National Institute for Health and Care Excellence

Final

Depression in children and young people, 2015 evidence review

NICE guideline NG134

Evidence review underpinning recommendations 1.6.7, 1.6.10, 1.6.11 and 1.6.14 on combination therapy in the NICE guideline

March 2015

Final version

National Institute for Health and Care Excellence

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic-specific members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic-specific members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic-specific members' is referred to this means the recruited group of members with topic-specific expertise.

All of the standing members and the topic-specific members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The area on psychological therapies for the treatment of depression in children and young people was updated in 2019.

The NICE guideline on depression in children and young people (NICE clinical guideline CG28) was reviewed in 2013 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence relating to two areas of the guidance:

- The psychological therapies for the treatment of depression in children and young people;
- The use of antidepressant treatment and psychological therapy, either alone or together for the treatment of depression in children and young people.

The full report can be found here: http://www.nice.org.uk/guidance/cg28/resources/cg28-depression-in-children-and-young-people-review-decision-oct-132

Recommendations in this addendum fall into 3 categories:

1. New recommendations relating to psychological therapy and the combination of psychological therapy and antidepressant treatment for depression in children and young people have been made in this addendum and are labelled **[new 2015]**.
2. Recommendations labelled **[2015]** have been reviewed, but the Committee concluded that there was not enough new evidence to change them.
3. Recommendations highlighted in grey and labelled **[2005]** are only included to provide context.

Some recommendations can be made with more certainty than others. The wording used in the recommendations labelled **[new 2015]** in this addendum denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

In recommendations labelled **[new 2015]** we use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

In recommendations labelled **[new 2015]** we use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely

to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.2 Recommendations

1. Consider combined therapy (fluoxetine[a] and psychological therapy) for initial treatment of moderate to severe depression in young people (12–18 years), as an alternative to psychological therapy followed by combined therapy and to recommendations 5, 6 and 7. **[new 2015]**

2. If moderate to severe depression in a child or young person is unresponsive to psychological therapy after four to six treatment sessions, a multidisciplinary review should be carried out. **[2005]**

3. Following multidisciplinary review, if the child or young person's depression is not responding to psychological therapy as a result of other coexisting factors such as the presence of comorbid conditions, persisting psychosocial risk factors such as family discord, or the presence of parental mental ill-health, alternative or perhaps additional psychological therapy for the parent or other family members, or alternative psychological therapy for the patient, should be considered. **[2005]**

4. Following multidisciplinary review, offer fluoxetine[b] if moderate to severe depression in a young person (12–18 years) is unresponsive to a specific psychological therapy after 4 to 6 sessions. **[2015]**

5. Following multidisciplinary review, cautiously consider fluoxetine[ac] if moderate to severe depression in a child (5–11 years) is unresponsive to a specific psychological therapy after 4 to 6 sessions, although the evidence for fluoxetine's effectiveness in this age group is not established. **[2015]**

6. Do not offer antidepressant medication to a child or young person with moderate to severe depression except in combination with a concurrent psychological therapy. Specific arrangements must be made for careful monitoring of adverse drug reactions, as well as for reviewing mental state and general progress; for example, weekly contact with the child or young person and their parent(s) or carer(s) for the first 4 weeks of treatment. The precise frequency will need to be decided on an individual basis, and recorded in the notes. In the event that psychological therapies are declined, medication may still be given, but as the young person will not be reviewed at psychological therapy sessions, the prescribing doctor should closely monitor the child or young person's progress on a regular basis and focus particularly on emergent adverse drug reactions. **[2015]**

[a] At the time of publication (March 2015), Fluoxetine did not have UK marketing authorisation for use in young people (aged 12-18), without a previous trial of psychological therapy that was ineffective. For combined antidepressant treatment and psychological therapy as an initial treatment, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[b] At the time of publication (March 2015), Fluoxetine was the only antidepressant with UK marketing authorisation for use for children and young people aged 8 to 18 years.

[c] At the time of publication (March 2015), Fluoxetine did not have UK marketing authorisation for use for children under the age of 8 years. For children under the age of 8 years, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

1.3 Patient-centred care

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. People should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent, the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with depression. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1.4 Methods

This update was developed based on the process and methods described in the guidelines manual 2012. Where there are deviations from the process and methods, these are stated in the interim process and methods guide for updates pilot programme 2013.

Important outcomes were chosen and prioritised by the topic-specific members of the Committee using a ranking method. The relative value of different outcomes was discussed, and the final rankings were completed by each topic-specific member independently, collated, and then agreed by the standing Committee members before the review was carried out.

The same minimum clinically important differences were used as those that were agreed by the guideline development group for the original NICE guideline on depression in children and young people. For comparisons of an active intervention with no treatment, minimum clinically important differences were taken to be 0.2 and 5 for dichotomous outcomes and -0.4 and 0.4 standardised mean differences (SMDs) for continuous outcomes. For comparisons of two active interventions, minimum clinically important differences were taken to be 0.5 and 2 for dichotomous outcomes and -0.2 and 0.2 SMDs for continuous outcomes.

For each question, the quality of evidence for each important outcome for each comparison was appraised using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (see appendix H). All included studies were randomised controlled trials. Typical reasons for downgrading the evidence for risk of bias included lack of blinding (of participants or outcome assessors), inadequate or unclear allocation concealment, and inadequate or unclear random sequence generation. Inconsistency was only assessed when data was combined in a meta-analysis. The degree of heterogeneity was assessed, and 95% confidence intervals were examined to determine whether serious inconsistency was present, using the methods described by the GRADE working group. Indirectness was assessed by noting whether the evidence directly applied to the review question; no cases of serious indirectness were noted. Imprecision was assessed by determining whether 95% confidence intervals incorporated clinically significant harm, no effect and clinically significant benefit. If all three were incorporated in the confidence interval, imprecision was judged very serious. If two of the three were incorporated, imprecision was considered serious. Other factors such as publication bias were also considered, but none gave rise to serious uncertainty.

2 Evidence review and recommendations

Introduction

Evidence reviews were conducted for two areas of the depression in children and young people clinical guideline. Review question 1 covers the use of different psychological therapies for the treatment of depression in children and young people. Review questions 2 and 3 cover the use and timing of antidepressant treatment and psychological therapy, separately or together in the treatment of depression in children and young people.

2.1 Review question 1: psychological therapies for the treatment of depression in children and young people

Please note that review question 1 was updated in 2019 and the evidence from 2015 has been removed.

2.2 Review questions 2 and 3: antidepressants, psychological therapy and combination therapy for the treatment of depression in children and young people

The aim of this review was:

- to compare the effectiveness of antidepressant and psychological therapies, separately or in combination, for the treatment of depression in children and young people.
- to compare the effectiveness of initiating psychological therapy and antidepressant treatment concurrently with initiating antidepressant treatment following a delay, only if the initial psychological therapy was ineffective,

Two systematic reviews were carried out (review questions 2 and 3), and are described separately below. However, the linking evidence to recommendations section (section 2.2.9) and the recommendations in section 2.2.10 relate to both review questions.

2.2.1 Review question 2

For children and young people with depression, what is the relative effectiveness of:

- Different antidepressants alone, compared to
- Different psychological therapies alone, compared to
- A combination of one psychological therapy (or psychological therapies) and one antidepressant (or antidepressants)?

2.2.2 Evidence review, question 2

A published Cochrane systematic review was identified that answered the review question (Cox et al. 2012). The Cochrane systematic review was updated and re-analysed by the original authors for the purpose of producing the evidence for this clinical guideline addendum (Cox et al 2015):

- An update search was run (14th June 2014) to identify any additional studies published since the original search date.
- The following additional subgroup analyses were considered:
  - Analysis by different type of antidepressant medication
  - Analysis by different psychological therapy
  - Analysis by age (6-11, 12-18 years)
  - Analysis by depression severity (mild, moderate, severe)

Details of the included systematic review are given in an evidence table in appendix G.2, and a summary is given in Table 1. Full details of the systematic review, including forest plots and details of included and excluded studies are freely available online ([link to be inserted on publication of the updated review], link to the previous version of the review: http://dx.doi.org/10.1002/14651858.CD008324.pub2)

The following outcomes from the review (listed in order of importance) were considered important for decision making: level of function (functional status), improvement in depressive symptoms, suicide-related serious adverse events, remission from depressive disorder, suicide-related outcomes (suicidal ideation), remission defined as criterion improvement in depressive symptoms, acceptability of treatment measured by number of dropouts for any reason (the last two outcomes were ranked equally). For further details about how these outcomes were defined, see the review protocol in Appendix C.2. The quality of evidence for each outcome in this Cochrane systematic review was assessed using

GRADE methodology, as described in section 1.4. Full GRADE profiles are shown in Appendix H.2.

Table 1: Summary of included study

Study reference	Study Design	Study population	Intervention & comparator	Outcomes reported
Cox 2014	Systematic review of randomised trials	Children and young people with diagnosed depressive disorder	Antidepressants vs psychological therapy vs combined treatment (antidepressants + psychological therapy)	• level of function (functional status) • improvement in depressive symptoms • remission from depressive disorder, • suicide-related outcomes (suicidal ideation) • remission defined as criterion improvement in depressive symptoms • acceptability of treatment measured by number of dropouts for any reason

2.2.3 Health economic evidence, review question 2

A systematic search was conducted (independently of the aforementioned published systematic review, Cox et al. 2015) to identify economic evaluations of psychological or pharmacological interventions for depression in children and young people (see appendix D.3). 1648 articles were identified by the search. The titles and abstracts were screened and 15 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 12 articles were excluded as they did not meet the criteria and 3 articles met the criteria and were included. Two articles reported the same study, so there were 2 included studies. One of these studies is relevant to review question 1 and the other is relevant to review question 2. A list of excluded studies together with the reason for their exclusion is provided in appendix F.3.

Table 2: Summary of included economic evaluation

Study, Population, Applicability, Limitations	Inter-ventions	Incremental Analysis			Conclusions	Uncertainty
		Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Goodyer et al. (2008) Byford et al. (2007) United Kingdom 208 adolescents aged 11 to 17 inclusive with major depression (associated	SSRIs plus CBT SSRIs (comparator)	2,115	-0.0297	Dominated[c]	There was significant recovery at all time points in both arms. There was no treatment effectiveness for the addition of CBT to SSRIs for the primary or secondary outcome measures at	2% probability that SSRIs plus CBT is cost-effective compared to SSRIs alone (£50,000 threshold)

Study, Population, Applicability, Limitations	Inter-ventions	Incremental Analysis			Conclusions	Uncertainty
		Cost (£)	Effect (QALYs)	ICER (£/QALY)		
randomised controlled trial) Partially applicable[a] Minor Limitations [b]					any time point. A combination of CBT plus SSRIs is not more cost-effective in the short-term than SSRIs alone for treating adolescents with major depression in receipt of routine specialist clinical care.	

Acronyms: CBT: cognitive behavioural therapy; SSRI: selective serotonin reuptake inhibitor; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio

(a) There were no CBT only, usual care, or placebo arms in the underlying study. All participants received a brief initial psychological intervention, SSRIs and active clinical care regardless of subsequent randomisation. All other forms of ongoing psychiatric treatment were permitted during the study period except for CBT if the subject was randomised to the SSRI alone arm of the study.

(b) Time horizon was 12 months.

(c) Dominated: Intervention results in increased costs and a reduction in health benefits when relative to the comparator

2.2.4 Evidence statements, review question 2

Although many psychological therapies met the inclusion criteria for the review, all of the included studies used cognitive behavioural therapy (CBT). All of the evidence included in the review was from young people over the age of 11 with the exception of 1 small trial (33 participants) which included children and young people.

Psychological therapy vs antidepressants

There was moderate-quality evidence from 1 trial comparing CBT with antidepressants in 220 young people showing a difference in clinician rated post-treatment depression symptoms in favour of antidepressants but no clear difference in depression symptoms in the long term. There was no clear difference in remission rates, and low-quality evidence from two trials in 269 young people suggesting that there might be less suicidal ideation with CBT measured post treatment. In the long term, there was some low-quality evidence that this difference in suicidal ideation might be sustained, but no clear evidence of other important differences between treatments.

Antidepressants and psychological therapy vs psychological therapy alone or with placebo

There was moderate-quality evidence from 1 trial with 218 young people that the combination of antidepressant and CBT gave lower post treatment clinician-rated depression symptom scores than CBT alone. However, there was no clear evidence of a difference in other outcomes, with the exception of low-quality evidence from 1 trial with 218 young people suggesting there may be a higher remission rate with the combination after treatment (risk ratio 2.31 95% CI 1.41 to 3.76). At 12-month follow up, there was low-quality evidence from 1

trial with 218 young people of lower clinician- and self-rated depression scores for combination compared with psychological therapy alone, but with no clear evidence of a difference for other outcomes.

When the active combination of antidepressants and psychological therapy was compared to a placebo tablet with psychological therapy, 3 trials with 239 young people provided moderate-quality evidence of lower clinician-rated symptom scores with the combination of active treatments, and 3 trials with 123 young people gave low-quality evidence of lower self-rated depression scores in the active combination immediately post treatment. There was moderate-quality evidence from 173 young people in 2 trials of no clinically important difference in remission rate post treatment.

Antidepressants and psychological therapy vs antidepressants alone

Comparing psychological therapy plus antidepressants to antidepressants alone, there was no clear evidence of a difference across a number of outcomes immediately post treatment or at 6-9 months follow up involving between 1 and 5 trials and 216 to 683 young people. At 12 months follow up, there was some low-quality evidence of better functioning (1 trial, 152 young people) and self-rated depression scores (2 trials, 368 young people) with the combination, although this was of uncertain clinical importance, and there was no clear difference for other outcomes.

One economic evaluation conducted alongside a randomised controlled trial found that there was no economic value of combination treatment (SSRI plus CBT) compared to an antidepressant (SSRI) alone as the increase in cost was not offset by any health gains or reductions in the use of other resources. The study was partially applicable. Although it was conducted in the UK and the participants had more severe depression, there was no CBT only, usual care, or placebo arms. All participants received a brief initial psychological intervention, SSRIs and active clinical care regardless of subsequent randomisation. All other forms of ongoing psychiatric treatment were permitted during the study period except for CBT if the subject was randomised to the SSRI alone arm of the study. The economic evaluation had a time horizon of 12 months in line with the underlying study. No economic evaluations that examined the cost-effectiveness of CBT alone, or SSRIs compared to usual care or placebo, were included in the literature review of economic evidence.

