Depression:
Evidence Update April 2012

A summary of selected new evidence relevant to NICE clinical guideline 90 'The treatment and management of depression in adults' (2009)

Evidence Update 13

Contents

Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:

⊙ [1]**Depression. NICE clinical guideline 90 (2009). Available from www.nice.org.uk/guidance/CG90**

Over 6400 pieces of evidence were identified and assessed of which 29 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Other NICE guidance

The following guidance is also of relevance to management of depression in adults in the UK, however this Evidence Update does not discuss any potential effect the new evidence may have on these recommendations because there is a separate Evidence Update (available from www.evidence.nhs.uk/evidence-update-12) for this guidance:

⊙ [1]**Depression in adults with a chronic physical health problem. NICE clinical guideline 91 (2009). Available from www.nice.org.uk/guidance/CG91**

Quality standards

- Depression in adults. NICE quality standard. Available from www.nice.org.uk/guidance/qualitystandards/depressioninadults/home.jsp

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

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[1] NICE-accredited guidance is denoted by the Accreditation Mark ⊙

Key messages

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages for this Evidence Update. It also indicates the EUAG's opinion on whether new evidence identified by the Evidence Update reinforces or has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence, which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance that may be affected, please see the full commentaries.

Key message	Effect on guidance	
	Potential change	No change
Stepped care • Evidence supports current guidance to provide the least intrusive intervention that is likely to be effective as the first step in care.		✓
Step 1: recognition, assessment and initial management • Although unlikely to affect current guidance, limited evidence suggests that the value of psychiatric assessments to support GPs might be a consideration for research conducted within the UK healthcare setting.		✓
Step 2: recognised depression – persistent subthreshold depressive symptoms or mild to moderate depression • Evidence suggests possible benefits from peer support, self-help delivered without professional support and other low cost, low intensity psychosocial interventions that are not currently included in guidance.	✓	
• The recommendation for physical activity programmes receives some support from current evidence, and limited evidence also suggests that shorter programmes may be as effective as longer programmes.		✓
Step 3: persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial intervention, and moderate and severe depression • Evidence supports current guidance that a generic selective serotonin reuptake inhibitor is usually the preferred first choice of antidepressant drug, though new evidence may suggest a more specific choice could be a consideration for future guidance reviews.	✓	
• Evidence confirms that interpersonal therapy is an effective high-intensity psychological treatment, in accordance with current guidance.		✓

Key message	Effect on guidance	
	Potential change	**No change**
Treatment choice based on depression subtypes and personal characteristics • Problem-solving therapy in elderly depressed patients, delivered by highly qualified or experienced therapists, appears to reduce depressive symptoms in parallel with a reduction in disability, compared with usual therapy, suggesting that such an intervention may be a consideration for future guidance reviews.	✓	
Enhanced care for depression • Evidence suggests that pharmacist interventions could improve adherence to antidepressants, although further research is needed.		✓
• Evidence supports current recommendations for collaborative and coordinated multiprofessional care.		✓
Sequencing treatments after initial inadequate response • Current recommendations for augmentation of antidepressant therapies with antipsychotics appear to be supported by evidence.		✓
Continuation and relapse prevention • Evidence appears to support current recommendations for continued therapy to prevent relapse, although further research is needed to determine the optimal treatment regimen.		✓
• Evidence demonstrating the value of psychological therapies to reduce relapses supports current guidance.		✓
Step 4: complex and severe depression • Evidence appears to support current recommendations for complex and severe depression.		✓

1   Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided.

1.1   Care of all people with depression

No new evidence was found for this section.

1.2   Stepped care

NICE clinical guideline (CG) 90 recommends a stepped-care model for the provision of interventions to treat and manage adults with depression. **Seekles et al. (2011)** reported a randomised controlled trial (RCT) to assess the value of stepped care (n = 60) compared with usual care (n = 60) among adults with depressive and/or anxiety disorders in a Dutch primary care setting (where the healthcare system and primary care setting are comparable to those in the UK). Symptoms decreased significantly over time with both groups, with no significant difference between study arms at any time point, as assessed using the Inventory of Depressive Symptoms (stepped care: 250; usual care: 254; p = 0.55; values reported as means after 6 months) or Hospital Anxiety and Depression Scale (stepped care: 7.9; usual care: 8.8; p = 0.22; values reported as means after 6 months). Poor adherence to the stepped-care model was observed (63% drop out overall), particularly in the unsupervised self-help step.

The authors discussed the challenges of obtaining evidence to assess the value of stepped care, all of which are applicable to the UK primary care setting. Recruitment to the study was difficult, resulting in smaller populations than intended, which limits any conclusions that could potentially be made. Usual care, informed by evidence-based guidelines and with mental health specialists working in primary care, may already provide a good level of service.

