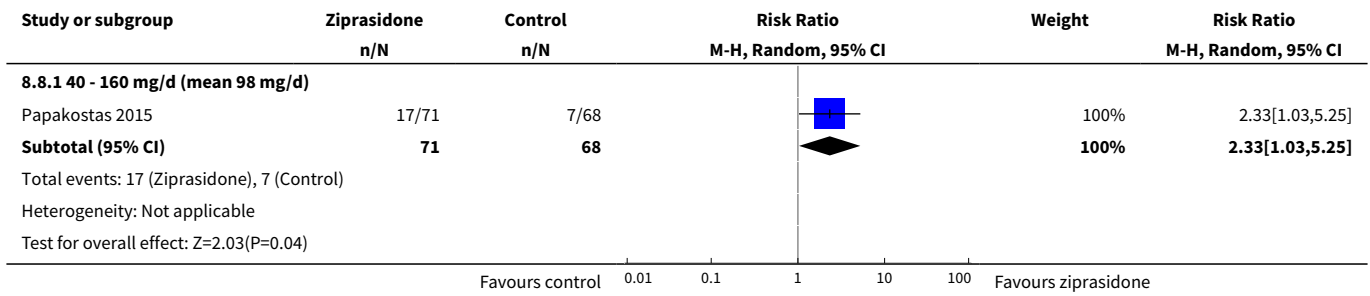## Analysis 8.6. Comparison 8 Augment current antidepressant with ziprasidone (antipsychotic), Outcome 6 Response (≥ 50% reduction in QIDS-SR).

Study or subgroup	Ziprasidone n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.6.1 40 - 160 mg/d (mean 98 mg/d)					
Papakostas 2015	22/71	9/68		100%	2.34[1.16,4.72]
Subtotal (95% CI)	**71**	**68**		**100%**	**2.34[1.16,4.72]**
Total events: 22 (Ziprasidone), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.38(P=0.02)					

Favours control 0.01 0.1 1 10 100 Favours ziprasidone

Analysis 8.7. Comparison 8 Augment current antidepressant with ziprasidone (antipsychotic), Outcome 7 Remission (MADRS/HAM-D).

Study or subgroup	Busiprone n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.7.1 80 mg/d					
Dunner 2007	1/21	1/20		100%	0.95[0.06,14.22]
Subtotal (95% CI)	**21**	**20**		**100%**	**0.95[0.06,14.22]**
Total events: 1 (Busiprone), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
8.7.2 160 mg/d					
Dunner 2007	4/19	1/20		100%	4.21[0.52,34.36]
Subtotal (95% CI)	**19**	**20**		**100%**	**4.21[0.52,34.36]**
Total events: 4 (Busiprone), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.34(P=0.18)					
8.7.3 40 - 160 mg/d (mean 98 mg/d)					
Papakostas 2015	27/71	21/68		100%	1.23[0.77,1.96]
Subtotal (95% CI)	**71**	**68**		**100%**	**1.23[0.77,1.96]**
Total events: 27 (Busiprone), 21 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.88(P=0.38)					
8.7.4 Any dose					
Dunner 2007	5/40	1/20		4.73%	2.5[0.31,19.99]
Papakostas 2015	27/71	21/68		95.27%	1.23[0.77,1.96]
Subtotal (95% CI)	**111**	**88**		**100%**	**1.27[0.81,2]**
Total events: 32 (Busiprone), 22 (Control)					
Heterogeneity: Tau²=0; Chi²=0.44, df=1(P=0.51); I²=0%					
Test for overall effect: Z=1.05(P=0.29)					
Test for subgroup differences: Chi²=1.31, df=1 (P=0.73), I²=0%					

Favours control 0.01 0.1 1 10 100 Favours ziprasidone

Analysis 8.8. Comparison 8 Augment current antidepressant with ziprasidone (antipsychotic), Outcome 8 Remission (QIDS-SR).