2.2.5 Review question 3

For children and young people with depression, what is the relative effectiveness of:

- Initiating psychological therapy first, followed by additional antidepressants only if psychological therapy is initially ineffective, compared to,
- Initiating psychological therapy and antidepressants simultaneously.

2.2.6 Evidence review, review question 3

A systematic search was conducted (see appendix D.2) which identified 1832 articles. The titles and abstracts were screened and 1 article was identified as potentially relevant. A full-text version of this article was obtained and reviewed against the criteria specified in the review protocol (appendix C.3). The article was excluded as it did not meet the criteria and so there were no included studies.

2.2.7 Health economic evidence, review question 3

A systematic search was conducted to identify economic evaluations of psychological or pharmacological interventions for depression in children and young people (see appendix D.3). 1648 articles were identified by the search. The titles and abstracts were screened and 15 articles were identified as potentially relevant. Full-text versions of these articles were

obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 12 articles were excluded as they did not meet the criteria and 3 articles met the criteria and were included. Two articles reported the same study, so there were 2 included studies. One of these studies is relevant to review question 1 and the other is relevant to review question 2. No economic evaluations were identified that were relevant to review question 3. A list of excluded studies together with the reason for their exclusion is provided in appendix F.3.

2.2.8 Evidence statements, review question 3

No studies were included that compared the effectiveness of the initiation of psychological therapy and antidepressant treatment concurrently with the initiation of antidepressant treatment only if psychological therapy was ineffective.

No economic studies were included that compared the effectiveness of the initiation of psychological therapy and antidepressant treatment concurrently with the initiation of antidepressant treatment only if psychological therapy was ineffective.

2.2.9 Evidence to recommendations for review questions 2 and 3

Relative value of different outcomes	**Review question 2** The outcomes that were considered important for decision making (listed in order of importance as prioritised by the topic-specific committee members using a ranking method) were: level of function (functional status), improvement in depressive symptoms, suicide-related serious adverse events, remission from depressive disorder, suicide-related outcomes (suicidal ideation), remission defined as criterion improvement in depressive symptoms, acceptability of treatment measured by number of dropouts for any reason (the last two outcomes were ranked equally). The relative value of outcomes was similar to that for question 1. The Committee valued functional status highly because it provides a measure of the impact of depression on a child or young person's ability to carry out everyday activities such as attending school. Depression symptoms were also valued highly as they provide a measure of severity of the depressive disorder. Suicide-related outcomes were considered important because suicide is a very serious, but rare consequence of depression in children and young people. Suicidal ideation was valued less highly than suicide-related adverse events because although suicidal ideation is related to future suicide-related adverse events, many children or young people with suicidal ideation do not go on to attempt suicide. Number of dropouts was valued less highly than other outcomes because the topic-specific members of the Committee considered that they were hard to interpret; as children or young people discontinue psychological therapies and antidepressant treatment for many reasons, including recovery, or because they find treatment unacceptable. Remission from depressive disorder as judged by clinical interview was rated more highly that remission judged by reduction in depression symptoms below a cut-off criterion because the later outcome was considered to be already partly incorporated in the depression symptoms outcome, and remission judged by clinical interview was considered to be a more reliable measure of recovery from depressive disorder. **Review question 3** The outcomes that were considered important for decision making (listed in order of importance as prioritised by the topic-specific committee members using a ranking method) were: level of function, depression symptoms, remission rate, suicidal ideation, suicide-related adverse events, discontinuation from treatment due to adverse events, discontinuation from

	treatment for any reason. As there were no included studies for this review question, the relative value of different outcomes was not discussed further by the Committee.
Trade-off between benefits and harms	**Review question 2** For the comparison between antidepressants and psychological therapies, a reduction in depression symptoms with antidepressant treatment immediately post-treatment was offset against a possible reduction in suicidal ideation with psychological therapy (although this reduction was of uncertain clinical importance). The topic-specific committee members noted that antidepressants are likely to have a more rapid action than psychological therapy, and this could explain the reduction in depression symptoms with antidepressants compared with psychological therapy in the short term, but not the long term. When comparing combined treatment with antidepressants alone, there was no clear evidence favouring one intervention over another. For combined treatment compared with psychological therapy alone (with or without a placebo tablet), the Committee considered that the evidence favoured combined treatment, with evidence of a reduction in depression symptoms, at least immediately following treatment, and some evidence of an increase in remission rate post-treatment with combination therapy compared with psychological therapy alone. For this comparison there were no harms identified to trade-off against these benefits, and so the Committee considered that overall, the evidence favoured combined therapy compared with psychological therapy alone. **Review question 3** No studies were included in the review comparing initiation of antidepressant treatment and psychological therapies concurrently with initiation of antidepressant treatment only if psychological therapy was ineffective. Therefore it was not possible to compare the trade-off of benefits and harms for review question 3.
Trade-off between net health benefits and resource use	**Review question 2** For the comparison between antidepressants and psychological therapies, a reduction in depression symptoms with antidepressant treatment immediately post-treatment was offset against a possible reduction in suicidal ideation with psychological therapy. The topic-specific committee members noted that antidepressants are likely to have a more rapid action than psychological therapy, and this could explain the reduction in depression symptoms with antidepressants compared with psychological therapy in the short term, but not the long term. When comparing combined treatment with antidepressants alone, there was no clear evidence favouring one intervention over another. For combined treatment compared with psychological therapy alone (with or without a placebo tablet), the Committee considered that the evidence favoured combined treatment, with evidence of a reduction in depression symptoms, at least immediately following treatment, and some evidence of an increase in remission rates post-treatment with combination therapy compared with psychological therapy alone. For this comparison there were no harms identified to trade-off against these benefits, and so the Committee considered that overall, the evidence favoured combined therapy compared with psychological therapy alone. The Committee agreed that a particular strength of the single economic evaluation included in the health economics evidence was that the underlying trial was conducted in the UK and most of the participants had more severe depression, similar to people seen in CAMHS services.

	However, the lack of CBT only, usual care, or placebo arms in the underlying study limited the applicability of the economic evaluation's findings to the cost-effectiveness evidence used to inform the update of the current guideline recommendations. This is because the recommendations in the original guideline stipulate psychological therapy as the first line intervention with antidepressant treatment provided only if this is ineffective. Similarly, antidepressants are not to be used in isolation without psychological therapy. The lack of a placebo arm in the underlying trial was also seen as impacting applicability as other trials considered in the clinical review showed a significant response in placebo arms and the cost implications of this should be an important consideration in economic evaluations on this topic. All participants received a brief initial psychological intervention, SSRIs and active clinical care regardless of subsequent randomisation. All other forms of ongoing psychiatric treatment were permitted during the study period except for CBT if the subject was randomised to the SSRI alone arm of the study. The committee determined that the 12 month time horizon was a methodological limitation as this did not account for future presentations to healthcare providers that would occur due to relapse if the effectiveness of interventions decreased over time and there was no way to compare this between interventions given the lack of clinical evidence. The Committee concluded it was difficult to come to any firm stance on the relative cost-effectiveness of antidepressants, psychological interventions and combination treatment. **Review question 3** No studies were included that compared the initiation of antidepressant treatment and psychological therapies concurrently with initiation of antidepressant treatment only if psychological therapy was ineffective. Therefore, no benefits have been identified for the interventions related to this review question. No studies were identified in the review on the economic impacts of initiating antidepressant treatment and psychological therapies concurrently compared to initiating antidepressant treatment only if psychological therapy was ineffective. Therefore, it was not possible to compare the trade-off between net health benefits and resource use for review question 3.
Quality of evidence	**Review question 2** Overall, the quality of evidence for review question 2 was moderate to low. With the exception of studies comparing psychological therapy and antidepressants to psychological therapy and a placebo tablet, participants were not blinded to treatment allocation. For most comparisons and outcomes, evidence was available for follow up periods of up to 12 months for the majority of outcomes. However, the Committee noted that there was no evidence on suicide-related adverse events for any comparison, which is an important limitation, given the serious nature of this outcome. A further limitation was that evidence from a number of different antidepressants was combined in the evidence review, not all of which would be routinely used in clinical practice (in particular tricyclic antidepressants). However, the Committee noted that there was little evidence of inconsistency between studies, which might be expected if there were important differences between antidepressants. The Committee noted that there was almost no evidence for children aged 5 -11. **Review question 3** There were no included studies for this review question.
Other considerations	The Committee noted that the recommendations from the previous NICE guideline on depression in children and young people recommended combined treatment only if psychological therapy was ineffective. The Committee considered that the evidence from review question 2 favoured

	combined treatment over psychological therapy alone, but that there was no evidence on whether psychological therapy and antidepressants should be initiated concurrently, or whether antidepressants should only be initiated if psychological therapy is ineffective (review question 3). The Committee were concerned that given that there was clear evidence for the benefit of combined treatment (question 2) and the lack of evidence for a delay in the initiation of antidepressant treatment (question 3), there was a danger that young people (12-18 years) might be denied access to antidepressant therapy that might be beneficial. Consequently, the Committee recommended that the option of initiating antidepressant treatment and psychological treatment concurrently as an alternative to the normal pathway of care should be available, based on clinical judgement and the individual needs and preferences of young people and their family members or carers (recommendation 4). However, the Committee felt that the standard pathway of care outlined in the original guideline (recommendations 7, 8 and 9) should remain unchanged given that these recommendations were based on the expert consensus of the previous Guideline Development Group together with evidence from a number of review questions that were not part of this guideline update. It was not possible to assess the effect of depression severity on the relative effectiveness of antidepressants, psychological therapy and combined treatment. However, the Committee agreed that concurrent combined treatment should only be recommended as a possible option for young people (12 – 18 years) with moderate-severe depression because of the model of care set out in the original guideline (the original guideline recommended that antidepressants should only be offered in a tier 3 setting, and that mild depression should be initially treated in a tier 1 or 2 setting). The Committee agreed that this option should only be considered for young people aged 12-18 and not children aged 5 – 11, due to the lack of evidence of the effectiveness of combined treatment in the younger age group. Review question 2 included evidence from a number of antidepressants, however, the Committee decided that only fluoxetine should be recommended because at the time of publication (March 2015) it is the only antidepressant licensed for use in children. Additionally, the original NICE guideline on depression in children and young people reviewed the evidence for different antidepressants (in a review question that was not part of this guideline update) and concluded that fluoxetine should be recommended as an initial choice of antidepressant in children and young people. The original NICE guideline on depression in children and young people included a research recommendation for a trial comparing fluoxetine with psychological therapy and combination treatment. This question was partly, but not fully answered by the studies reviewed for review question 2, and so the Committee agreed that this research recommendation (research recommendation 3) should remain. In particular, the Committee noted that there was very little evidence the effectiveness of combined treatment for children (5-11 years), and the Committee thought that this was an important area for future research. In addition, the Committee made a new research recommendation (research recommendation 4) based on review question 3, for which no evidence was identified.

2.2.10 Recommendations

4. **Consider combined therapy (fluoxetine[d] and psychological therapy) for initial treatment of moderate to severe depression in young people (12–18 years), as an alternative to psychological therapy followed by combined therapy and to recommendations 5, 6 and 7. [new 2015]**

7. **Following multidisciplinary review, offer fluoxetine[e] if moderate to severe depression in a young person (12–18 years) is unresponsive to a specific psychological therapy after 4 to 6 sessions. [2015]**

8. **Following multidisciplinary review, cautiously consider fluoxetine[cf] if moderate to severe depression in a child (5–11 years) is unresponsive to a specific psychological therapy after 4 to 6 sessions, although the evidence for fluoxetine's effectiveness in this age group is not established. [2015]**

9. **Do not offer antidepressant medication to a child or young person with moderate to severe depression except in combination with a concurrent psychological therapy. Specific arrangements must be made for careful monitoring of adverse drug reactions, as well as for reviewing mental state and general progress; for example, weekly contact with the child or young person and their parent(s) or carer(s) for the first 4 weeks of treatment. The precise frequency will need to be decided on an individual basis, and recorded in the notes. In the event that psychological therapies are declined, medication may still be given, but as the young person will not be reviewed at psychological therapy sessions, the prescribing doctor should closely monitor the child or young person's progress on a regular basis and focus particularly on emergent adverse drug reactions. [2015]**

2.2.11 Research recommendations

3. **An appropriately blinded, randomised controlled trial should be conducted to assess the efficacy (including measures of family and social functioning as well as depression) and the cost effectiveness of fluoxetine, psychological therapy, the combination of fluoxetine and psychological therapy compared with each other and placebo in a broadly based sample of children and young people diagnosed with moderate to severe depression (using minimal exclusion criteria).The trial should be powered to examine the effect of treatment in children and young people separately and involve a follow up of 12 to 18 months (but no less than 6 months). [2015]**

4. **For children and young people with depression, what is the relative effectiveness of:**

[d] At the time of publication (March 2015), Fluoxetine did not have UK marketing authorisation for use in young people (aged 12-18), without a previous trial of psychological therapy that was ineffective. For combined antidepressant treatment and psychological therapy as an initial treatment, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[e] At the time of publication (March 2015), Fluoxetine was the only antidepressant with UK marketing authorisation for use for children and young people aged 8 to 18 years.

[f] At the time of publication (March 2015), Fluoxetine did not have UK marketing authorisation for use for children under the age of 8 years. For children under the age of 8 years, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

- **starting psychological therapy first, followed by additional antidepressants only if psychological therapy alone is ineffective**
- **starting psychological therapy and antidepressants at the same time?**

Why is this important?

The timing of combination psychological therapy and antidepressant treatment was one of the areas identified for review in this update. However, no evidence was found that met the inclusion criteria for the review. As a result, this remains an important area of clinical uncertainty. A randomised controlled trial is needed to resolve this uncertainty and show which treatment strategy is most effective.

PICO	**Population:** Children and young people with diagnosed depressive disorder **Intervention:** Initiation of psychological therapy first, followed by additional antidepressants only if psychological therapy is initially ineffective. **Comparator:** Initiation of psychological therapy and antidepressants simultaneously. **Outcomes:** Functional status, depression symptoms following treatment, remission from depressive disorder, suicidal ideation, discontinuation due to adverse events, discontinuation for any reason
Current evidence base	This research question is based on review question 3, for which no trials met the inclusion criteria for the evidence review.
Study design	Randomised controlled trial
Other comments	The trial should be powered such that the results for children (aged 5-11) and young people (aged 12-18) can be assessed separately.

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4 Glossary and abbreviations

Please refer to the NICE glossary.