NICE CG90 advises low-intensity psychological interventions (including guided self-help programmes, computerised cognitive behavioural therapy [CBT] and structured group physical activity) before stepping up to high-intensity psychological interventions (including CBT, interpersonal therapy [IPT], behavioural activation and behavioural couples therapy). A systematic review by **Cuijpers et al. (2010)** provides limited evidence supporting such stepped care. The study evaluated 21 RCTs (13 conducted in the USA, three in the UK, two each in Sweden and Canada and one in Australia; 810 patients with depression and/or anxiety) that compared guided self-help with face-to-face psychotherapy. The studies included were variable in quality; the populations also varied with only five studies using standard diagnostic criteria for depression. The effect of guided self-help was no different to face-to-face treatment (Cohen's standardised mean difference [d] = −0.02; 95% confidence interval [CI] −0.20 to 0.15), and no difference was noted between the two treatments after 1 year of follow-up (d = −0.27; 95% CI −0.62 to 0.07). No significant difference was seen between dropouts from self-help and face-to-face treatments (relative risk [RR] = 1.14; 95% CI 0.77 to 1.67; p = 0.52). Although this review addressed an important question, it did not provide information on comparative costs, despite the resource implications.

A meta-analysis by **Driessen et al. (2010)** assessed whether pretreatment severity of depression affects the efficacy of psychological interventions for the treatment of depression in the outpatient setting. The study reviewed 132 RCTs with a total of 10,134 participants; four studies that reported efficacious psychological interventions were used for within-study severity analysis. Psychological treatment was consistently more effective than control when measured using the Beck Depression Inventory (BDI; d = 0.80; 95% CI 0.69 to 0.91; 74 studies), the revised BDI (d = 0.40; 95% CI 0.16 to 0.65; 12 studies), and the Hamilton

Depression Rating Scale (Ham-D; d = 0.88; 95% CI 0.74 to 1.01; 48 studies). A significantly greater effect was seen in patients with high severity symptoms pretreatment (d = 0.63; 95% CI 0.31 to 0.94; p < 0.01) than with low severity symptoms (d = 0.22; 95% CI −0.05 to 0.49; p = 0.11; p = 0.05 for between-group effect size difference).

Although the authors noted several limitations in the analysis (including studies lacking definition of depression, differences in depression rating scales, lack of high quality studies in severe depression and lack of quality assurance in data extraction), the evidence is consistent with NICE CG90 guidance on stepped care, which recommends treatment should start with interventions that are the least intrusive of those likely to be effective.

Key references
Cuijpers P, Donker T, van Straten A et al. (2010) Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. Psychological Medicine 40: 1943–57
Abstract: www.journals.cambridge.org/action/displayAbstract?fromPage=online&aid=7917284

Driessen E, Cuijpers P, Hollon SD et al. (2010) Does pretreatment severity moderate the efficacy of psychological treatment of adult outpatient depression? A meta-analysis. Journal of Consulting and Clinical Psychology 78: 668–80
Abstract: www.psycnet.apa.org/journals/ccp/78/5/668/

Seekles W, van Straten A, Beekman A et al. (2011) Stepped care treatment for depression and anxiety in primary care: a randomized controlled trial. Trials 12: 171
Full text: www.trialsjournal.com/content/pdf/1745-6215-12-171.pdf

1.3 Step 1: recognition, assessment and initial management

NICE CG90 does not explicitly discuss referral pathways. Although referral of patients who have not responded to treatment to a practitioner with a specialist interest in treating depression is recommended, there is no mention of referral to specialist services to aid assessment and diagnosis. Such issues were considered in a systematic review by **van der Feltz-Cornelis et al. (2010)** to assess the effect of psychiatric consultations in the primary care setting for patients with somatoform and depressive disorders compared with usual care. The ten RCTs (3408 patients) were all conducted in the USA so have limited relevance to the UK healthcare setting. Additionally, the interventions were complex so could be considered 'collaborative care' with any effect not just attributable to the involvement of a psychiatrist. However, a significant beneficial effect was seen, particularly with regard to reduction in utilisation of healthcare services (d = 0.51; 95% CI 0.31 to 0.71). Although the evidence from this study is not sufficient to change practice, it suggests that the value of psychiatric assessments to support GPs might be a consideration for research conducted within the UK healthcare setting.

Key reference
van der Feltz-Cornelis CM, Van Os TWDP, Van Marwijk HWJ et al. (2010) Effect of psychiatric consultation models in primary care: a systematic review and meta-analysis of randomized clinical trials. Journal of Psychosomatic Research 68: 521–33
Abstract: www.jpsychores.com/article/S0022-3999%2809%2900459-0/abstract

1.4 Step 2: recognised depression – persistent subthreshold depressive symptoms or mild to moderate depression

Low-intensity psychosocial interventions

At step 2, NICE CG90 recommends offering one or more low-intensity psychosocial interventions (specifically, individual guided self-help based on CBT, computerised CBT or structured group physical activity). The current guidance does not include mention of self-help interventions without involvement of a professional coach or therapist to guide the patient (that is, self-guided self-help). The efficacy of such an approach was investigated in a meta-

analysis of self-guided psychological treatment by **Cuijpers et al. (2011)**. Seven RCTs were included involving 1362 participants. The analysis demonstrated a small but significant effect of self-guided self-help on depression (d = 0.28; 95% CI 0.14 to 0.42; p < 0.001); at follow up after 4–12 months, the effect size was d = 0.23. However, drop out from self-guided self-help is high and further research is needed, because studies specified as self-guidance (for example, bibliotherapy) may inadvertently include hidden help and support that makes interpretation difficult. Nevertheless, this evidence suggests that inclusion of self-guided self-help may be a potential consideration for future reviews of NICE CG90.