Study or subgroup	Ziprasidone n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.8.1 40 - 160 mg/d (mean 98 mg/d)					
Papakostas 2015	17/71	7/68		100%	2.33[1.03,5.25]
Subtotal (95% CI)	**71**	**68**		**100%**	**2.33[1.03,5.25]**
Total events: 17 (Ziprasidone), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.03(P=0.04)					

Favours control 0.01 0.1 1 10 100 Favours ziprasidone

ADDITIONAL TABLES

Table 1. Hierarchy of reasons for exclusion

Reason for Exclusion	No of articles excluded (%)
Not an RCT	106 (18.5)
Not a standard pharmacological treatment	131 (22.9)
No control group/not a comparison of interest	100 (17.5)
Not TRD/at point of randomisation	112 (19.5)
Not unipolar depression	27 (4.7)
Diagnostic criteria not applied at point of randomisation	59 (10.3)
Age	6 (1.0)
Trial terminated	1 (0.2)
Review article - refs checked	31 (5.4)
Total	**573 (100)**

RCT: randomised controlled trial

TRD: Treatment-resistant depression

Table 2. Reasons for dropouts *(Continued)*

Study	N	time point	intervention	Reasons for drop out	
				Intervention	Control (continue on AD monotherapy)
Appelberg 2001	108	6 weeks	Busiprone (augmentation of AD)	Protocol violation n = 3	Protocol violation n = 3
				Side effects n = 1	Did not attend final assessment n = 2
				Moved house n = 1	Stopped taking study medication n = 2

Table 2. Reasons for dropouts *(Continued)*

				Did not attend final assessment n = 1	Spouse threw away study medication n = 1
					Suspected angina n = 1
					Heavy alcohol misuse n = 1
Dunner 2007	64	8 weeks	Ziprasi-done (aug-mentation of AD)	80 mg/d: Treatment-related adverse event n = 9 Withdrew consent n = 1 Miscellaneous n = 1 160 mg/d: Treatment-related adverse event n = 7 Withdrew consent n = 1 Miscellaneous n = 2	Withdrew consent n = 4 Miscellaneous n = 1
Durgam 2016	819	8 weeks	Cariprazine (augmenta-tion of AD)	1 mg/d to 2 mg/d: Adverse event n = 18 Insufficient response n = 4 Protocol violation n = 10 Withdrew consent n = 13 Lost to follow-up n = 2 2 mg/d to 4.5 mg/d: Adverse event n = 36 Protocol violation n = 9 Withdrew consent n = 14 Lost to follow-up n = 4	Adverse event n = 8 Insufficient response n = 2 Protocol violation n = 6 Withdrew consent n = 11 Lost to follow-up n = 2 Other n = 2
El-Khalili 2010 (PEARL)	446	6 weeks	Quetiapine (augmenta-tion of AD)	150 mg/d: Adverse event n = 16 Lack of therapeutic response n = 2 Severe non-compliance with study protocol n = 2 Did not complete ≥ 36 days of study treatment n = 1 Lost to follow-up n = 8 Not willing to continue n = 4 Eligibility criteria not fulfilled n = 1 300 mg/d:	Adverse event n = 1 Lack of therapeutic response n = 4 Lost to follow-up n = 10 Not willing to continue n = 8