Additional terms used in this document are listed below:

Child: For the purpose of this guideline, the term 'child' is used for people aged 5 to 11.

Child and Adolescent Mental Health Service (CAMS): The organisations responsible for the treatment of children and young people with depression in secondary care.

Cognitive behavioural therapy: A psychological therapy that is used to treat depression by changing thoughts and behaviour.

Family therapy: A psychological therapy which includes a child or young person's family members and aims to identify and resolve problems that may contribute to a child or young person's depression.

Interpersonal psychotherapy: A psychological therapy used to treat depression by identifying and resolving interpersonal problems.

Psychodynamic psychotherapy: A psychological therapy based on the theories of Sigmund Freud that aims to treat depression by identifying and exploring conscious and unconscious emotions associated with depression.

Young person: For the purpose of this guideline, the term 'young person' is used to refer to people aged 12 to 18.

Brief details of the rating scales used in studies included in the evidence review are given in Table 3.

Table 3: Rating scales used in included studies

Outcome assessed	Scale	Variants	Description	Intended age range
Functional status	Global assessment of function (GAF)	-	Rating of social, occupational, and psychological functioning (not specific to depression). Higher scores indicate better function.	Adults
Functional status	Children's global assessment scale (CGAS)	-	Adaptation of the adult global assessment of function. Higher scores indicate better function.	Under 18
Depression symptoms	Beck depression inventory (BDI)	BDI-1A, BDI-II	Self-report measure of depression severity at current time. Higher scores indicate more depression symptoms.	13+
Depression symptoms	Child depression inventory (CDI)	CDI-II, long, short, parent and teacher versions	Adaptation of the adult Beck depression inventory. Higher scores indicate more depression symptoms.	7-17
Depression symptoms	Reynolds adolescent depression scale (RADS)	RADS-2, RADS-short form	Self-report questionnaire that aims to identify and quantify depressive symptoms in adolescents (gives score representing severity of depressive symptoms). Higher	13-18

Outcome assessed	Scale	Variants	Description	Intended age range
			scores indicate more depression symptoms.	
Depression symptoms	Mood and feelings questionnaire (MFQ)	Short-MFQ, Parent MFQ-P, Child MFQ-C	Self-report questionnaire that aims to assess depressive symptoms. Higher scores indicate more depression symptoms.	8-17
Depression symptoms	Center for epidemiological studies depression scale (CES-D)	CES-D-R (revised version)	Self-report questionnaire designed to measure depressive symptoms in the past week in the general population (designed for epidemiological studies). Higher scores indicate more depression symptoms.	Adults
Depression symptoms, remission	Schedule for Affective disorders and Schizophrenia for school-age children (K-SADS)	Present and lifetime version (K-SADS-PL)	Structured diagnostic interview for range of psychiatric disorders including major depressive disorder. Can also be used to assess symptom severity, but is time consuming so may be inefficient as a way of measuring changes in symptoms. Higher scores indicate more depression symptoms.	6-17
Depression symptoms, remission	Hamilton rating scale for depression (HAM-D)	Also abbreviated to HDRS	Structured interview that determines the presence and severity of depression. Higher scores indicate more depression symptoms.	Adults
Depression symptoms, remission	Child depression rating scale (CDRS)	CDRS-R (revised version)	Adaptation of the Hamilton rating scale for depression for adults. Higher scores indicate more depression symptoms.	6-12
Suicidal ideation	Suicidal ideation questionnaire - Junior version (SIQ-JR)	-	15-item questionnaire to assess suicidal ideation. Higher scores indicate greater suicidal ideation.	Adolescents
Suicidal ideation	Scale for suicidal ideation (SSI)	-	19 item clinician rating scale to assess suicidal ideation. Higher scores indicate greater suicidal ideation.	Adults

5 Acknowledgement

We thank the Cochrane Depression, Anxiety and Neurosis Group (in particular Rachel Churchill, Georgina Cox, Patch Callahan, Vivien Hunot, Sally Merry, Alexandra Parker, and Sarah Hetrick) for their assistance with the evidence review for review question 2.

Appendices

Appendix A: Committee members and NICE teams

A.1 Standing Committee members

Name	Role
Susan Bewley (Chair)	Professor of Complex Obstetrics, Kings College London
Gita Bhutani	Clinical Psychologist, Lancashire Care NHS Foundation Trust
Simon Corbett	Cardiologist, University Hospital Southampton NHS Foundation Trust
John Graham	Consultant Oncologist & Trust Cancer Lead Clinician, Taunton & Somerset Hospital
Peter Hoskin	Consultant in Clinical Oncology, Mount Vernon Hospital
Roberta James	Programme Lead, Scottish Intercollegiate Guidelines Network (SIGN)
Asma Khalil	Obstetrician, St George's Hospital University London
Manoj Mistry	Lay member
Amaka Offiah	Reader in Paediatric Musculoskeletal Imaging and Honorary Consultant Paediatric Radiologist, University of Sheffield
Mark Rodgers	Research Fellow, University of York
Nicholas Steel	Clinical Senior Lecturer in Primary Care, Norwich Medical School
Sietse Wieringa	General Practitioner, Barts & the London School of Medicine & Dentistry

A.2 Topic-specific Committee members

Name	Role
Peter Fonagy	Programme Director, Head of Research Department, UCL
Lynn Henderson	Senior CAMHS Nurse, Tees, Esk and Wear Valleys NHS Foundation Trust
Peta Mees	Senior Child/Adolescent Psychotherapist, CAMHS East London Foundation Trust
Maria Moldavsky	Consultant Child/Adolescent Psychiatrist, Nottingham University
Anna Wilson	Lay member

A.3 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Advisor
Emma Banks	Co-ordinator
Elizabeth Barrett	Information Specialist
Paul Crosland	Health Economist
Nicole Elliott	Associate Director
Kathryn Hopkins	Technical Analyst
Susannah Moon	Programme Manager
Rebecca Parsons	Project Manager
Charlotte Purves	Administrator
Toni Tan	Technical Advisor

A.4 NICE project team

Name	Role
Martin Allaby	Clinical Advisor
Ben Doak	Guideline Commissioning Manager
James Hall	Senior Medical Editor
Bhash Naidoo	Health Economic Advisor
Mark Baker	Guideline Lead
Judith Thornton	Technical Lead
Jennifer Wells	Guideline Co-ordinator
Erin Whittingham	Public Involvement Advisor

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Appendix B: Declaration of interests

(declared under the new NICE policy, 2014)

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
Susan Bewley	Self-employed academic and obstetric expert.	30/05/2013	Personal financial interest	Declare and participate
Susan Bewley	100 hour per annum teaching contract with Kings College London.	30/05/2013	Personal financial interest	Declare and participate
Susan Bewley	In the last 12 months received income or fees for: • Research projects as a principal or co-investigator or giving expert advice (presently these include projects on major postpartum haemorrhage, the organisation of maternity care, gestation time for abortion) • Academic supervision (PhD on implementation of external cephalic version, chair of 35/39 TSC on the timing of induction) • Teaching (BSc law and ethics tutor at KCL, occasional fees for lectures on obstetrics) • Medico-legal reports (approx. 2/year) and Medical Defence Union cases committee and council • External reviews for NHS organisations related to my obstetric expertise (serious incident and maternal mortality investigations, RCOG review) • Chairing NICE GDG • Expert advice to NHS Quest (development of a maternity 'safety thermometer') • Royalties from edited books • Advice to Marie Stopes International about obstetric standards	30/05/2013	Personal financial interest	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
Susan Bewley	Expenses paid to attend conferences to lecture on obstetric topics. In the last year this included speaking to a Human Rights conference at the Hague, the Royal Society of Edinburgh, and the International Society of Psychosomatic Obstetrics and Gynaecology, and attending the British Maternal Fetal Medicine Society conference. Received a community grant to attend the British HIV Association conference.	30/05/2013	Personal financial interest	Declare and participate
Susan Bewley	Joint intellectual property rights in a new neonatal resuscitation trolley, but these were negotiated to be handed over to Liverpool University and Inditherm. In return, the inventors have negotiated that a fee generated on the sale of each trolley will be given to charity.	30/05/2013	Non-personal financial interest	Declare and participate
Susan Bewley	Expressed views in publications about obstetric matters, largely based on evidence.	30/05/2013	Personal non-financial interest	Declare and participate
Susan Bewley	A trustee and committee member of Healthwatch (a charity devoted to evidence and “for treatments that work”) and a trustee of Sophia (a charity devoted to women with HIV and the UK arm of the Global Coalition for Women and AIDS).	30/05/2013	Personal non-financial interest	Declare and participate
Susan Bewley	Member of the following editorial boards: Medical Law Review, International Journal of Childbirth, JASS (Journal Article Summary Service); Member of the London Clinical Senate; Member of the Mayor's Office for Policing and Crime Violence Against Women and Girls Panel; Member All-Parliamentary Party Group on Maternity; Trustee of Maternity Action (a charity which aims to end inequality	11/04/2014	Personal non-financial interest	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
	and improve the health and well-being of pregnant women, partners and young children), one of seven members of the Women's Health and Equality Consortium which is a Strategic Partner of the Department of Health.			
Susan Bewley	Expert advice to Salamander Trust (funded by WHO to perform a global community consultation of women living with HIV to inform Sexual and Reproductive Health and Human Rights guideline update).	11/04/2014	Personal financial interest	Declare and participate
Susan Bewley	Expenses paid to attend and present at 'Changing Motherhood' and 'Assisted reproduction that harms' conferences.	11/04/2014	Personal financial interest	Declare and participate
Gita Bhutani	Chair of Psychological Professions Network North West	27/03/2014	Personal non-financial interest	Declare and participate
Gita Bhutani	Member of British Psychological Society; Division of Clinical Psychology; Faculty of Leadership and Management Committee Member	27/03/2014	Personal non-financial interest	Declare and participate
Gita Bhutani	Project lead on BPS Division of Clinical Psychology project on 'Comprehensively representing the complexity of psychological services'	17/11/14		
Gita Bhutani	Analytical support in partnership with Liverpool University on Liverpool Health Partners project on Patient Quality and Safert	17/11/14		
Simon Corbett	Network Service Adviser for the British Cardiovascular Society. This role incorporates the regional specialty adviser role for the Royal College of Physicians.	21/05/2014	Personal non-financial interest	Declare and participate
Simon Corbett	Acting Director for Clinical Effectiveness for employer (University Hospital Southampton NHS Foundation Trust). Part of	21/05/2014	Personal non-financial interest	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
	this role involves the dissemination and implementation of NICE guidance in the Trust.			
John Graham	Director of National Collaborating Centre for Cancer – this post is funded through a contract with NICE to produce NICE's clinical guidelines.	06/12/13	Non-personal financial interest	Declare and participate
John Graham	Principal investigator for ongoing clinical trials in prostate cancer: 1) With Custirsen funded by OncoGenex Technologies Inc and Teva Pharmaceutical Industries Ltd. 2) Orteronel Affinity Trial funded by Millenium Pharmaceuticals Inc 3) Principal investigator for a study of radium-223 in prostate cancer that is funded by Bayer Pharmaceuticals	06/12/13	Non-personal financial interest	Declare and participate
John Graham	Principal investigator for 8 ongoing clinical trials in breast and prostate cancer run via the National Cancer Research Network (not pharmaceutical industry funded)	06/12/13	Non-personal financial interest	Declare and participate
John Graham	Member of the trial management groups for 2 prostate cancer trials: RT01 and CHHIP. Both are closed to recruitment but continuing to report trial results.	06/12/13	Personal non-financial interest	Declare and participate
John Graham	Consultancy work for NICE International on a project with the Philippines Department of Health to produce clinical guidelines on breast cancer. Travel expenses paid	18/06/14	Personal non-financial interest	Declare and participate
John Graham	Council member of the South-West England Clinical Senate	03/11/14	Personal non-financial non specific	Declare and participate
Peter Hoskin	Investigator in research studies sponsored by various companies with payment for expenses to	04/06/13	Non-personal financial interest	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
	NHS Trust and department which fund research staff. Recent studies have been on behalf of Millenium, Astellas, Ipsen and Amgen.			
Peter Hoskin	Fellow of the Royal College of Radiologists and member of Faculty Board, Specialist Training Board and Chair of Exam Board.	04/06/13	Personal non-financial interest	Declare and participate
Peter Hoskin	Consultant to the IAEA; Undertake by invitation lectures and working group meetings for which expenses may be paid.	04/06/13	Personal financial interest	Declare and participate
Peter Hoskin	Department reimbursed for studies on alpharadin by Astellas.	04/06/13	Non-personal financial interest	Declare and participate
Peter Hoskin	Department reimbursed for studies on MDV 3100 by Medivation. and Astellas	04/06/13	Non-personal financial interest	Declare and participate
Peter Hoskin	Department receives grants from Astellas for trials in prostate cancer.	04/06/13	Non-personal financial interest	Declare and participate
Peter Hoskin	Department receives grants from Bayer for trials in prostate cancer.	04/06/13	Non-personal financial interest	Declare and participate
Peter Hoskin	Department received grants from Millennium for trials in prostate cancer.	04/06/13	Non-personal financial interest	Declare and participate
Peter Hoskin	Trustee for funding research within the unit/department. Funded by Donations/Legacies. No Non-Hodgkin's lymphoma research has been funded in the last 12 months.	04/06/13	Personal non-financial interest	Declare and participate
Peter Hoskin	Chair Steering Group for National Cancer Intelligence Network (NCIN)	04/06/13	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the faculty board of the Royal College of Radiologists.	04/06/13	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the specialist training committee for the Royal College of Radiologists.	04/06/13	Personal non-financial interest	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
Peter Hoskin	Editorial board member for the Journal of Contemporary Brachytherapy.	04/06/13	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the East of England senate.	04/06/13	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the NICE standing committee for rapid updates / and non-Hodgkin's lymphoma GDG.	04/06/13	Personal non-financial interest	Declare and participate
Roberta James	Programme Lead at Scottish Intercollegiate Guidelines Network (SIGN)	26/05/14	Personal financial interest	Declare and participate
Roberta James	Member of Guideline Implementability Research and Application network (GIRAnet).	26/05/14	Personal non-financial interest	Declare and participate
Roberta James	Expert group member of Project on a Framework for Rating Evidence in Public Health (PRECEPT).	26/05/14	Personal non-financial interest	Declare and participate
Asma Khalil	Member of the National Clinical Reference Group for Fetal Medicine	26/10/14	Personal non-financial	Declare and participate
Asma Khalil	Co-chair of the "Improving Outcomes" working group, South West London Maternity Network	26/10/14	Personal non-financial	Declare and participate
Asma Khalil	Associate Editor for the journal Biomedical Central Pregnancy and Childbirth	26/10/14	Personal non-financial	Declare and participate
Asma Khalil	Member of the Maternal and Fetal Medicine National Clinical Study Group	26/10/14	Personal non-financial	Declare and participate
Asma Khalil	Assistant Convenor for the MRCOG Part1 course, RCOG	26/10/14	Personal non-financial	Declare and participate
Asma Khalil	Principal Investigator at St George's Hospital for several NIHR funded studies, e.g. Non-invasive Prenatal Testing	26/10/14	Personal non-financial	Declare and participate
Asma Khalil	Chief Investigator for Cardiovascular changes in Pregnancy (CVP) study and Quantitative fetal fibronectin, Cervical length and ActimPartus® for the prediction of Preterm birth in	26/10/14	Personal non-financial	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
	Symptomatic women (QFCAPS)			
Asma Khalil	Collaboration with commercial companies, such as USCOM®, Roche Diagnostics®, Alere Diagnostics® and proact medical Ltd® (research equipment and/or consumables)	26/10/14	Personal non-financial	Declare and participate
Asma Khalil	Reviewer for the National Maternal Near-miss Surveillance Programme (UKNes)	26/10/14	Personal non-financial	Declare and participate
Manoj Mistry	Public member of Pennine Care NHS FT in the capacity as a carer	11/07/14	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI representative for the Health Research Authority (London)	11/07/14	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI representative for the Health Quality Improvement Partnership (London)	11/07/14	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI representative for the Primary Care Research in Manchester Engagement Resource group at the University of Manchester.	11/07/14	Personal non-financial interest	Declare and participate
Manoj Mistry	Carer representative on NICE Guideline Development Group: 'Transition between inpatient hospital settings and community or care home settings for adults with social care needs.'	11/07/2014	Personal non-financial interest	Declare and participate
Manoj Mistry	Appointed Lay representative for the MSc (Clinical Bioinformatics) at the University of Manchester	11/07/14	Personal non-financial interest	Declare and participate
Manoj Mistry	Appointed 'Lay Educational Visitor' with the Health and Care Professions Council. (London)	11/07/14	Personal non-financial interest	Declare and participate
Manoj Mistry	Appointed Lay representative at the Clinical Research Facility (collaboration between Central Manchester University Hospital NHS	29/10/14	Personal non-financial interest	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
	FT/University of Manchester)			
Manoj Mistry	Public Representative Interviewer at the Medical School, Lancaster University	06/01/15	Personal non-financial interest	Declare and participate
Manoj Mistry	Public Member of NUHS 'Research for Patient Benefit Programme Committee' (North West region)	09/01/15	Personal non-financial interest	Declare and participate
Amaka Offiah	Provision of expert advice to Her Majesty's Courts in cases of suspected child abuse.	07/09/13	Personal financial interest	Declare and participate
Amaka Offiah	Recipient of honoraria and expenses for lectures and guidelines development from BioMarin.	22/06/14	Personal financial interest	Declare and participate
Amaka Offiah	Chairperson Skeletal Dysplasia Group for Teaching and Research	22/06/2014	Personal non-financial interest	Declare and participate
Amaka Offiah	Chairperson Child Abuse Taskforce of the European Society of Pediatric Radiology.	22/06/14	Personal non-financial interest	Declare and participate
Amaka Offiah	Member Joint RCR/RCPCH NAI Working Party for Guideline Update - Imaging in Suspected Non-Accidental Injury.	22/06/14	Personal non-financial interest	Declare and participate
Amaka Offiah	Member of the Royal College of Radiology Academic Committee.	22/06/14	Personal non-financial interest	Declare and participate
Amaka Offiah	Committee member of the International Consortium for Vertebral Anomalies and Scoliosis.	22/06/14	Personal non-financial interest	Declare and participate
Amaka Offiah	Member of South Yorkshire (Sheffield) Research Ethics Committee.	22/06/14	Personal non-financial interest	Declare and participate
Amaka Offiah	Medical Academic Staff Committee Representative of the Yorkshire Regional Council of the BMA.	22/06/14	Personal non-financial interest	Declare and participate
Amaka Offiah	Partner Governor of the Sheffield Children's NHS Foundation Trust (representing the University of Sheffield).	22/06/14	Personal non-financial interest	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
Amaka Offiah	Editorial Committee Member of the journal Paediatric Radiology.	22/06/14	Personal non-financial interest	Declare and participate
Amaka Offiah	Recipient of research funding from NIHR, ARUK, The Sheffield Children's Charity, Skeletal Dysplasia Group for Teaching and Research	22/06/14	Non-personal financial interest	Declare and participate
Amaka Offiah	Member of the Sheffield Children's Hospital Research and Innovations Committee	10/14	Personal non-financial	Declare and participate
Mark Rodgers	Associate editor of the journal Systematic Reviews that publishes research on health and social care.	21/05/14	Personal non-financial non-specific interest	Declare and participate
Mark Rodgers	Research fellow in health services research; has provided independent academic reviews of clinical effectiveness and diagnostic accuracy evidence for funders including NIHR and NICE.	21/05/14	Non-personal non-financial non-specific interest	Declare and participate
Mark Rodgers	Employee of the Centre for Reviews and Dissemination (University of York) which provides Evidence Review Group (ERG) reports and Technology Assessment Reports (TARs) as part of the NICE technology appraisals process.	27/10/14	Non-personal financial non-specific	Declare and participate
Nicholas Steel	Currently finishing work as the principal investigator on a National Institute of Health Research (NIHR) funded project on: 'Are NICE clinical guidelines for primary care based on evidence from primary care?'	31/12/13	Non-personal financial interest	Declare and participate
Nicholas Steel	National Institute for Health Research (NIHR) Health Services & Delivery Research Programme Healthcare Delivery Research Panel member	06/06/14	Personal non-financial interest	Declare and participate
Nicholas Steel	NIHR Regional Advisory Committee for the Research for Patient Benefit	06/06/14	Personal non-financial interest	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
	Programme East of England region			
Nicholas Steel	Norfolk & Suffolk Primary & Community Care Research Steering Group	06/06/14	Personal non-financial interest	Declare and participate
Nicholas Steel	Advisory Committee on Clinical Excellence Awards (ACCEA) East of England	06/06/14	Personal non-financial interest	Declare and participate
Nicholas Steel	'Implementation Science' Editorial Board member	06/06/14	Personal non-financial interest	Declare and participate
Nicholas Steel	'Quality in Primary Care' Editorial Board member	06/06/14	Personal non-financial interest	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Examiner	06/06/14	Personal non-financial interest	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Development Committee	06/06/14	Personal non-financial interest	Declare and participate
Nicholas Steel	Honorary Public Health Academic Consultant, Public Health England	06/06/14	Personal non-financial interest	Declare and participate
Nicholas Steel	Publication in press: Steel N, Abdelhamid A, Stokes T, Edwards H, Fleetcroft R, Howe A, Qureshi N. Publications cited in national clinical guidelines for primary care were of uncertain relevance: literature review. In Press Journal of Clinical Epidemiology	06/06/14	Personal non-financial interest	Declare and participate
Sietse Wieringa	At the Centre for Primary care & Public Health at Barts & The London School of Medicine & Dentistry/Queen Mary University I am working on a literature review of 'mindlines' (related to communities of practice) and a qualitative study of a large group of GPs on a virtual social network sharing medical knowledge. I was funded for this via an NIHR In practice fellowship.	14/05/14	Personal financial interest	Declare and participate