A meta-analysis by **van't Hof et al. (2011)** examined 17 RCTs of psychological treatments involving 3100 participants in low-income to middle-income countries, and found an overall benefit of such therapies compared with usual care (d = 1.02; 95% CI 0.76 to 1.28), particularly for CBT-type interventions (d = 1.25; 95% CI 0.94 to 1.55) compared with other interventions (d = 0.57; 95% CI 0.03 to 1.11; p = 0.032). The treatments included were highly varied and the heterogeneity in the analysis was high, but not related to the conduct of the studies. Although the implications for guidelines in the UK are limited, the low cost of some interventions (for example, use of lay counsellors and primary care workers) shown to be effective makes them worthy of further investigation in a developed healthcare setting.

A systematic review by **Krogh et al. (2011)** evaluated the effect of prescribing exercise to patients presenting to a trained health worker in a clinical setting and given a diagnosis of depression. Only four studies were identified, two of which were in primary care; no significant effect was seen (standardised mean difference [SMD] = −0.47; 95% CI −1.13 to 0.18). To increase the number of studies evaluated, the inclusion criteria were relaxed to allow trials with patients diagnosed with depression according to a diagnostic system, regardless of setting. A significant benefit of exercise was seen after pooling the 13 RCTs (n = 740) included in this analysis (SMD = −0.40; 95% CI −0.66 to −0.14), but no benefit was seen with programmes lasting longer than 10 weeks (SMD = −0.12; 95% CI −0.30 to 0.05; seven studies). Only five of the 13 studies included long-term follow-up of participants to examine the effect of exercise after completion of the programme; little effect on depression was found (SMD = −0.01; 95% CI −0.28 to 0.26). The recommendation in NICE CG90 for physical activity programmes receives some support from this evidence, and limited evidence may also suggest that shorter programme lengths may be as effective as longer ones.

Key references
Cuijpers P, Donker T, Johansson R et al. (2011) Self-guided psychological treatment for depressive symptoms: a meta-analysis. PLoS ONE 6: e21274
Full text: www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0021274

Krogh J, Nordentoft M, Sterne JAC et al. (2011) The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials. Journal of Clinical Psychiatry 72: 529–38
Abstract: www.article.psychiatrist.com/dao_1-login.asp?ID=10007122&RSID=35271304530341

van t'Hof, Cuijpers P, Waheed W et al. (2011) Psychological treatments for depression and anxiety disorders in low- and middle-income countries: a meta-analysis. African Journal of Psychiatry 14: 200–7
Full text: www.ajop.co.za/Journals/july2011/Psychological treatments.pdf

Group cognitive behavioural therapy

NICE CG90 recommends group-based CBT at step 2 for people who decline low-intensity psychosocial interventions. A systematic review by **Pfeiffer et al. (2011)** assessed the efficacy of peer support compared with group-based CBT in seven studies (301 participants; three studies included only women, one study included only HIV-positive men and one study was of caregivers with depression who were responsible for someone with a serious mental illness). No significant difference was found between treatment approaches (SMD = 0.10; 95% CI −0.20 to 0.39; p = 0.53). The review also compared peer support to usual care (seven

studies; 869 participants) and found benefits in reducing depressive symptoms (SMD = −0.59; 95% CI −0.98 to −0.21; p = 0.002). The findings are limited by the lack of generalisability to clinical patients because all the participants in the included studies were selected on the basis of depressive symptoms elicited by questionnaires, the benefits of peer support (mainly groups rather than pairs) were not evident in studies with blind ratings, and peer groups were of people with specific factors in common (for example, HIV) so may not be generalisable to groups with no common factor. Although the evidence is unlikely to affect NICE CG90, in view of the low cost of peer support, further research on its value at step 2 (and other steps) is desirable.

Key reference
Pfeiffer PN, Heisler M, Piette JD et al. (2011) Efficacy of peer support interventions for depression: a meta-analysis. General Hospital Psychiatry 33: 29–36
Full text: www.ncbi.nlm.nih.gov/pmc/articles/PMC3052992/?tool=pubmed

Drug treatment

NICE CG90 does not recommend the routine use of antidepressants to treat persistent subthreshold depressive symptoms or mild depression because the risk–benefit ratio is poor, although they may be considered for some patients. This view was supported by a systematic review and meta-analysis by **Barbui et al. (2011)** that included six RCTs of antidepressants (amitryptyline, fluoxetine, isocarboxazid and paroxetine) compared with placebo in 468 patients with minor depression. There was no significant difference between treatment arms in response to treatment or acceptability (in terms of treatment discontinuation).

Key reference
Barbui C, Cipriani A, Patel V et al. (2011) Efficacy of antidepressants and benzodiazepines in minor depression: systematic review and meta-analysis. British Journal of Psychiatry 198: 11–16
Full text: www.bjp.rcpsych.org/content/198/1/11.full.pdf+html

1.5 Step 3: persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression

Antidepressant drugs

When an antidepressant is to be prescribed, NICE CG90 advises that it should normally be a selective serotonin reuptake inhibitor (SSRI) in a generic form because SSRIs are as effective as other antidepressants and have a favourable risk–benefit ratio. Recent evidence supports this guidance.