Table 2. Reasons for dropouts *(Continued)*

				Adverse event n = 27	
				Did not complete ≥ 36 days of study treatment n = 1	
				Lost to follow-up n = 7	
				Not willing to continue n = 6	
				Eligibility criteria not fulfilled n = 1	
				Other n = 3	
Ferreri 2001	104	6 weeks	Mianserine (switched from AD) Mianersine (augmentation of AD)	Switched to mianserin alone: Ineffectiveness n = 1 Lost to follow-up n = 2 Intolerance/ adverse events n = 8 Substantial improvement n = 0 Personal reason n = 1 Augmented with mianserin: Ineffectiveness n = 1 Lost to followup n = 2 Intolerance/ adverse events n = 2 Substantial improvement n = 1 Personal reason n = 1	Ineffectiveness n = 6 Lost to follow-up n = 1 Intolerance/ adverse events n = 0 Substantial improvement n = 0 Personal reason n = 1
Kessler 2018	480	52 weeks	Mirtazapine (augmentation of AD)	Withdrew from study n = 6 Not willing to take part n = 2 Health n = 1 Other n = 3 Lost to follow-up n = 44	Withdrew from study n = 12 Not willing to take part n = 8 Health n = 2 Other n = 2 Lost to follow-up n = 28
McIntyre 2007	58	6 weeks	Quetiapine (augmentation of AD)	Adverse events n = 8 Consent withdrawal n = 2 Protocol violation n = 1	Lack of efficacy n = 9 Adverse events n = 2 Lost to follow-up n = 2
Papakostas 2015	139	8 weeks	Ziprasidone (augmentation of AD)	Intolerance n = 10 Inefficacy n = 3 Lost to follow-up n = 3 Other n = 6	Inefficacy n = 1 Lost to follow-up n = 7 Other n = 7
Shelton 2001	20	8 weeks	Olanzapine (augmentation of AD)	Protocol violation n = 1	Lack of efficacy n = 1 Personal conflict n = 1 Protocol violation n = 1

AD: antidepressant

Table 3. Adverse events *(Continued)*

Study (intervention)	All AEs		Serious AEs		Serious AE details/notes
	Intervention	Control	Intervention	Control	
Appelberg 2001 (augment with busiprone)	n.r.	n.r.	0/54 (0%)	0/54 (0%)	"No serious adverse events were observed. No statistically significant differences were observed in UKU scores between treatment groups throughout the study" (p.450, Safety). 1 participant in the busiprone arm was reported to have dropped out of the study due to side effects.
Bauer 2009 (ONYX) (augment with quetiapine)	150 mg/d: 108/166 (65%) 300 mg/d: 121/161 (75%)	86/160 (54%)	150 mg/d: 2/166 (1.2%) 300 mg/d: 3/161 (1.8%)	3/160 (1.9%)	Serious AEs were investigator-defined. No further detail provided
Durgam 2016 (augment with cariprazine)	1 mg/d to 2 mg/d: 189/273 (69.2%) 2 mg/d to 4.5 mg/d: 214/273 (78.4%)	157/266 (59%)	1 mg/d to 2 mg/d: 0/273 (0%) 2 mg/d to 4.5 mg/d: 2/273 (0.7%)	1/266 (0.4%)	Serious AEs were depression (placebo); agitation (cariprazine 2 mg/d to 4.5 mg/d); and panic attack, dyspnoea and non-cardiac chest pain (one patient experienced three events, cariprazine 2 mg/d to 4.5 mg/d).
Dunner 2007 (augment with ziprasidone)	80 mg/d: 21/21 (100%) 160 mg/d: 16/19 (84.2%)	8/20 (40%)	80 mg/d: 0/21 160 mg/d: 0/19	0/20	"No serious adverse events were reported" (p.1071).
El-Khalili 2010 (PEARL) (augment with quetiapine)	150 mg/d: 122/148 (82.4%) 300 mg/d: 130/149 (87.2%0	99/148 (66.9%)	150 mg/d: 0/148 300 mg/d: 0/149	0/148	"Two serious AEs were reported during the study period. One patient experienced a transient ischaemic attack (placebo) and one patient experienced worsening of cervical spondylitis (quetiapine XR 150 mg/d); neither was considered treatment related by the investigator." (p.925)
Ferreri 2001 (switch to/augment with mianserin)	switch: 24/34 (70.5%); augment:17/38 (44.7%)	9/32 (28.1%)	n.r.	n.r.	No information on serious adverse events reported
Kessler 2018 augment with mirtazapine	12 weeks: 167/241 (69.3%)	12 weeks: 91/239 (38.1%)	At 12 weeks: 8/241 (3.32%)	At 12 weeks: 3/239 (1.25%)	Serious SAEs at 12 weeks: Mirtazapine: central nervous system/transient ischaemic attack (TIA) (n = 1), cardiovascular (n = 1), dental (n = 1), gynaecological (n = 1), pancreatitis (n = 1), psychiatric (n = 2) and respiratory (n = 1). Four serious SAEs in this group were con-