Member name	Interest declared	Date declared	Type of interest	Decision
Standing committee members				
Sietse Wieringa	I co-own a small social enterprise called ZorgIdee that develops ideas to help GPs to collaborate. There are no current funders.	14/05/14	Personal financial interest	Declare and participate
Sietse Wieringa	Board member of the Platform of Medical Leadership in the Netherlands, via which I am involved in a mixed methods study for the development of a medical leadership competency framework. The study group receives funds from KNMG (Royal Dutch College of Medicine) and SBOH which receives its funds from the Dutch Ministry of Health.	14/05/14	Non-personal financial interest	Declare and participate
Sietse Wieringa	Member of NHG (Dutch GP Society), which produces guidelines and I worked for this organisation in the past.	14/05/14	Personal non-financial interest	Declare and participate
Sietse Wieringa	Member of Generation Next, a think tank and network of young GPs. It's indirectly funded by the Ministry of Health.	14/05/14	Personal non-financial interest	Declare and participate
Topic-specific members				
Peter Fonagy	None	24/04/14		No action
Lynn Henderson	Registration with the Nursing and Midwifery Council (Registered Nurse - Learning Disabilities)	11/14	Personal non-financial	Declare and participate
Lynn Henderson	Graduate Membership of the British Psychological Society; Division of Clinical Psychology	11/14	Personal non-financial	Declare and participate
Lynn Henderson	Membership of the British Association of Behavioural and Cognitive Psychotherapies	11/14	Personal non-financial	Declare and participate
Peta Mees	None	24/04/14		No action
Maria Moldavsky	None	24/04/14		No action
Anna Wilson	None	24/04/14		No action

Appendix C: Review protocols

C.1 Review question 1

Please note that review question 1 was updated in 2019 and the evidence from 2015 has been removed.

C.2 Review question 2

	Details
Review Question	For children and young people with depression, what is the relative effectiveness of: - different antidepressants alone, compared to - different psychological therapies alone, compared to - a combination of one psychological therapy (or psychological therapies) and one antidepressant (or antidepressants)?
Objectives	The surveillance review of the Depression in children and young people guidance identified a new systematic review published by the Cochrane collaboration comparing combined psychological therapy and antidepressants with either treatment alone. This new evidence might impact current guidelines, so the aim of the review is to determine the combined effectiveness of the two treatments compared with either treatment individually. We are currently investigating how the systematic review can be used to answer this question. The Cochrane review can be found at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008324.pub2/full
Type of Review	Intervention
Language	English
Study Design	Randomised controlled trials, Systematic reviews of randomised controlled trials
Status	Published papers (full text only)
Population	Children and young people aged 5-18 Diagnosis of depressive disorder as defined by the International classification of diseases (ICD) or the diagnostic and statistical manual (DSM) classifications **Subgroups:** Different psychological therapies and antidepressant treatments will be considered separately Children aged 5-11, young people aged 12-18 with further stratification to age 12-15 and 16-18 if possible Children or young people with mild, moderate or severe depression (as defined in ICD-10)
Intervention	Psychological therapies alone Antidepressants alone Any one psychological therapy (or more than one psychological therapy) and any one antidepressants (or more than one antidepressant) given in combination
Comparator	Any of the above interventions
Outcomes	**Ranked in order of importance:** Level of function (functional status, measure of general function using validated tool) Improvement in depressive symptoms

	Details
	Suicide-related serious adverse events (encompassing ideation and attempted suicide including acts with unknown intent)Remission from depressive disorder Suicide-related outcomes (suicidal ideation, measured on a standardised, validated measure) Remission defined as criterion improvement in depressive symptoms, Acceptability of treatment measured by number of dropouts for any reason (equal ranking)
Other criteria for inclusion / exclusion of studies	**Inclusion criteria:** Systematic reviews must have the same inclusion and exclusion criteria as defined in this protocol, and meet the quality standards defined in the NICE clinical guidelines methods handbook. **Exclusion criteria**: Narrative reviews, observational studies (including comparative and non-comparative studies, case series and case reports) will not be included Studies with populations diagnosed with bipolar depression
Review strategies	An existing systematic review (Cox et al 2012) that meets the criteria specified in this protocol was identified, and will form the basis for this evidence review. Further details of how this review was updated and used are provided in Section 2.2.2.

C.3 Review question 3

	Details
Review Question	For children and young people with depression, what is the relative effectiveness of: - Initiating psychological therapy first, followed by additional antidepressants only if psychological therapy is initially ineffective compared to, - Initiating psychological therapy and antidepressants simultaneously
Objectives	As part of the surveillance review, a group of experts were consulted about areas of the guideline that needed to be updated. Several experts suggested that the current recommendation on the timing of psychological therapy and antidepressant treatment may need to be updated. The aim of this review is to determine the effectiveness of antidepressant treatment initiated at the same time as psychological therapy, compared with antidepressant treatment given only if initial psychological therapy is ineffective.
Type of Review	Intervention
Language	English
Study Design	Randomised controlled trials, Systematic reviews of randomised controlled trials
Status	Published papers (full text only)
Population	Children and young people aged 5-18 Diagnosis of depressive disorder as defined by the International classification of diseases (ICD) or the diagnostic and statistical manual (DSM) classifications **Subgroups:** Different psychological therapies and antidepressant treatments will be considered separately Children aged 5-11, young people aged 12-18 Children or young people with mild, moderate or severe depression (as defined in ICD-10)

	Details
Intervention	Psychological therapy initiated first, followed by additional antidepressants only if psychological therapy is initially ineffective
Comparator	Psychological therapy and antidepressants initiated simultaneously
Outcomes	**Ranked in order of importance:** Level of function (functional status, measure of general function assessed using validated tool) Depression symptoms following treatment (assessed using validated questionnaire or structured interview, reported as absolute measure or an improvement from baseline) Remission (as defined in study) Suicidal ideation (assessed using questionnaire) Suicide-related adverse events during or following treatment Discontinuation from treatment due to adverse events Discontinuation from treatment for any reason All outcomes will be extracted and reported for all time points following treatment.
Other criteria for inclusion / exclusion of studies	**Inclusion criteria:** - Systematic reviews must have the same inclusion and exclusion criteria as defined in this protocol, and meet the quality standards defined in the NICE clinical guidelines methods handbook. - Studies must compare the following groups: a) all participants are treated with psychological therapy and antidepressants at the same time vs b) all participants are treated with psychological therapy and a subset who fail to respond after this initial treatment are also treated with antidepressants while psychological therapy continues. **Exclusion criteria:** Narrative reviews, observational studies (including comparative and non-comparative studies, case series and case reports) will not be included
Review strategies	• Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarised in evidence statements

Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown together with the MEDLINE search strategy. The same strategy was translated for the other databases listed.

D.1 Review question 1

Please note that review question 1 was updated in 2019 and the evidence from 2015 has been removed.