A comprehensive meta-analysis to assess the comparative benefits and harms of second generation antidepressants in major depressive disorder was conducted for the US Agency for Healthcare Research and Quality by **Gartlehner et al. (2011)**. A total of 234 studies were included (of which 118 were head-to-head RCTs). The efficacy assessment included 93 studies involving more than 20,000 patients and the harm assessment included 48 observational studies (each of which included more than 1000 patients) and 93 RCTs.

No clinically relevant differences in efficacy or effectiveness were noted for the treatment of acute, continuation and maintenance phases of major depressive disorder. Although significantly greater response rates were observed in head-to-head trials with escitalopram compared with citalopram (odds ratio [OR] = 1.49; 95% CI 1.07 to 2.01), sertraline compared with fluoxetine (OR = 1.42; 95% CI 1.08 to 1.85) and venlafaxine compared with fluoxetine (OR = 1.47; 95% CI 1.16 to 1.86), absolute differences were modest.

With regard to harm, overall discontinuation rates were similar between SSRIs and other second generation antidepressants (range of means 15–25%). Compared with SSRIs as a class, there was a higher risk of discontinuation of therapy because of adverse events with duloxetine (67%; 95% CI 17 to 139%) and venlafaxine (40%; 95% CI 16 to 73%). Discontinuation rates due to lack of efficacy were similar in SSRIs and other second generation antidepressants with the exception of venlafaxine which had a 34% (95% CI 47 to 93%) lower risk than SSRIs. The authors noted that most trials were conducted in highly selected populations, with a possibility that publication bias could affect some comparisons. In accordance with NICE CG90, this study found no evidence to prefer any specific antidepressant over others on the basis of differences in efficacy.

Ali and Lam (2011) assessed the efficacy of escitalopram in major depressive disorder compared with other antidepressant drugs in a systematic review of six pooled analysis and six meta-analysis studies; it was not clear if data from the same trial was considered in more than one analysis. Escitalopram was marginally more effective than other antidepressants (weighted mean differences versus citalopram ranging from 1.13 to 1.73 Montgomery–Asberg Depression Rating Scale (MADRS) points were observed in three of the included meta-analyses [n = 1359, 2009 and 2476], although in two of these analyses the authors did not consider the results clinically relevant). The authors also noted that several pooled analysis studies (ranging from n = 121 to n = 2345) found marginally greater efficacy differences of clinical importance in favour of escitalopram in patients with higher baseline severity of depression (MADRS ≥ 30 or Ham-D ≥ 25), with weighted mean differences of 1.4 to 3.8 MADRS points and response rate differences of 6.6–19.1%. NICE CG90 does not currently give advice concerning the choice of antidepressant drug for patients with more severe depression. It should be noted that a meta-analysis by Cipriani et al. (2009) also identified an antidepressant drug (sertraline) with superior efficacy to other SSRIs, although there were limitations to this study and the clinical difference is likely to be small, as discussed in the National Prescribing Centre's (NPC) MeReC Rapid Review 283.

A systematic review for the German Institute for Quality and Efficiency in Health Care by **Eyding et al. (2010)** included both published and unpublished RCTs comparing the selective noradrenaline reuptake inhibitor (NRI), reboxetine, with placebo and/or SSRIs, and was discussed in the NPC's MeReC Rapid Review 1977. Remission and response rates (benefit outcomes) were considered, in addition to adverse events and withdrawals due to adverse events (harm outcomes). A total of 13 acute treatment trials were included in the analysis involving 4098 patients; information from 74% of these patients was unpublished. Reboxetine showed no significant difference in remission rates from placebo (OR = 1.17, 95% CI 0.91 to 1.51; p = 0.216); a point estimate of difference in response rate could not be calculated because of substantial heterogeneity. Reboxetine was inferior to placebo for both harm outcomes (p < 0.001). Reboxetine was shown to be inferior to SSRIs (fluoxetine, paroxetine and citalopram) for remission rates (OR = 0.80; 95% CI 0.67 to 0.96; p = 0.015) and response rates (OR = 0.80; 95% CI 0.67 to 0.95; p = 0.01); reboxetine was inferior to fluoxetine for withdrawals due to adverse events (p = 0.031). The authors noted that published data overestimated the benefits of reboxetine compared with placebo (by up to 115%) and SSRIs (by up to 23%), and underestimated harm. Although NICE CG90 does not offer recommendations on specific choice of drug treatments, this evidence suggests additional advice on reboxetine may be a potential consideration for future guidance reviews.