Table 3. Adverse events *(Continued)*

					sidered to be not related to the intervention, two unlikely to be related and two possibly related. Placebo: infection (n = 1) and musculoskeletal trauma (n = 2). (all three serious SAEs in this group were considered to be not related to the intervention). Adverse events beyond 12 weeks were reported by frequency of event. Numbers of patients experiencing ≥ 1 adverse event not provided
McIntyre 2007 (augment with quetiapine)	n.r.	n.r.	0/29 (0%)	0/29 (0%)	"No serious AEs were reported." (p.491, Safety and tolerability). Most commonly occurring adverse events reported in table 2 (type and frequency broken down by treatment) but numbers of participants experiencing ≥ 1 adverse event not reported
Papakostas 2015 (augment with ziprasidone)	n.r.	n.r.	2/71 (2.8%)	2/68 (2.9%)	Serious AEs: Ziprasidone (one hospitalisation because of treatment-emergent suicidal thoughts and one because of a fall). Placebo (hospitalisations for treatment-emergent viral meningitis and pneumonia respectively). Data for all adverse events reported by frequency of event. Numbers of patients experiencing ≥ 1 adverse event not reported
Shelton 2001 (augment with olanzapine)	n.r.	n.r.	n.r.	n.r.	Most commonly occurring adverse events described in the text but numbers (and treatment) of participants experiencing AEs not reported

AE: adverse event

n.r.: Not reported

TIA: transient ischaemic attack

APPENDICES

Appendix 1. MEDLINE (Ovid): CCMD's core search strategy used to inform the Group's specialised register

A weekly search alert based on condition + RCT filter only

1. *[MeSH Headings]:*

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/

2. *[Title/ Author Keywords]:*

(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia

or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.

3. *[RCT filter]:*
(controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

4. (1 and 2 and 3)

Records were screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs were tagged to the appropriate study record.

Similar weekly search alerts were also be conducted on OVID Embase and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

Appendix 2. Review search strategies

1 MEDLINE (Ovid)

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <(1 January 2016 to 31 December 2018) >

1 Depressive Disorder, Treatment-Resistant/
2 (depress* and ((antidepress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or medication* or psychotropic or treatment* or respon*) adj2 fail*)).ti,ab,kf.
3 (depress* and ((antidepress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or psychotropic medication* or treatment*) adj2 ("no respon*" or "not respon*" or nonrespon* or non-respon* or unrespon*))).ti,ab,kf.
4 (depress* adj3 (refractor* or resistan* or chronic* or persist*)).ti,ab,kf.
5 (depress* adj3 (relaps* or recurr*)).ti,kf.
6 (depress* and (augment* or potentiat*)).mp.
7 or/1-6
8 randomized controlled trial.pt. or exp randomized controlled trial/ or exp Randomized Controlled Trials as Topic/
9 controlled clinical trial.pt.
10 (RCT or randomi#ed or at random or (random* adj3 (assign* or allocat* or divide* or division or number*))).ti,ab,kf.
11 ((placebo or sham or mock or fake or dummy) and (control* or group?)).ti,ab,kf.
12 double-blind*.ti,ab,kf,hw.
13 trial.ti.
14 ((cluster or crossover* or cross-over*) adj3 (random* or trial or study or control* or group?)).ti,ab,kf.
15 or/8-14
16 7 and 15
17 letter/
18 editorial/
19 news/
20 exp historical article/
21 Anecdotes as topic/
22 comment/
23 case report/
24 (letter or comment*).ti.
25 exp animals/ not humans/
26 exp Animals, Laboratory/
27 exp Animal Experimentation/ not (exp human experimentation/ or humans/)
28 exp Models, Animal/
29 exp rodentia/
30 (rat or rats or mouse or mice or rodent*).ti.
31 or/17-30
32 16 not 31
33 (2016* or 2017*).yr,dc,ed,ep.
34 (in-data-review or in-process or publisher).st.
35 33 or 34