D.2 Review question 3

Table 4: Clinical search summary

Database	Date searched	Number retrieved
CDSR (Wiley)	21/07/2014	14
Database of Abstracts of Reviews of Effects – DARE (Wiley)	21/07/2014	8
HTA database (CRD, Ovid, Wiley)*	21/07/2014	1
CENTRAL (Ovid, Wiley)*	21/07/2014	359
MEDLINE (Ovid)	21/07/2014	794
MEDLINE In-Process (Ovid)	21/07/2014	23
EMBASE (Ovid)	21/07/2014	1161
PsycINFO (Ovid)	21/07/2014	273

Table 5: Clinical search terms (MEDLINE)

Line number	Search term	Number retrieved
1	Depression/	76834
2	exp Depressive Disorder/	81268
3	(depress* or dysthymi* or dysphori* or melanchol* or sadness).tw.	303191
4	"seasonal affective disorder*".tw.	1032
5	1 or 2 or 3 or 4	339365
6	exp Cognitive Therapy/	16137
7	Therapy, Computer-Assisted/	5099
8	((cogniti* adj4 therap*) or cbt).tw.	12609
9	exp Psychotherapy/	151300
10	(psychotherap* or logotherap*).tw.	30057
11	((self adj4 model*) or sm).tw.	19702
12	Relaxation Therapy/	5737
13	(relax* adj4 (therap* or techni*)).tw.	2886
14	Behavior Therapy/	23859
15	((behavi* or condition*) adj4 (therap* or modifi*)).tw.	33457
16	((social adj4 skill* adj4 train*) or sst).tw.	3271
17	Family Therapy/	7652

Line number	Search term	Number retrieved
18	Psychotherapy, group/	11860
19	((famil* or group) adj4 (therap* or techni*)).tw.	34703
20	((control adj4 enhancement adj4 (training or therap*)) or pascet).tw.	18
21	((((non adj4 directive) or nondirective) adj4 supportive adj4 therap*) or ndst).tw.	82
22	(((client adj4 cent*) or rogerian) adj4 therap*).tw.	204
23	"guided self help".tw.	175
24	Self care/px or self care/mt	7912
25	Mindfulness/	150
26	mindfulness.tw.	1517
27	or/6-26	242268
28	exp Antidepressive agents/	121580
29	Serotonin uptake inhibitors/	16021
30	(antidepress* or anti depress* or anti-depress* or SSRI* or SNRI*).tw.	49171
31	(serotonin adj4 inhibitor*).tw.	12537
32	Fluoxetine/ or Paroxetine/ or Sertraline/ or Citalopram/ or Mianserin/ or Trazadone/ or Lofepramine/ or Imipramine/ or Amitrypyline/ or Clomipramine/ or Doxepin/ or Trimipramine/ or Nortriptyline/ or Fluvoxamine/ or Dothiepin/	32078
33	(fluoxetine or prozac or sarafem or ladose or fontex).tw.	8913
34	(paroxetine or paxil or pexeva or brisdelle or rexetin).tw.	4270
35	(sertraline or zoloft or lustral or daxid or deprax or altruline or besitran or eleval or emergen or gladem or implicane or sedoran or sealdin or serivo or lowfin or stimuloton or serimel or seretral or tresleen).tw.	2977
36	(citalopram or celexa or cipramil).tw.	3695
37	(escitalopram or lexapro or cipralex).tw.	1184
38	(mirtazapine or avanza or axit or mirtax or mirtazon or remeron or zisprin).tw.	1282
39	(venlaflaxine or effexor or efexor).tw	44
40	(nefazodone or dutonin or nefador or serzone).tw.	617
41	(mianserin or depnon or lantanon or lerivon or lumin or norval or tolvon or tolmin).tw	1974
42	(trazodone or depyrel or desyrel or molipaxin or oleptro or trazodil or trazorel or trialodine or trittico).tw.	1396
43	(lofepramine or emdalen or gamanil or lomont or tymelyt).tw.	134
44	(imipramine or tofranil or melipramine).tw.	8853
45	(amitryptyline or elavil or endep or levate).tw.	138
46	(clomipramine or anafranil).tw.	2664
47	(doxepin or deptran or sinequan or zonalon or prudoxin).tw.	1006
48	(trimipramine or surmontil or rhotrimine or stangyl).tw.	412
49	(nortriptyline or sensoval or aventyl or pamelor or norpress or allegron or noritren or nortrilen).tw.	2050
50	(fluvoxamine or floxyfral or luvox or fevarin).tw	2173
51	(dothiepin or dosulepin or prothiaden or dothep or theaden or dopress).tw	145269
52	or/28-51	
53	5 and 27 and 52	5369

Line number	Search term	Number retrieved
54	Meta-Analysis.pt.	49609
55	Meta-Analysis as Topic/	13883
56	Review.pt.	1891591
57	exp Review Literature as Topic/	7659
58	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.	58709
59	(review$ or overview$).ti.	266000
60	(systematic$ adj5 (review$ or overview$)).tw.	53513
61	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.	4262
62	((studies or trial$) adj2 (review$ or overview$)).tw.	24522
63	(integrat$ adj3 (research or review$ or literature)).tw.	5343
64	(pool$ adj2 (analy$ or data)).tw.	13832
65	(handsearch$ or (hand adj3 search$)).tw.	5275
66	(manual$ adj3 search$).tw.	3035
67	or/54-66	2049612
68	animals/ not humans/	3874902
69	67 not 68	1914950
70	Randomized Controlled Trial.pt.	378135
71	Controlled Clinical Trial.pt.	88788
72	Clinical Trial.pt	489420
73	exp Clinical Trials as Topic/	282765
74	Placebos/	32777
75	Random Allocation/	81193
76	Double-Blind Method/	126877
77	Single-Blind Method/	19330
78	Cross-Over Studies/	34523
79	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.	731808
80	(random$ adj3 allocat$).tw.	20477
81	placebo$.tw	152302
82	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.	124304
83	(crossover$ or (cross adj over$)).tw.	56630
84	or/70-83	1374611
85	animals/ not humans/	3874902
86	84 not 85	1281373
87	69 or 86	2960697
88	53 and 87	3360
89	limit 88 to english language	2938
90	infan*.mp,so	1026122
91	minor.mp,so	158784
92	minors*.mp,so.	4389
93	boy.mp,so.	42153
94	boys.mp,so.	58475
95	boyfriend*.mp,so.	502
96	boyhood.mp,so.	74
97	girl*.mp,so.	100919

Line number	Search term	Number retrieved
98	kid.mp,so.	1150
99	kids.mp,so.	3440
100	child*.mp,so.	1849388
101	adolescen*.mp,so	1642016
102	juvenil*.mp,so.	64691
103	youth*.mp,so	42756
104	teen*.mp,so.	20594
105	under*age*.mp,so.	1629
106	pubescen*.mp,so.	1276
107	exp pediatrics/	43680
108	pediatric*.mp,so.	307197
109	paediatric*.mp,so.	47900
110	peadiatric*.mp,so.	17
111	school*.mp,so.	214135
112	or/90-111	3408759
113	89 and 112	794

D.3 Economic search

Table 6: Economic search summary

Database	Date searched	Number retrieved
MEDLINE (Ovid)	13/08/2014	790
MEDLINE In-Process (Ovid)	13/08/2014	29
EMBASE (Ovid)	13/08/2014	1083
CINAHL (EBSCOhost/HDAS)*	13/08/2014	28
NHS Economic Evaluation Database - NHS EED (Wiley)	13/08/2014	28
Health Economic Evaluations Database – HEED (Wiley)	13/08/2014	69

Table 7: Economic search strategy (MEDLINE)

Line number	Search term	Number retrieved
1	Depression/	77827
2	exp Depressive Disorder/	82052
3	(depress* or dysthymi* or dysphori* or melanchol* or sadness).tw.	306408
4	"seasonal affective disorder*".tw.	1036
5	1 or 2 or 3 or 4	342805
6	exp Cognitive Therapy/	16401
7	Therapy, Computer-Assisted/	5153
8	((cogniti* adj4 therap*) or cbt).tw.	12826
9	exp Psychotherapy/	152434
10	(psychotherap* or logotherap*).tw.	30277
11	((self adj4 model*) or sm).tw.	19884

Line number	Search term	Number retrieved
12	Relaxation Therapy/	5784
13	(relax* adj4 (therap* or techni*)).tw.	2924
14	Behavior Therapy/	4003
15	((behavi* or condition*) adj4 (therap* or modifi*)).tw.	33874
16	((social adj4 skill* adj4 train*) or sst).tw.	3311
17	Family Therapy/	7684
18	Psychotherapy, group/	11931
19	((famil* or group) adj4 (therap* or techni*)).tw.	35147
20	((control adj4 enhancement adj4 (training or therap*)) or pascet).tw.	19
21	((((non adj4 directive) or nondirective) adj4 supportive adj4 therap*) or ndst).tw.	82
22	(((client adj4 cent*) or rogerian) adj4 therap*).tw.	205
23	"guided self help".tw.	183
24	Self care/px or self care/mt	8030
25	Mindfulness/	174
26	mindfulness.tw.	1570
27	or/6-26	259390
28	infan*.mp,so	1036568
29	minor.mp,so	160057
30	minors*.mp,so	4413
31	boy.mp,so.	42474
32	boys.mp,so.	59231
33	boyfriend*.mp,so.	506
34	boyhood.mp,so. boyhood.mp,so.	74
35	girl*.mp,so	102028
36	kid.mp,so	1160
37	kids.mp,so.	3480
38	child*.mp,so.	1867800
39	adolescen*.mp,so.	1659575
40	juvenil*.mp,so.	65167
41	youth*.mp,so.	43312
42	teen*.mp,so.	20806
43	under*age*.mp,so	1651
44	pubescen*.mp,so	1288
45	exp pediatrics/	44176
46	pediatric*.mp,so.	310421
47	paediatric*.mp,so	48841
48	peadiatric*.mp,so.	17
49	school*.mp,so.	216333
50	or/28-49	3442267
51	5 and 27 and 50	6779
52	Economics/	27091
53	exp "Costs and Cost Analysis"/	183765
54	Economics, Dental/	1862
55	exp Economics, Hospital/	19742

Line number	Search term	Number retrieved
56	exp Economics, Medical/	13639
57	Economics, Nursing/	3984
58	Economics, Pharmaceutical/	2566
59	Budgets/	9801
60	exp Models, Economic/	10356
61	Markov Chains/	10025
62	Monte Carlo Method/	20235
63	Decision Trees/	8888
64	econom$.tw.	156997
65	cba.tw.	8747
66	cea.tw.	16209
67	cua.tw.	801
68	markov$.tw.	11672
69	(monte adj carlo).tw.	20868
70	(decision adj3 (tree$ or analys$)).tw.	8343
71	(cost or costs or costing$ or costly or costed).tw.	306952
72	(price$ or pricing$).tw.	23150
73	budget$.tw.	17267
74	expenditure$.tw.	35506
75	(value adj3 (money or monetary)).tw.	1372
76	(pharmacoeconomic$ or (pharmaco adj economic$)).tw.	3424
77	or/52-76	656743
78	"Quality of Life"/	120745
79	quality of life.tw.	138855
80	"Value of Life"/	5926
81	Quality-Adjusted Life Years/	7211
82	quality adjusted life.tw.	6070
83	(qaly$ or qald$ or qale$ or qtime$).tw.	5002
84	disability adjusted life.tw.	1178
85	daly$.tw.	1166
86	Health Status Indicators/	20305
87	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.	15454
88	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.	989
89	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.	2644
90	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.	22
91	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.	333
92	(euroqol or euro qol or eq5d or eq 5d).tw.	3843
93	(qol or hql or hqol or hrqol).tw.	24648
94	(hye or hyes).tw.	54
95	health$ year$ equivalent$.tw.	39

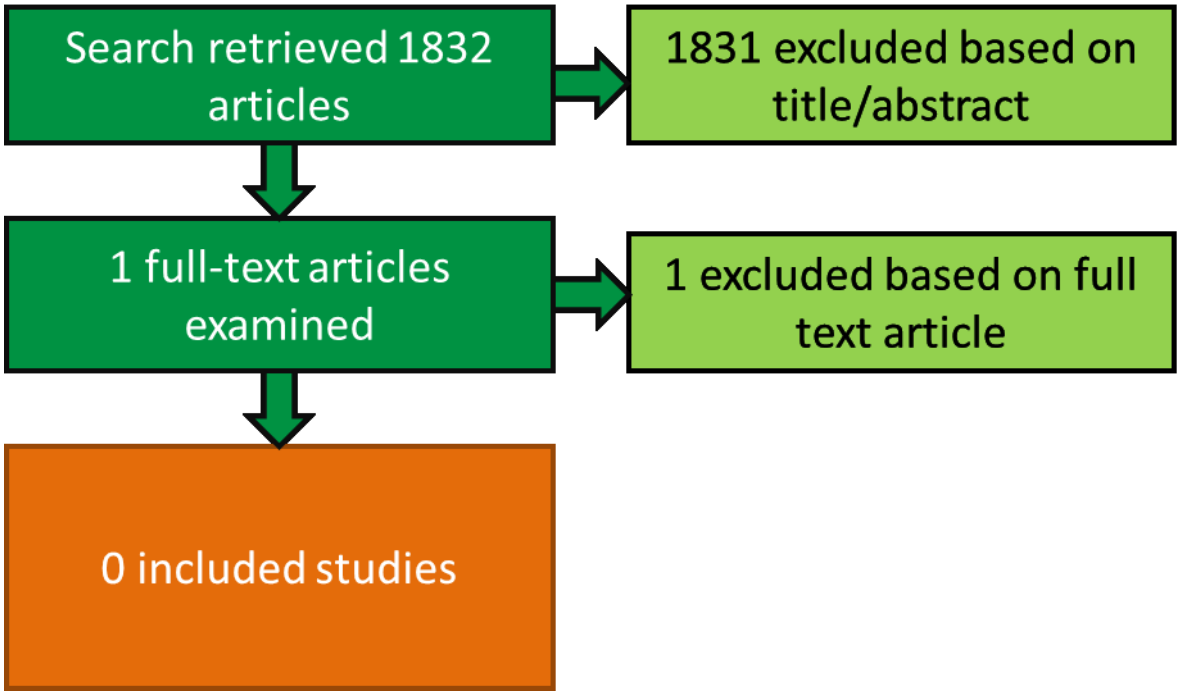
Line number	Search term	Number retrieved
96	utilit$.tw.	112003
97	(hui or hui1 or hui2 or hui3).tw.	864
98	disutili$.tw.	213
99	rosser.tw.	71
100	quality of wellbeing.tw.	7
101	quality of well-being.tw.	335
102	qwb.tw.	171
103	willingness to pay.tw.	2184
104	standard gamble$.tw.	656
105	time trade off.tw.	736
106	time tradeoff.tw.	201
107	tto.tw.	585
708	or/78-107	320867
109	77 or 108	933806
110	51 and 109	870
111	animals/ not humans/	3900724
112	110 not 111	870
113	limit 112 to english language	790