A systematic review by **Schueler et al. (2010)** assessed 54 RCTs of venlafaxine (n = 12,816), 14 RCTs of duloxetine (n = 4528) and two direct comparisons (n = 836) in major depression; 23 studies were previously unpublished. All the studies were of short-term treatment, limiting the ability to draw relevant conclusions for long-term management. Both therapies were significantly more effective than placebo (in terms of remission and response rates) but with significantly reduced tolerability (in terms of discontinuation due to adverse

events). Compared with SSRIs, venlafaxine showed significantly improved response rate (OR = 1.20; 95% CI 1.07 to 1.35) but not remission rate (OR = 1.12; 95% CI 0.98 to 1.28); there were no significant differences between venlafaxine and tricyclic antidepressants (TCAs) for either efficacy outcome. Discontinuation due to adverse events was significantly higher with venlafaxine compared with SSRIs (OR = 1.38; 95% CI 1.15 to 1.66) but was similar to TCAs. There was no significant difference in efficacy between duloxetine and SSRIs, although there were significantly more discontinuations due to adverse events (OR = 1.53; 95% CI 1.10 to 2.13). In the direct comparisons, venlafaxine resulted in a higher response rate than duloxetine, but this did not reach statistical significance; differences in remission rate could not be analysed because of heterogeneity. Duloxetine resulted in significantly higher discontinuation rates due to adverse events than venlafaxine (OR = 1.79; 95% CI 1.16 to 2.78). This evidence supports NICE CG90 advice that there is an increased likelihood of discontinuation due to tolerability issues with venlafaxine and duloxetine compared with SSRIs. This evidence may also have implications for sequencing of treatments.

Key references
Ali MK, Lam RW (2011) Comparative efficacy of escitalopram in the treatment of major depressive disorder. Neuropsychiatric Disease and Treatment 7: 39–49
Full text: www.dovepress.com/getfile.php?fileID=8671

Eyding D, Leigemann M, Grouven U et al. (2010) Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. British Medical Journal 341: c4737
Full text: www.bmj.com/content/341/bmj.c4737.full

Gartlehner G, Hansen RA, Morgan LC et al. (2011) Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Annals of Internal Medicine 155: 772–85
Full text: www.annals.org/content/155/11/772.full.pdf+html

Schueler Y-B, Koesters M, Wieseler B et al. (2011) A systematic review of duloxetine and venlafaxine in major depression, including unpublished data. Acta Psychiatrica Scandinavica 123: 247–65
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1600-0447.2010.01599.x/abstract

Supporting reference
Cipriani A, Furukawa TA, Salanti G et al. (2009) Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 373: 746–58
Abstract: www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)60046-5/abstract

Antipsychotic drugs

A Cochrane review by **Komossa et al. (2010)** included a total of 28 RCTs of treatment with second-generation antipsychotics in 8487 participants diagnosed with major depressive disorder or dysthymia. Four RCTs (3414 participants with single episode or recurrent major depression) compared quetiapine monotherapy with placebo. Although significant efficacy benefits of treatment were noted, the authors suggested that the results should be interpreted with caution due to the limited evidence base. Furthermore, acceptability to patients was significantly reduced because of increased adverse events. The review also included one RCT (n = 309) comparing quetiapine and duloxetine, which found no efficacy benefits but reduced tolerability. NICE CG90 recommendations do not include quetiapine as therapy at step 3 (although quetiapine augmentatation may be considered after initial inadequate response) and this limited evidence supports this view.

Key reference
Komossa K, Depping AM, Guadchau A et al. (2010) Second-generation antipsychotics for major depressive disorder and dysthymia. Cochrane Database of Systematic Reviews issue 12: CD008121
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD008121.pub2/full

Psychological interventions

A meta-analysis of 38 studies (4356 patients) by **Cuijpers et al. (2011)** evaluated the efficacy of the high-intensity psychological intervention, interpersonal therapy (IPT), in patients with depression. Comparators included no treatment, usual care, other psychological treatments and pharmacotherapy. In the 16 studies comparing IPT and standard or no treatment, the overall effect size was 0.63 (95% CI 0.36 to 0.90). There was no significant difference between IPT and other psychological treatments (10 studies; d = 0.04; 95% CI −0.14 to 0.21). Pharmacotherapy was more effective than IPT (10 studies; d = −0.19; 95% CI −0.38 to −0.01). The evidence appears to support the NICE CG90 recommendation for IPT as a step 3 treatment. This study also examined IPT as part of maintenance treatment so provides evidence to inform practice for relapse prevention.

Key reference
Cuijpers P, Geraedts AS, van Oppen P et al. (2011) Interpersonal psychotherapy for depression: a meta-analysis. American Journal of Psychiatry 168: 581–92
Abstract: www.ajp.psychiatryonline.org/article.aspx?Volume=168&page=581&journalID=13

1.6 Treatment choice based on depression subtypes and personal characteristics

An RCT by **Alexopoulos et al. (2011)** compared the effect of 12 sessions of problem-solving therapy (delivered by doctorate level clinical psychologists and experienced social workers) with supportive therapy in 221 older depressed adults (> 59 years) with executive impairment, and considered whether any differences were mediated by improvement in depressive symptoms. Depression was assessed using the Ham-D scale, disability was assessed using the World Health Organization Disability Assessment Schedule II (WHODAS II), and a mixed-effects model was developed to analyse changes in disability over time. Problem-solving therapy (PST) was more effective than supportive therapy (ST) during 12 weeks of treatment (reduction in WHODAS II scores greater in the PST than in the ST group by approximately 0.18 points per week; p < 0.001). After treatment (12–36 weeks) WHODAS II scores increased in both groups but the advantage of PST remained significant (data expressed graphically). Depressive symptoms were reduced in parallel with reduction in disability, so that for every point change in Ham-D score at weeks 12 and 24, there was a change of 0.18 in WHODAS II score at weeks 24 and 36, respectively. This study provides evidence that may assist selection of psychological interventions for older patients with cognitive impairment and may be a consideration for future reviews of NICE CG90.