36 32 and 35

2 Embase (Ovid)

(1 January 2016 to 31 December 2018)

1 treatment resistant depression/
2 (depress* and ((antidepress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or medication* or psychotropic or treatment* or respon*) adj2 fail*)).ti,ab,kf.
3 (depress* and ((antidepress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or psychotropic medication* or treatment*) adj2 ("no respon*" or "not respon*" or nonrespon* or non-respon* or unrespon*))).ti,ab,kf.
4 (depress* adj3 (refractor* or resistan* or chronic* or persist*)).ti,ab,kf.
5 (depress* adj3 (relaps* or recurr*)).ti,kf.
6 (depress* and (augment* or potentiat*)).mp.
7 or/1-6
8 randomized controlled trial/ or "randomized controlled trial (topic)"/
9 crossover procedure/
10 "double blind procedure"/
11 "single-blind procedure"/
12 (RCT or randomi#ed or at random or (random* adj3 (assign* or allocat* or divide* or division or number*))).ti,ab,kf.
13 trial.ti.
14 ((cluster or crossover* or cross-over*) adj3 (random* or trial or study or control* or group?)).ti,ab,kf.
15 double-blind*.ti,ab.
16 ((placebo or sham or mock or fake or dummy) and (control* or group?)).ti,ab,kf.
17 or/8-16
18 7 and 17
19 letter.pt. or letter/
20 note.pt.
21 editorial.pt.
22 case report/ or case study/
23 (letter or comment*).ti.
24 exp animal/ not human/
25 nonhuman/
26 exp experimental animal/
27 exp animal experiment/
28 exp animal model/
29 exp rodent/
30 (rat or rats or mouse or mice or rodent*).ti.
31 or/19-30
32 18 not 31

3 PsycINFO (Ovid)

(1 January 2016 to 31 December 2018)

1 (depress* and ((antidepress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or medication* or psychotropic or treatment* or respon*) adj2 fail*)).ti,ab,id.
2 (depress* and ((antidepress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or psychotropic medication* or treatment*) adj2 ("no respon*" or "not respon*" or nonrespon* or non-respon* or unrespon*))).ti,ab,id.
3 (depress* adj3 (refractor* or resistan* or chronic* or persist*)).ti,ab,id.
4 (depress* and (augment* or potentiat*)).mp.
5 treatment resistant depression/
6 (depress* adj3 (relaps* or recurr*)).ti,id.
7 or/1-6
8 clinical trials/
9 (RCT or randomi#ed or at random or (random* adj3 (assign* or allocat* or divide* or division or number*))).ti,ab,id.
10 double-blind*.ti,ab,id,hw.
11 ((placebo or sham or mock or fake or dummy) and (control* or group?)).ti,ab,id.
12 trial.ti.
13 ((cluster or crossover* or cross-over*) adj3 (random* or trial or study or control* or group?)).ti,ab,id.
14 or/8-13
15 7 and 14
16 (authored book or book or edited book).pt.
17 scientific communication/

18 case report/
19 (letter or comment*).ti.
20 exp animals/ or animal models/
21 (rat or rats or mouse or mice or rodent*).ti.
22 or/16-21
23 15 not 22