Appendix E: Review flowcharts

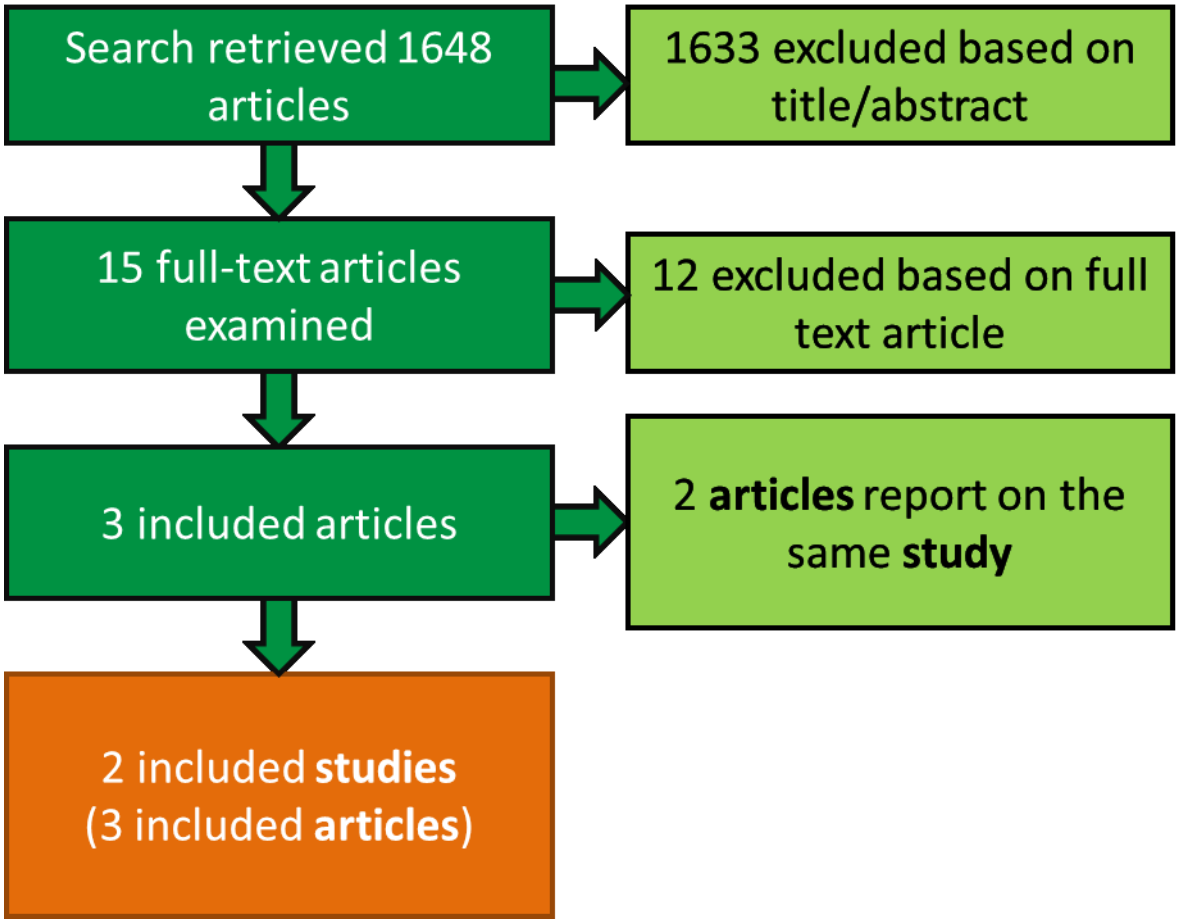
E.1 Review question 1

Please note that review question 1 was updated in 2019 and the evidence from 2015 has been removed.

E.2 Review question 3



E.3 Economic search



Appendix F: Excluded studies

F.1 Review question 1

Please note that review question 1 was updated in 2019 and the evidence from 2015 has been removed.

F.2 Review question 3

Reference	Reason for exclusion
Rohde P, Silva SG, Tonev ST et al. (2008) Achievement and maintenance of sustained response during the Treatment for Adolescents With Depression Study continuation and maintenance therapy. Archives of General Psychiatry 65: 447-55	Intervention and comparator do not match review protocol (continuation therapy for those who did not respond to initial treatment was augmentation of original treatment, not addition of antidepressants in those initially receiving psychotherapy).

F.3 Economic studies

Reference	Reason for exclusion
Arnberg FK, Linton SJ, Hultcrantz M et al. (2014) Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. PLoS ONE [Electronic Resource] 9: e98118.	Only included cost-effectiveness study is for anxiety
Domino ME, Burns BJ, Silva SG et al. (2008) Cost-effectiveness of treatments for adolescent depression: results from TADS. American Journal of Psychiatry 165: 588-96.	Insufficient applicability – US costs, societal perspective, unclear mapping of QALYs
Domino ME, Foster EM, Vitiello B et al. (2009) Relative cost-effectiveness of treatments for adolescent depression: 36-week results from the TADS randomized trial. Journal of the American Academy of Child & Adolescent Psychiatry 48: 711-20.	Insufficient applicability – US costs, societal perspective, unclear mapping of QALYs
Green JM, Wood AJ, Kerfoot MJ et al. (2011) Group therapy for adolescents with repeated self-harm: randomised controlled trial with economic evaluation. BMJ 342: d682.	Irrelevant population (self-harm)
Haby MM, Tonge B, Littlefield L et al. (2004) Cost-effectiveness of cognitive behavioural therapy and selective serotonin reuptake inhibitors for major depression in children and adolescents. Australian & New Zealand Journal of Psychiatry 38: 579-91.	Insufficient applicability – Australian costs, health effects in DALYs
Hollinghurst S, Peters TJ, Kaur S et al. (2010) Cost-effectiveness of therapist-delivered online cognitive-behavioural therapy for depression: randomised controlled trial. British Journal of Psychiatry 197: 297-304.	Adult population
Kaltenthaler E, Shackley P, Stevens K et al. (2002) A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety. [Review] [91 refs]. Health Technology Assessment (Winchester, England) 6: 1-89.	Adult population

Reference	Reason for exclusion
Lynch FL, Dickerson JF, Clarke G et al. (2011) Incremental cost-effectiveness of combined therapy vs medication only for youth with selective serotonin reuptake inhibitor-resistant depression: treatment of SSRI-resistant depression in adolescents trial findings. Archives of General Psychiatry 68: 253-62.	Insufficient applicability – US costs, QALYs not based on EQ-5D
Mihalopoulos C, Vos T, Pirkis J et al. (2012) The population cost-effectiveness of interventions designed to prevent childhood depression. Pediatrics 129: e723-e730.	Interventions designed to prevent childhood depression on at a population level
Romeo R, Byford S, Knapp M (2005) Annotation: Economic evaluations of child and adolescent mental health interventions: A systematic review. Journal of Child Psychology and Psychiatry and Allied Disciplines 46: 919-30.	No included studies for depression
Vos T (2005) Cost-effectiveness of cognitive-behavioural therapy and drug interventions for major depression. Australian and New Zealand Journal of Psychiatry 39:683-692	Insufficient applicability – Australian costs, health effects in DALYs
Watanabe N, Hunot V, Omori IM et al. (2007) Psychotherapy for depression among children and adolescents: a systematic review. Acta Psychiatrica Scandinavica 116: 84-95.	No included studies on cost-effectiveness

Appendix G: Evidence tables

G.1 Review question 1

Please note that review question 1 was updated in 2019 and the evidence from 2015 has been removed.

G.2 Review question 2

Table 8: Cox et al. 2014

Bibliographic reference	**Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE. (2014) Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database of Systematic Reviews (pre-publication version)**
Study type	Systematic review
Aim	To evaluate the effectiveness of psychological therapies and antidepressant medication, alone and in combination, for the treatment of depressive disorder in children and adolescents. We have examined clinical outcomes including remission, clinician and self-reported depression measures, and suicide-related outcomes.
Patient characteristics	**Inclusion criteria:** - Published or unpublished randomised controlled trials - Participants aged 6-18 - Primary diagnosis of depressive disorder diagnosed by a clinician using diagnostic and statistical manual or international classification of diseases criteria - Data available for at least pre and post intervention assessments. **Exclusion criteria:** - Quasi randomised controlled trials and cross over trials **Search strategy:** - The Cochrane depression, anxiety and neurosis group specialised register was searched on 14th June 2014. - Register contains trials identified from weekly generic searches of MEDLINE, EMBASE and PsychINFO, quarterly searches of CENTRAL and specific searches of additional databases. Trials are also identified from international trial registers, drug companies, hand searching of key journals, conference proceedings and non-cochrane systematic reviews.

Bibliographic reference	**Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE. (2014) Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database of Systematic Reviews (pre-publication version)**
	- The reference list of included studies was also checked for trials that may meet the inclusion criteria and authors of included studies were contacted to identified studies that might have been missed. **Planned analysis:** It was intended to conduct subgroup analysis for the following: - Different antidepressants - Different psychological therapies - Children aged 6-12, young people aged 13-18 - Severity of illness (mild, moderate severe)
Number of Patients	n/a (systematic review)
Intervention	Antidepressant treatment Psychological therapy Combination therapy
Comparison	Any of the above
Length of follow up	Outcomes reported at 3 time points: - Post treatment - 6-9 months follow up - 12 months up
Location	International review group. Systematic review of studies from different locations.
Outcomes measures and effect size	**Search results:** The original search (2012) retrieved 10413 references, and the updated search (2014) retrieved an additional 428. The full-text version of 89 references from the original search and 18 from the update search were considered for inclusion, and 9 references from the original search and 1 from the update search met the inclusion criteria and were included in the review. **Analysis:** Outcome data was meta-analysed where possible. The planned subgroup analysis were not possible for the following reasons: - A wide variety of antidepressant medication was used across trials, with too few trials for each medication for meaningful subgroup analysis. - Cognitive behavioural therapy was the only psychological therapy used in the included studies. - All except one trial included adolescents only, so analysis based on age subgroups was not possible.

Bibliographic reference	Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE. (2014) Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database of Systematic Reviews (pre-publication version)

- Outcomes in the included studies were not reported separately based on depression severity, and inclusion criteria for different studies did not differ based on depression severity, therefore subgroup analysis based on depression severity was not possible.

Psychological therapy versus antidepressant medication

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Remission by clinical interview (post-intervention) ITT	2	268	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.95]
1.3 Remission by clinical interview (six to nine months follow-up) ITT	1	48	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.50, 1.65]
1.5 Dropouts (post-intervention)	2	271	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.15, 2.87]
1.6 Dropouts (six to nine months follow-up)	2	223	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.70, 1.82]
1.9 Suicidal ideation (post-intervention)	2	268	Mean Difference (IV, Random, 95% CI)	-3.12 [-5.91, -0.33]
1.10 Suicidal ideation (six to nine months follow-up)	2	268	Mean Difference (IV, Random, 95% CI)	-2.89 [-5.49, -0.28]
1.11 Suicidal ideation (12 months follow-up)	1	220	Mean Difference (IV, Random, 95% CI)	-2.50 [-5.09, 0.09]
1.12 Remission by cut-off (post-intervention)	1	220	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.41, 1.22]
1.13 Remission by cut-off (six to nine months follow-up)	1	220	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.95, 1.48]
1.14 Remission by cut-off (12 months follow-up)	1	220	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.77, 1.15]
1.15 Depression symptoms clinician rated (CDRS-R) (post-intervention)	1	220	Mean Difference (IV, Random, 95% CI)	5.76 [3.46, 8.06]

Bibliographic reference	Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE. (2014) Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database of Systematic Reviews (pre-publication version)

1.16 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up)	1	220	Mean Difference (IV, Random, 95% CI)	0.05 [-2.11, 2.21]
1.17 Depression symptoms clinician rated (CDRS-R) (12 months follow-up)	1	220	Mean Difference (IV, Random, 95% CI)	0.90 [-0.93, 2.73]
1.18 Depression symptoms self-rated (post-intervention)	2	255	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.69, 1.01]
1.19 Depression symptoms self-rated (six to nine months follow-up)	2	268	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.51, 0.42]
1.20 Depression symptoms self-rated (12 months follow-up)	1	220	Mean Difference (IV, Random, 95% CI)	0.50 [-2.74, 3.74]
1.21 Functioning (post-intervention)	1	42	Mean Difference (IV, Random, 95% CI)	2.19 [-3.36, 7.74]
1.22 Functioning (six to nine months follow-up)	1	37	Mean Difference (IV, Random, 95% CI)	-0.39 [-6.66, 5.88]

Combination therapy versus antidepressant medication

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Remission by clinical interview (post-intervention)	3	419	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.99, 1.36]
2.3 Remission by clinical interview (six to nine months follow-up)	2	203	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.97, 1.25]
2.5 Remission by clinical interview (12 months follow-up)	1	152	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.04]
2.6 Dropouts (post-intervention)	5	699	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.58, 1.23]
2.7 Dropouts (six to nine months follow-up)	3	420	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.61, 1.50]

Bibliographic reference	Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE. (2014) Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database of Systematic Reviews (pre-publication version)				
	2.8 Dropouts (12 months follow-up)	1	103	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.01, 1.80]
	2.12 Suicidal ideation (post-intervention)	2	267	Mean Difference (IV, Random, 95% CI)	-2.57 [-5.53, 0.40]
	2.13 Suicidal ideation (six to nine months follow-up)	2	267	Mean Difference (IV, Random, 95% CI)	-1.89 [-4.50, 0.72]
	2.14 Suicidal ideation (12 months follow-up)	1	216	Mean Difference (IV, Random, 95% CI)	-1.60 [-4.18, 0.98]
	2.15 Remission by cut-off (post-intervention)	1	216	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.07, 2.49]
	2.16 Remission by cut-off (six to nine months follow-up)	1	216	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.74, 1.22]
	2.17 Remission by cut-off (12 months follow-up)	2	319	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.84, 1.53]
	2.18 Depression symptoms clinician rated (CDRS-R) (post-intervention)	2	415	Mean Difference (IV, Random, 95% CI)	-0.27 [-4.95, 4.41]
	2.19 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up)	2	408	Mean Difference (IV, Random, 95% CI)	-0.27 [-2.26, 1.72]
	2.20 Depression symptoms clinician rated (CDRS-R) (12 months follow-up)	1	216	Mean Difference (IV, Random, 95% CI)	-0.70 [-2.46, 1.06]
	2.21 Depression symptoms self-rated (post-intervention)	5	683	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.36, 0.09]
	2.22 Depression symptoms self-rated (six to nine months follow-up)	4	610	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.28, 0.17]
	2.23 Depression symptoms self-rated (12 months follow-up)	2	368	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.46, -0.05]
	2.24 Functioning (post-intervention)	3	396	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.11, 0.28]