Key reference
Alexopoulous GS, Raue PJ, Kiosses DN et al. (2011) Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction. Effect on disability. Archives of General Psychiatry 68: 33–41
Abstract: www.archpsyc.ama-assn.org/cgi/content/abstract/68/1/33

1.7 Enhanced care for depression

A systematic review conducted by **Rubio-Valera et al. (2011)** included six RCTs that evaluated the impact of pharmacist interventions on improving adherence to antidepressants in depressed patients in an outpatient setting (459 patients receiving pharmacist care and 428 patients receiving usual care). Interventions included patient education and monitoring, monitoring and management of toxicity and adverse effects, adherence promotion, provision of information, and recommendations or implementation of medication adjustments. The review found no significant heterogeneity between the included studies, although different outcome measures were used, which could limit internal validity. Pharmacist interventions had a positive impact on adherence, with a pooled OR of 1.64 (95% CI 1.24 to 2.17). The authors noted the limitations of short follow-up (2–12 months) and paucity of studies outside

of the USA (one study was conducted in the Netherlands and one in Australia; all other studies were conducted in the USA).

Evidence suggests that pharmacist interventions could improve adherence to antidepressants, although further research is needed to assess the impact of interventions by pharmacists in the UK or comparable healthcare settings.

NICE CG90 recommends that medication management is likely to be effective only when provided as part of a more complex intervention, with consideration given to providing collaborative and coordinated multiprofessional care. This view is supported by evidence from a systematic review conducted by **Oestergaard and Møldrup (2011)** that included 19 publications (13 were systematic reviews and six were meta-analyses, which between them analysed a total of 455 studies) of non-pharmacological interventions in depression. The number of participants included was not stated. Interventions to improve adherence, multifaceted interventions and combined pharmacotherapy and psychotherapy were evaluated; all but four of the studies included were of moderate or high quality. Collaborative care (defined as an approach of coordinating interventions that incorporate the efforts of several different providers in managed care) improved depression at 6 months compared with standard care (SMD = 0.25; 95% CI 0.18 to 0.31; data from one meta-analysis of 11 studies). Treatment that combined psychotherapy and pharmacotherapy showed a moderate effect in reduced relapse rates compared with medication alone (d = 0.68; data from one meta-analysis of 20 studies).

Key references
Ostergaard S, Møldrup C (2011) Improving outcomes for patients with depression by enhancing antidepressant therapy with non-pharmacological interventions: a systematic review of reviews. Public Health 125: 357–67
Abstract: www.publichealthjrnl.com/article/S0033-3506%2811%2900037-0/abstract

Rubio-Valera M, Serrano-Blanco A, Magdalena-Belio J et al. (2011) Effectiveness of pharmacist care in the improvement of adherence to antidepressants: a systematic review and meta-analysis. The Annals of Pharmacotherapy 45: 39–48
Abstract: www.theannals.com/content/45/1/39.abstract

1.8   Sequencing treatments after initial inadequate response

Combining and augmenting medications

NICE CG90 recommends the addition of an antipsychotic medication, such as quetiapine, in patients with an inadequate response to antidepressants. Recent evidence supports this recommendation.

In the Cochrane review by **Komossa et al. (2010)** (see 'Antipsychotic drugs' in section 1.5 for details), in patients with major depressive disorder there was significant improvement in measures of efficacy when antidepressant therapy was augmented with aripiprazole (three RCTs; n = 1092; OR = 0.48; 95% CI 0.37 to 0.63), quetiapine (three RCTs; n = 995; OR = 0.68; 95% CI 0.52 to 0.90) and risperidone (two RCTs; n = 371; OR = 0.57; 95% CI 0.36 to 0.89). Limited efficacy benefits were noted with olanzapine augmentation therapy (five RCTs; n = 808; mean difference in MADRS score at endpoint = −2.84; 95% CI −5.48 to −0.20). The side-effect burden was increased with all additional therapies except risperidone. This evidence appears to support the current guidance in NICE CG90, although studies were not necessarily conducted in populations with depression that had failed to respond to SSRIs. However, the recommendation is also supported by a meta-analysis by Nelson and Papakostas (2009) of 16 RCTs (3480 participants) that compared adjunctive atypical antipsychotic treatment (five trials with olanzapine, five with quetiapine, three with risperidone and three with aripiprazole) or placebo in patients with non-psychotic unipolar major depressive disorder resistant to prior antidepressant treatment. Adjunctive atypical antipsychotic treatment was significantly more effective than placebo for both response to

treatment, defined as ≥ 50% improvement from baseline in MADRS or Ham-D scale (OR = 1.69; 95% CI 1.46 to 1.95; p < 0.00001) and remission (OR = 2.00; 95% CI 1.69 to 2.37; p < 0.00001). There was no difference between adjunctive treatments, and results were not affected by trial duration. Discontinuation rates for adverse events were higher for atypical antipsychotic treatment than placebo (OR = 3.91; 95% CI 2.68 to 5.72; p < 0.00001).