4 Cochrane Central Register of Controlled Trials (CENTRAL), Issue 12, 2018

(1 January 2016 to 31 December 2018)
#1MeSH descriptor: [Depressive Disorder, Treatment-Resistant] explode all trees
#2(depress* and ((antidepress* or SSRI* or SNRI* or (serotonin near/3 (uptake or reuptake or re-uptake)) or medication* or psychotropic or treatment* or respon*) near/2 fail*)):ti,ab,kw
#3(depress* and ((antidepress* or SSRI* or SNRI* or (serotonin near/3 (uptake or reuptake or re-uptake)) or "psychotropic medication" or "psychotropic medications" or treatment*) near/2 ("no respon*" or "not respon*" or nonrespon* or non-respon* or unrespon*))):ti,ab,kw
#4(depress* near/3 (refractor* or resistan* or chronic* or persist*)):ti,ab,kw
#5(depress* near/3 (relaps* or recurr*)):ti,kw
#6(depress* and (augment* or potentiat*)):ti,ab,kw
#7#1 or #2 or #3 or #4 or #5 or #6

5 Web of Science (Clarivate Analytics)

(1 January 2016 to 31 December 2018)

 # 15 #11 not #14
 # 14 #13 OR #12
 # 13 TS=((animal* near/2 experiment*) or (animal* near/2 model*) or (animal* near/2 laborator*))
 # 12 TI= (rat or rats or mouse or mice or rodent* or animal* or comment* or letter or "case study" or "case report" or anecdote* or editorial* or news)
 # 11 #10 AND #6
 # 10 #9 OR #8 OR #7
 # 9 TI= trial
 # 8 TS= (RCT or randomized or randomised or "at random" or (random* near/3 (assign* or allocat* or divide* or division or number*)))
 # 7 TS= ((controlled near/2 "clinical trial") or double-blind* or ((placebo or sham or mock or fake or dummy) and (control* or group?)) or ((cluster or crossover* or cross-over*) near/3 (random* or trial or study or control* or group?)))
 # 6 #5 OR #4 OR #3 OR #2 OR #1
 # 5 TS=(depress* and (augment* or potentiat*))
 # 4 TS=(depress* near/3 (relaps* or recurr*))
 # 3 TS=(depress* near/3 (refractor* or resistan* or chronic* or persist*))
 # 2 TS=(depress* and ((antidepress* or SSRI* or SNRI* or (serotonin near/3 (uptake or reuptake or re-uptake)) or "psychotropic medication" or "psychotropic medications" or treatment*) near/2 ("no respon*" or "not respon*" or nonrespon* or non-respon* or unrespon*)))
 # 1 TS=((depress* and ((antidepress* or SSRI* or SNRI* or (serotonin near/3 (uptake or reuptake or re-uptake)) or medication* or psychotropic or treatment* or respon*) near/2 fail*)))

6 International trials registers search (all years)

Types of Study = Interventional

Condition 1 = treatment resistant depression

Condition 2 = refractory depression

Condition 3 = recurrent depression

Condition 4 = chronic depression

CONTRIBUTIONS OF AUTHORS

DECLARATIONS OF INTEREST

GL has received payments for lectures from pharmaceutical companies.

PD, SI, DK, and NW have no conflicts to declare.

DK was the chief investigator for the MIR study (Kessler 2018); GL and NW were co-investigators.

Author CW deceased: declarations of interest published in the protocol (Williams 2013)."CW has no conflicts to declare".

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Internal sources

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External sources

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- NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol, UK, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we defined the comparator intervention as 'antidepressant medication - either continuing on the initial antidepressant monotherapy or another antidepressant.'. Hence, switching to another antidepressant was listed in the protocol as both an intervention and comparator of interest. In order to make a meaningful comparison, studies need to include a group that continue on existing antidepressant monotherapy. We therefore decided not to consider switching to another antidepressant a suitable control condition and amended our inclusion criteria accordingly.

We also stated that missing data would be addressed in additional analyses assuming best (all who dropped out had positive outcomes) and worst (all who dropped out had negative outcomes) case scenarios. However, we later agreed that this was not necessary because study level data were more robust than participant level data imputations determined by review authors.