Bibliographic reference	Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE. (2014) Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database of Systematic Reviews (pre-publication version)

2.25 Functioning (six to nine months follow-up)	3	385	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.12, 0.28]
2.26 Functioning (12 months follow-up)	1	152	Mean Difference (IV, Random, 95% CI)	3.00 [0.40, 5.60]

Combination therapy versus psychological therapy

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Remission by clinical interview (post-intervention) ITT	2	265	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.69, 2.43]
3.3 Remission by clinical interview (six to nine months follow-up) ITT	1	47	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.88, 2.54]
3.5 Dropouts (post-intervention)	2	265	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.18, 8.68]
3.6 Dropouts (six to nine months follow-up)	2	231	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.51, 1.32]
3.9 Suicidal ideation (post-intervention)	2	265	Mean Difference (IV, Random, 95% CI)	0.60 [-2.25, 3.45]
3.10 Suicidal ideation (six to nine months follow-up)	2	265	Mean Difference (IV, Random, 95% CI)	1.78 [-2.29, 5.85]
3.11 Suicidal ideation (12 months follow-up)	1	218	Mean Difference (IV, Random, 95% CI)	0.90 [-1.37, 3.17]
3.12 Remission by cut-off (post-intervention)	1	218	Risk Ratio (M-H, Random, 95% CI)	2.31 [1.41, 3.76]
3.13 Remission by cut-off (six to nine months follow-up)	1	218	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.01]
3.14 Remission by cut-off (12 months follow-up)	1	218	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.86, 1.29]
3.15 Depression symptoms clinician rated (CDRS-R) (post-intervention)	1	218	Mean Difference (IV, Random, 95% CI)	-8.27 [-10.58, -5.96]

Bibliographic reference	Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE. (2014) Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database of Systematic Reviews (pre-publication version)

3.16 Depression symptoms clinician rated (CDRS-R) (six to nine months follow-up)	1	218	Mean Difference (IV, Random, 95% CI)	-0.87 [-3.10, 1.36]
3.17 Depression symptoms clinician rated (CDRS-R) (12 months follow-up)	1	218	Mean Difference (IV, Random, 95% CI)	-1.60 [-3.49, 0.29]
3.18 Depression symptoms self-rated (post-intervention)	2	265	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-1.41, 0.84]
3.19 Depression symptoms self-rated (six to nine months follow-up)	2	265	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.63, 0.31]
3.20 Depression symptoms self-rated (12 months follow-up)	1	218	Mean Difference (IV, Random, 95% CI)	-3.10 [-6.38, 0.18]
3.21 Functioning (post-intervention)	1	43	Mean Difference (IV, Random, 95% CI)	-2.38 [-8.65, 3.89]
3.22 Functioning (six to nine months follow-up)	1	38	Mean Difference (IV, Random, 95% CI)	0.43 [-7.04, 7.90]

Combination therapy versus psychological therapy plus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Dropouts (post-intervention)	4	249	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.53, 1.86]
4.2 Suicidal ideation (post-intervention)	1	126	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.36, 0.24]
4.3 Remission by cut-off (post-intervention)	2	173	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.05, 1.79]
4.4 Remission by cut-off (12 months follow-up)	1	56	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.35, 3.89]
4.5 Depression symptoms clinician rated (CDRS-R) (post-intervention)	3	239	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.78, -0.26]

Bibliographic reference	**Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG, Hetrick SE. (2014) Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database of Systematic Reviews (pre-publication version)**
	4.6 Depression symptoms self-rated (post-intervention) | 3 | 123 | Std. Mean Difference (IV, Random, 95% CI) | -0.34 [-0.70, 0.02] **Outcomes reported but not extracted here:** Remission calculated from observed cases (Remission reported using intention to treat principle extracted here), suicidal ideation as a dichotomised outcome (continuous outcome extracted here).
Source of funding	Headspace, Australia. Australian Government funding for the National Youth Mental Health Foundation
Comments	This systematic review was updated in consultation with NICE to meet the requirements of the clinical guideline update.

G.3 Economic studies

Please note that review question 1 was updated in 2019 and the evidence from 2015 has been reviewed.

Table 9: Full economic evaluation evidence, review question 2, antidepressants and psychological therapies for children and young people with depression

Bibliographic reference	**Goodyer IM, Dubicka B, Wilkinson P et al. (2008) A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. Health Technology Assessment (Winchester, England) 12: iii-iiv.** **Byford S, Barrett B, Roberts C et al. (2007) Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. British Journal of Psychiatry 191: 521-7.**
Evaluation design	

Interventions	SSRIs plus CBT
Comparators	SSRIs
Base-line cohort characteristics	• Associated randomised controlled trial • 208 adolescents aged 11-17 years inclusive, both sexes, with major or sub-threshold depression (at least four DSM-IV depressive symptoms (including one core mood of sadness, irritability or anhedonia) occurred during the same 2 week period and was present on assessment)
Type of Analysis	Cost-utility analysis
Structure	Randomised controlled trial
Cycle length	Not applicable
Time horizon	28 weeks
Country	United Kingdom
Perspective	Broad service-providing perspective, including that of the health, social services, education, voluntary and private sectors
Currency unit	£
Cost year	2004
Discounting	Not applicable due to short time horizon

Bibliographic reference	**Goodyer IM, Dubicka B, Wilkinson P et al. (2008) A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. Health Technology Assessment (Winchester, England) 12: iii-iiv.** **Byford S, Barrett B, Roberts C et al. (2007) Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. British Journal of Psychiatry 191: 521-7.**
Results	

Comparison	SSRIs plus CBT vs. SSRIs
Incremental cost	£2,115[a]
Incremental effects	-0.0297[a]
Incremental cost effectiveness ratio	Dominated
Conclusion	There was significant recovery at all time points in both arms. There was no treatment effectiveness for the addition of CBT to SSRIs for the primary or secondary outcome measures at any time point. There was no evidence to support the hypothesis that SSRIs plus CBT is a more cost-effective strategy than SSRIs only for adolescents with major depression in receipt of routine care.

Data sources

Base-line data	Associated randomised controlled trial.
Effectiveness data	Associated randomised controlled trial with Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA) as the primary outcome and EQ-5D as one of the secondary outcomes
Cost data	• Associated randomised controlled trial. • Resource use was collected using the Child and Adolescent Service Use Schedule developed by the authors. • Intervention sessions were costed on the basis of the salary of the professional who took the session including on-costs and overheads. • Medication costs taken from BNF. • Hospital contacts costed using NHS Reference Costs. • Unit costs of community services were taken from national publications. • Productivity losses used the human capital approach (multiplying days off work due to illness by the parent's salary; productivity losses were included in a sensitivity analysis only, not in the base case analysis)
Utility data	Associated randomised controlled trial.

<table>
<tr><td>Bibliographic reference</td><td>Goodyer IM, Dubicka B, Wilkinson P et al. (2008) A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. Health Technology Assessment (Winchester, England) 12: iii-iiv.
Byford S, Barrett B, Roberts C et al. (2007) Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. British Journal of Psychiatry 191: 521-7.</td></tr>
<tr><td>Uncertainty</td><td>
<table>
<tr><td>One-way sensitivity analysis</td><td>• Seniority of therapists changed to reflect likely clinical practice: did not alter the finding of no significant difference between groups
• Full cost of non-attendance included: SSRIs plus CBT group became significantly more expensive than the SSRIs group
• Cost of supervisors’ time added: SSRIs plus CBT group became significantly more expensive than the SSRIs group
• Cost of two high-cost individuals who spent the majority of the trial in hospital excluded: did not alter the finding of no significant difference between groups
• Travel and productivity losses borne by parents added: did not alter the finding of no significant difference between groups
• Local costs changed to national unit costs: did not alter the finding of no significant difference between groups
• HoNOSCA scores (primary outcome of trial) used as measure of health effect: SSRIs plus CBT is dominated by the SSRIs only group (0.81 points worse, £2,327 increase in cost, using bootstrapped means)</td></tr>
<tr><td>Probabilistic sensitivity analysis</td><td>• 2% probability that SSRIs plus CBT is more cost-effective than SSRIs only in terms of QALYs gained
• 26% probability that SSRI plus CBT is more cost-effective than SSRIs only in terms of improvements in HoNOSCA scores</td></tr>
</table>
</td></tr>
<tr><td>Applicability</td><td>Partially Applicable

There were no CBT only, usual care, or placebo arms in the underlying study. All participants received a brief initial psychological intervention, SSRIs and active clinical care regardless of subsequent randomisation. All other forms of ongoing psychiatric treatment were permitted during the study period except for CBT if the subject was randomised to the SSRI alone arm of the study.</td></tr>
</table>

Bibliographic reference	**Goodyer IM, Dubicka B, Wilkinson P et al. (2008) A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. Health Technology Assessment (Winchester, England) 12: iii-iiv.** **Byford S, Barrett B, Roberts C et al. (2007) Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. British Journal of Psychiatry 191: 521-7.**
Limitations	**Minor Limitations** Time horizon was 12 months. **Conflicts** One author reimbursed for attending UK educational meetings sponsored by Lilly.

Acronyms: EQ-5D: European Quality of Life – 5 Dimensions multi-attribute health status classification system; PSHE: Personal, Social and Health Education; CBT: cognitive-behavioural therapy; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; SMFQ: Short Mood and Feelings Questionnaire; DSM: Diagnostic and Statistical Manual of Mental Disorders

The two publications report slightly different results for the incremental analysis using QALYs. The full Health Technology Assessment, Goodyer et al. (2008), reports the bootstrapped incremental mean cost as £2,115 and the bootstrapped incremental mean effect as -0.0297 QALYs with an ICER of -£71,212 per QALY (SSRIs plus CBT is dominated). The British Journal of Psychiatry article, Byford et al. (2007), reports the bootstrapped incremental mean cost as £2,364 and the bootstrapped incremental mean effect as -0.023 QALYs with an ICER of -£102,965 per QALY (SSRIs plus CBT is dominated). The results from the most recent publication, the full Health Technology Assessment, were provided in the above table. The results reported in each publication are similar and conclusion identical.

Appendix H: GRADE profiles

H.1 Review question 1

Please note that review question 1 was updated in 2019 and the evidence from 2015 has been removed.

H.2 Review question 2

Table 10: Psychological therapy vs antidepressant medication

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psych. therapy	Antidepressant	Relative (95% CI)	Absolute	
Functioning (post-intervention) (Better indicated by higher values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	21	21	-	MD 2.19 higher (3.36 lower to 7.74 higher)	VERY LOW
Functioning (six to nine months follow-up) (Better indicated by higher values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	17	20	-	MD 0.39 lower (6.66 lower to 5.88 higher)	VERY LOW
Depression symptoms clinician rated (post-intervention) (measured with: CDRS-R; Better indicated by lower values)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	111	109	-	MD 5.76 higher (3.46 to 8.06 higher)	MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psych. therapy	Antidepressant	Relative (95% CI)	Absolute	
Depression symptoms clinician rated (six to nine months follow-up) (Better indicated by lower values)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	111	109	-	MD 0.05 higher (2.11 lower to 2.21 higher)	VERY LOW
Depression symptoms clinician rated (12 months follow-up) (measured with: CDRS-R; Better indicated by lower values)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	111	109	-	MD 0.9 higher (0.93 lower to 2.73 higher)	LOW
Depression symptoms self rated (post-intervention) (Better indicated by lower values)											
2[7,8]	randomised trials	serious[5]	serious[9]	no serious indirectness	very serious[3]	none	133	122	-	SMD 0.16 higher (0.69 lower to 1.01 higher)	VERY LOW
Depression symptoms self rated (six to nine months follow-up) (Better indicated by lower values)											
2[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[3]	none	133	135	-	SMD 0.04 lower (0.51 lower to 0.42 higher)	VERY LOW
Depression symptoms self rated (12 months follow-up) (Better indicated by lower values)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	111	109	-	MD 0.5 higher (2.74	VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psych. therapy	Antidepressant	Relative (95% CI)	Absolute	
										lower to 3.74 higher)	
Remission by clinical interview (post-intervention)											
2[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/133 (43.6%)	76/135 (56.3%)	RR 0.75 (0.59 to 0.95)	141 fewer per 1000 (from 28 fewer to 231 fewer)	MODERATE
Remission by clinical interview (six to nine months follow-up)											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/22 (45.5%)	13/26 (50%)	RR 0.91 (0.5 to 1.65)	45 fewer per 1000 (from 250 fewer to 325 more)	MODERATE
Suicidal ideation (post-intervention) (Better indicated by lower values)											
2[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[10]	none	133	135	-	MD 3.12 lower (5.91 to 0.33 lower)	LOW
Suicidal ideation (six to nine months follow-up) (Better indicated by lower values)											
2[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[10]	none	133	135	-	MD 2.89 lower (5.49 to 0.28 lower)	LOW
Suicidal ideation (12 months follow-up) (Better indicated by lower values)											
1[4]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[10]	none	111	109	-	MD 2.5 lower (5.09 lower to	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psych. therapy	Antidepressant	Relative (95% CI)	Absolute	
										0.09 higher)	
Remission by cut-off (post-intervention)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	18/111 (16.2%)	25/109 (22.9%)	RR 0.71 (0.41 to 1.22)	67 fewer per 1000 (from 135 fewer to 50 more)	LOW
Remission by cut-off (six to nine months follow-up)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/111 (64%)	59/109 (54.1%)	RR 1.18 (0.95 to 1.48)	97 more per 1000 (from 27 fewer to 260 more)	MODERATE
Remission by cut-off (12 months follow-up)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	69/111 (62.2%)	72/109 (66.1%)	RR 0.94 (0.77 to 1.15)	40 fewer per 1000 (from 152 fewer to 99 more)	MODERATE
Dropouts (post-intervention)											
2[7]	randomised trials	serious[8]	no serious inconsistency	serious[11]	very serious[3]	none	42/136 (30.9%)	43/135 (31.9%)	RR 0.65 (0.15 to 2.87)	111 fewer per 1000 (from 271 fewer to 596 more)	VERY LOW
Dropouts (six to nine months follow-up)											
2[7]	randomised trials	serious[8]	no serious inconsistency	serious[11]	no serious imprecision	none	28/114 (24.6%)	24/109 (22%)	RR 1.13 (0.7 to 1.82)	29 more per 1000 (from 66 fewer to	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psych. therapy	Antidepressant	Relative (95% CI)	Absolute	
										181 more)	