A pooled analysis of two RCTs that were prospectively designed to be pooled, was reported by **Bauer et al. (2010)**. Both RCTs, conducted in patients with major depressive disorder and an inadequate response to antidepressant therapy, assessed two doses of adjunctive extended release quetiapine fumarate (150 mg/day, n = 309; 300 mg/day, n = 307) and placebo (n = 303). Improvement in depressive symptoms (assessed by least squares means change in total MADRS score from randomisation) was apparent at every assessment for both the 150 mg and 300 mg groups compared with placebo (week 1: −7.8, −7.3, −5.1 respectively; p < 0.001 each dose; week 6: −14.5, −14.8, − 12.0 respectively; p < 0.001 each dose). After 6 weeks, remission rates were significantly higher with quetiapine fumarate 150 mg/day (35.6%; p < 0.01) and 300 mg/day (36.5%; p < 0.001) than placebo (24.1%). Although efficacy with the two doses was similar, patients taking the higher dose experienced more adverse events (80.8% vs 73.3%) and were more likely to withdraw from the study due to adverse events (15.4% vs 8.9%) than those taking the lower dose; these differences were not explored by statistical analysis. Although limited by the short duration and lack of insight into relative merits of extended release and standard quetiapine, this evidence appears to support the NICE CG90 recommendation for augmentation with antipsychotic medication.

Key reference
Bauer M, El-Khalili N, Datto C et al. (2010) A pooled analysis of two randomised, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. Journal of Affective Disorders 127: 19–30
Abstract: www.jad-journal.com/article/S0165-0327(10)00568-9/abstract

Supporting reference
Nelson JC, Papakostas GI (2009) Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. American Journal of Psychiatry 166: 980–91
Full text: www.ajp.psychiatryonline.org/article.aspx?volume=166&page=980

1.9   Continuation and relapse prevention

Using medication for relapse prevention

A meta-analysis of 54 RCTs (9268 patients) to assess relapse rates with continuing antidepressant therapy (after acute response to treatment) compared with placebo was reported by **Glue et al. (2010)**. The most commonly used interventions were SSRIs (21 studies; n = 4447) and mixed serotonin and noradrenaline reuptake inhibitors (21 studies; n = 2420); also included were studies with monoamine oxidase inhibitors (five studies; n = 129), selective noradrenaline reuptake inhibitors (two studies; n = 1406) and other antidepressants such as bupropion (eight studies; n = 866). Continued therapy with all drug classes reduced the risk of relapse compared with placebo (OR = 0.38; 95% CI 0.34 to 0.41; p < 0.00001). Duration of treatment (various combinations of short, intermediate or long pre-randomisation treatment with short or long post-randomisation treatment) and age of patient (elderly versus non-elderly) showed no impact on outcomes.

A systematic review and meta-analysis by **Kok et al. (2011)** examined continuation of antidepressant treatment after successful therapy in the elderly (> 55 years; mean age in individual studies ranged from 64 to 77 years) to establish tolerability and efficacy in preventing relapse. Eight placebo-controlled RCTs (n = 925; duration of observation from 24 weeks to 3 years; four of the eight trials were 2 years in length) were included. The absolute risk of suffering a relapse or recurrence using antidepressants (117 of 467 patients) compared with placebo (240 of 458 patients) was reduced by 28% (95% CI 21 to 36%;

p < 0.00001). In the five studies providing this information, there was no significant difference in dropout rate due to side-effects. There were no significant differences in efficacy or tolerability between treatment with SSRIs and TCAs.

The evidence confirms the recommendation of NICE CG90 (to continue therapy for at least 2 years if at risk of relapse), although further research is needed to determine the optimal treatment regimen for relapse prevention.

Key references
Glue P, Donovan MR, Kolluri S et al. (2010) Meta-analysis of relapse prevention antidepressants trials in depressive disorders. Australian and New Zealand Journal of Psychiatry 44: 697–705
Abstract: www.informahealthcare.com/doi/abs/10.3109/00048671003705441

Kok RM, Heeren TJ, Nolen WA (2011) Continuing treatment of depression in the elderly: a systematic review and meta-analysis of double-blinded randomized controlled trials with antidepressants. American Journal of Geriatric Psychiatry 19: 249–55
Abstract:
www.journals.lww.com/ajgponline/Abstract/2011/03000/Continuing_Treatment_of_Depression_in_the_Elderly_.8.aspx

Psychological interventions for relapse prevention

NICE CG90 recommends individual CBT or mindfulness-based cognitive therapy (MBCT) as psychological interventions for relapse prevention in people who are at significant risk of relapse. A systematic review and meta-analysis by **Chiesa and Serretti (2011)** found four RCTs comparing relapse prevention with MBCT (166 patients) and with usual therapy (160 patients) in patients with three or more prior depressive episodes. The analysis showed a reduction in risk of relapse in the 12 months following MBCT compared with the control group (OR = 0.36; 95% CI 0.19 to 0.48; p < 0.0003). Another systematic review and meta-analysis by **Piet and Hougaard (2011)** found six RCTs (593 participants) that evaluated the effect of MBCT for prevention of relapse or recurrence among patients with recurrent major depressive disorder in remission. Although the number of studies was small, the heterogeneity was low. The review confirmed previous conclusions that MBCT can reduce the risk of relapse when added to usual therapy (mean risk ratio = 0.66; 95% CI 0.53 to 0.82; p = 0.0001). The benefits pertained only to patients at particularly high risk of relapse (three or more previous episodes with unstable remission); no risk reduction was found for participants with only two previous episodes. Overall, the evidence appears to support the NICE CG90 recommendation for use of MBCT in relapse prevention for patients at significant risk of relapse, although there remains no comparison with other psychological therapies (for example, CBT).