[1] Melvin 2006
[2] Participants and outcome assessors unblinded
[3] Confidence intervals incorporate clinically important benefit and harm
[4] March/TADS 2004
[5] Participants unblinded.
[6] Confidence intervals incorporate clinically important harm and no clinically important effect
[7] Melvin 2006, March/TADS 2004
[8] Participants unblinded in both studies, outcome assessors unblinded in 1 study.
[9] Confidence intervals from contributing studies have little overlap and difference between studies is potentially clinically important (clinically important harm vs no clinically important effect).
[10] Confidence intervals incorporate clinically important benefit and no clinically important effect
[11] Dropouts are an indirect measure of treatment acceptibility

Table 11: Combination therapy vs antidepressant medication

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Antidepress.	Relative (95% CI)	Absolute	
Functioning (post-intervention) (Better indicated by higher values)											
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	200	196	-	SMD 0.09 higher (0.11 lower to 0.28 higher)	LOW
Functioning (six to nine months follow-up) (Better indicated by higher values)											
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	196	189	-	SMD 0.08 higher (0.12	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Antidepress.	Relative (95% CI)	Absolute	
										lower to 0.28 higher)	
Functioning (12 months follow-up) (Better indicated by higher values)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	77	75	-	MD 3 higher (0.4 to 5.6 higher)	LOW
Depression symptoms clinician rated (post-intervention) (measured with: CDRS-R; Better indicated by lower values)											
2[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[8]	none	207	208	-	MD 0.27 lower (4.95 lower to 4.41 higher)	VERY LOW
Depression symptoms clinician rated (six to nine months follow-up) (measured with: CDRS-R; Better indicated by lower values)											
2[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[8]	none	205	203	-	MD 0.27 lower (2.26 lower to 1.72 higher)	VERY LOW
Depression symptoms clinician rated (12 months follow-up) (measured with: CDRS-R; Better indicated by lower values)											
1[9]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	107	109	-	MD 0.7 lower (2.46 lower to 1.06 higher)	LOW
Depression symptoms self rated (post-intervention) (Better indicated by lower values)											
5[10]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	341	342	-	SMD 0.14	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Antidepress.	Relative (95% CI)	Absolute	
										lower (0.36 lower to 0.09 higher)	
Depression symptoms self rated (six to nine months follow-up) (Better indicated by lower values)											
4[11]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	307	303	-	SMD 0.06 lower (0.28 lower to 0.17 higher)	LOW
Depression symptoms self rated (12 months follow-up) (Better indicated by lower values)											
2[12]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	184	184	-	SMD 0.26 lower (0.46 to 0.05 lower)	LOW
Remission by clinical interview (post-intervention)											
3[13]	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126/209 (60.3%)	108/210 (51.4%)	RR 1.16 (0.99 to 1.36)	82 more per 1000 (from 5 fewer to 185 more)	MODERATE
Remission by clinical interview (six to nine months follow-up)											
2[14,15]	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/102 (84.3%)	75/101 (74.3%)	RR 1.1 (0.97 to 1.25)	74 more per 1000 (from 22 fewer to 186 more)	MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Antidepress.	Relative (95% CI)	Absolute	
Remission by clinical interview (12 months follow-up)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	69/77 (89.6%)	71/75 (94.7%)	RR 0.95 (0.86 to 1.04)	47 fewer per 1000 (from 133 fewer to 38 more)	MODERATE
Suicidal ideation (post-intervention) (Better indicated by lower values)											
2[16]	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	serious[3]	none	132	135	-	MD 2.57 lower (5.53 lower to 0.4 higher)	LOW
Suicidal ideation (six to nine months follow-up) (Better indicated by lower values)											
2[16]	randomised trials	serious[14]	serious17	no serious indirectness	serious[3]	none	132	135	-	MD 1.89 lower (4.5 lower to 0.72 higher)	VERY LOW
Suicidal ideation (12 months follow-up) (Better indicated by lower values)											
1[9]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	107	109	-	MD 1.6 lower (4.18 lower to 0.98 higher)	LOW
Remission by cut-off (post-intervention)											
1[9]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40/107 (37.4%)	25/109 (22.9%)	RR 1.63 (1.07 to 2.49)	144 more per 1000 (from 16	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Antidepress.	Relative (95% CI)	Absolute	
										more to 342 more)	
Remission by cut-off (six to nine months follow-up)											
1[9]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/107 (51.4%)	59/109 (54.1%)	RR 0.95 (0.74 to 1.22)	27 fewer per 1000 (from 141 fewer to 119 more)	MODERATE
Remission by cut-off (12 months follow-up)											
2[12]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	110/160 (68.8%)	100/159 (62.9%)	RR 1.13 (0.84 to 1.53)	82 more per 1000 (from 101 fewer to 333 more)	MODERATE
Dropouts (post-intervention)											
5[10]	randomised trials	serious[18]	no serious inconsistency	serious[19]	no serious imprecision	none	52/349 (14.9%)	63/350 (18%)	RR 0.84 (0.58 to 1.23)	29 fewer per 1000 (from 76 fewer to 41 more)	LOW
Dropouts (six to nine months follow-up)											
3[20]	randomised trials	serious[14]	no serious inconsistency	serious[19]	no serious imprecision	none	31/214 (14.5%)	31/206 (15%)	RR 0.96 (0.61 to 1.5)	6 fewer per 1000 (from 59 fewer to 75 more)	LOW
Dropouts (12 months follow-up)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Antidepress.	Relative (95% CI)	Absolute	
1[4]	randomised trials	serious[5]	no serious inconsistency	serious[19]	no serious imprecision	none	40/53 (75.5%)	28/50 (56%)	RR 1.35 (1.01 to 1.8)	196 more per 1000 (from 6 more to 448 more)	LOW

[1] ADAPT 2007, Clarke 2005, Melvin 2006
[2] Participants unblinded.
[3] Confidence intervals incorporate clinically important benefit and no clinically important effect
[4] Clarke 2005
[5] Participants unblinded and allocation concealment unclear.
[6] ADAPT 2007, March/TADS 2004
[7] Participants unblinded across studies. Unclear method of randomisation in 1 study.
[8] Confidence intervals incorporate clinically important benefit and harm
[9] March/TADS 2004
[10] ADAPT 2007, Clarke 2005, Kim 2012, Melvin 2006, March/TADS 2004
[11] ADAPT 2007, Clarke 2005, Melvin 2006, March/TADS 2004
[12] Clarke 2005, March/TADS 2004
[13] Clarke 2005, Melvin 2006, TADS 2004
[14] Participants unblinded across studies. assessors unblinded in one study.
[15] Clarke 2005, Melvin 2006
[16] Melvin 2006. March/TADS 2004
[17] Confidence intervals from contributing studies have little overlap and difference between studies is potentially clinically important (clinically important benefit vs no clinically important effect).
[18] Participants unblinded in all studies. Allocation concealment unclear in majority of studies.
[19] Dropouts are an indirect measure of treatment acceptibility
[20] ADAPT 2007, Melvin 2006, March/TADS 2004

Table 12: Combination therapy vs psychological therapy

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Psych. therapy	Relative (95% CI)	Absolute	
Functioning (post-intervention) (Better indicated by higher values)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Psych. therapy	Relative (95% CI)	Absolute	
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	22	21	-	MD 2.38 lower (8.65 lower to 3.89 higher)	VERY LOW
Functioning (six to nine months follow-up) (Better indicated by higher values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	21	17	-	MD 0.43 higher (7.04 lower to 7.9 higher)	VERY LOW
Depression symptoms clinician rated (post-intervention) (measured with: CDRS-R; Better indicated by lower values)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	107	111	-	MD 8.27 lower (10.58 to 5.96 lower)	MODERATE
Depression symptoms clinician rated (six to nine months follow-up) (measured with: CDRS-R; Better indicated by lower values)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	107	111	-	MD 0.87 lower (3.1 lower to 1.36 higher)	LOW
Depression symptoms clinician rated (12 months follow-up) (measured with: CDRS-R; Better indicated by lower values)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	107	111	-	MD 1.6 lower (3.49 lower to 0.29 higher)	LOW
Depression symptoms self rated (post-intervention) (Better indicated by lower values)											
2[7]	randomised trials	serious[8]	serious9	no serious indirectness	very serious[3]	none	132	133	-	SMD 0.28 lower (1.41	VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Psych. therapy	Relative (95% CI)	Absolute	
										lower to 0.84 higher)	
Depression symptoms self rated (six to nine months follow-up) (Better indicated by lower values)											
2[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[3]	none	132	133	-	SMD 0.16 lower (0.63 lower to 0.31 higher)	VERY LOW
Depression symptoms self rated (12 months follow-up) (Better indicated by lower values)											
1[4]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[6]	none	107	111	-	MD 3.1 lower (6.38 lower to 0.18 higher)	LOW
Remission by clinical interview (post-intervention)											
2[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[6]	none	82/132 (62.1%)	58/133 (43.6%)	RR 1.29 (0.69 to 2.43)	126 more per 1000 (from 135 fewer to 624 more)	LOW
Remission by clinical interview (six to nine months follow-up)											
1[1]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[6]	none	17/25 (68%)	10/22 (45.5%)	RR 1.5 (0.88 to 2.54)	227 more per 1000 (from 55 fewer to 700 more)	LOW
Suicidal ideation (post-intervention) (Better indicated by lower values)											
2[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[10]	none	132	133	-	MD 0.6 higher (2.25 lower to	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Psych. therapy	Relative (95% CI)	Absolute	
										3.45 higher)	
Suicidal ideation (six to nine months follow-up) (Better indicated by lower values)											
2[7]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[10]	none	132	133	-	MD 1.78 higher (2.29 lower to 5.85 higher)	LOW
Suicidal ideation (12 months follow-up) (Better indicated by lower values)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[10]	none	107	111	-	MD 0.9 higher (1.37 lower to 3.17 higher)	LOW
Remission by cut-off (post-intervention)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	40/107 (37.4%)	18/111 (16.2%)	RR 2.31 (1.41 to 3.76)	212 more per 1000 (from 66 more to 448 more)	LOW
Remission by cut-off (six to nine months follow-up)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/107 (51.4%)	71/111 (64%)	RR 0.8 (0.64 to 1.01)	128 fewer per 1000 (from 230 fewer to 6 more)	MODERATE
Remission by cut-off (12 months follow-up)											
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/107 (65.4%)	69/111 (62.2%)	RR 1.05 (0.86 to 1.29)	31 more per 1000 (from 87 fewer to 180 more)	MODERATE
Dropouts (post-intervention)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Psych. therapy	Relative (95% CI)	Absolute	
2[7]	randomised trials	serious[8]	no serious inconsistency	serious[11]	very serious[3]	none	28/132 (21.2%)	42/133 (31.6%)	RR 1.24 (0.18 to 8.68)	76 more per 1000 (from 259 fewer to 1000 more)	VERY LOW
Dropouts (six to nine months follow-up)											
2[7]	randomised trials	serious[8]	no serious inconsistency	serious[11]	no serious imprecision	none	24/120 (20%)	28/111 (25.2%)	RR 0.82 (0.51 to 1.32)	45 fewer per 1000 (from 124 fewer to 81 more)	LOW

[1] Melvin 2006
[2] Participants and assessors unblinded,
[3] Confidence intervals incorporate clinically important benefit and harm
[4] March/TADS 2004
[5] Participants unblinded.
[6] Confidence intervals incorporate clinically important benefit and no clinically important effect
[7] Melvin 2006, TADS 2004
[8] Participants unblinded in both studies, outcome assessors unblinded in 1 study.
[9] Confidence intervals from contributing studies have little overlap and difference between studies is potentially clinically important (clinically important benefit vs no clinically important effect).
[10] Confidence intervals incorporate clinically important harm and no clinically important effect
[11] Dropouts are an indirect measure of treatment acceptibility

Table 13: Combination therapy vs psychological therapy plus placebo

Quality assessment							No of patients		Effect		Quality	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Psych. therapy plus placebo	Relative (95% CI)	Absolute		
Depression symptoms clinician rated (post-intervention) (measured with: CDRS-R; Better indicated by lower values)												
3[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	118	121	-	SMD 0.52 lower (0.78 to	LOW	

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Psych. therapy plus placebo	Relative (95% CI)	Absolute	
										0.26 lower)	
Depression symptoms self rated (post-intervention) (Better indicated by lower values)											
3[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	60	63	-	SMD 0.34 lower (0.7 lower to 0.02 higher)	LOW
Suicidal ideation (post-intervention) (Better indicated by lower values)											
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[8]	none	63	63	-	MD 0.06 lower (0.36 lower to 0.24 higher)	VERY LOW
Remission by cut-off (post-intervention)											
2[9]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/87 (64.4%)	40/86 (46.5%)	RR 1.37 (1.05 to 1.79)	172 more per 1000 (from 23 more to 367 more)	MODERATE
Remission by cut-off (12 months follow-up)											
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious	none	5/29 (17.2%)	4/27 (14.8%)	RR 1.16 (0.35 to 3.89)	24 more per 1000 (from 96 fewer to 428 more)	VERY LOW
Dropouts (post-intervention)											
4[10]	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	20/123 (16.3%)	21/126 (16.7%)	RR 0.99 (0.53 to 1.86)	2 fewer per 1000 (from 78 fewer to 143 more)	MODERATE

[1] Bernstein 2000, Cornelius 2009, Riggs 2007
[2] Inadequate method of randomisation in 2 studies and outcome assessors unblinded in 1 study
[3] Dropouts are an indirect measure of treatment acceptibility
[4] Bernstein 2000, Cornelius 2009, Deas 2000
[5] Confidence intervals incorporate clinically important benefit and no clinically important effect
[6] Riggs 2007
[7] Inadequeate method of randomisation
[8] Confidence intervals incorporate clinically important benefit and harm
[9] Bernstein 2000, Riggs 2007
[10] Bernstein 2000, Cornelius 2009, Deas 2000, Riggs 2007

Appendix I: Forest plots

I.1 Review question 1

Please note that review question 1 was updated in 2019 and the evidence from 2015 has been removed.