In a meta-analysis by **Cuijpers et al. (2011)** (see 'Psychological interventions' in section 1.5 for details), four studies (n = 675) compared maintenance pharmacotherapy with or without the inclusion of IPT in patients who had recovered from a depressive disorder. Including IPT significantly reduced the recurrence rate compared with pharmacotherapy alone after successful treatment of acute depression (OR = 0.37; 95% CI 0.19 to 0.73; p < 0.01). Four studies (patient numbers not stated) compared the combination of maintenance IPT and pill placebo with pill placebo alone and also found protective effect of IPT against relapse (OR = 0.47; 95% CI 0.25 to 0.87). IPT as an alternative psychological intervention for relapse prevention may be a consideration for future reviews of NICE CG90.

A meta-analysis of strategies to prevent relapse in major depressive disorder by **Guidi et al. (2011)** included eight RCTs with 442 patients who received face-to-face psychotherapy (cognitive therapy, CBT or MBCT) after pharmacotherapy and 433 patients in a control treatment arm (antidepressant medication, clinical management or treatment as usual). The pooled RR for relapse or recurrence was 0.80 (95% CI 0.66 to 0.96) suggesting an advantage

of sequential administration of treatments. Subgroup analysis found significantly reduced relapse or recurrence with psychotherapy after drug treatment was discontinued compared with controls (RR = 0.65; 95% CI 0.46 to 0.91) but the effect of psychotherapy while drug treatment continued compared with controls was not significant (RR = 0.84; 95% CI 0.67 to 1.05). A meta-analysis (22 RCTs) by **Oestergaard and Møldrup (2011)** also found that a combination of psychological treatment and antidepressants was more effective than antidepressants alone in patients with moderate and severe depression in preventing relapse or promoting remission (greatest effect for time spent in remission observed at 4 months after commencing treatment, OR = 2.36; 95% CI 1.58 to 3.55; n = 566). This evidence supports the role of psychotherapy in preventing relapses recommended in the current guidance.

Key references
Chiesa A, Serretti A (2011) Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. Psychiatry Research 187: 441–53
Abstract: www.psy-journal.com/article/S0165-1781%2810%2900519-6/abstract

Guidi J, Fava GA, Fava M et al. (2011) Efficacy of sequential integration of psychotherapy and pharmacotherapy in major depressive disorder: a preliminary meta-analysis. Psychological Medicine 41: 321–31
Abstract: www.journals.cambridge.org/action/displayAbstract?fromPage=online&aid=7950736

Ostergaard S, Møldrup C (2011) Optimal duration of combined psychotherapy and pharmacotherapy for patients with moderate and severe depression: a meta-analysis. Journal of Affective Disorders 131: 24–36
Abstract: www.sciencedirect.com/science/article/pii/S0165032710005483

Piet J, Hougaard E (2011) The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. Clinical Psychological Review 31: 1032–40
Abstract: www.sciencedirect.com/science/article/pii/S0272735811000973

1.10   Step 4: complex and severe depression

Inpatient care, and crisis resolution and home treatment teams

A systematic review by **Cuijpers et al. (2011)** evaluated studies comparing the effect of psychological treatment on depression compared with usual care and structured pharmacological treatments in an inpatient setting. The quality of the 12 studies (570 patients) was limited, the psychological treatments assessed varied considerably in format and number of sessions, and there is limited ability to generalise from the studies to the current UK healthcare situation because the only UK study included was conducted in 1987 when healthcare practices were considerably different. Despite these limitations, the psychological interventions appeared to have a small but statistically significant additional effect on depression compared with alternative approaches (mean effect size for difference = 0.29; 95% CI 0.13 to 0.44; p < 0.001). This study adds to the rather limited evidence base on appropriate inpatient care and provides some support for the current recommendation of NICE CG90 that the full range of high-intensity psychological interventions is offered to patients receiving inpatient care for depression.

Key reference
Cuijpers P, Clignet F, van Meijel B et al. (2011) Psychological treatment of depression in inpatients: a systematic review and meta-analysis. Clinical Psychological Review 31: 353–60
Abstract: www.sciencedirect.com/science/article/pii/S0272735811000079

Electroconvulsive therapy

An RCT, conducted by **Kellner et al. (2010)**, compared three different electrode placements (bifrontal, bitemporal and right unilateral) in 230 patients with major depression (unipolar and bipolar). The study demonstrated a mean change from baseline in Ham-D score greater than 20 points in all three groups ($p < 0.0001$), but found electrode placement position resulted in no statistically significant differences in measures of depression or cognitive symptoms. Bitemporal placement appeared to result in more rapid response than right unilateral placement ($p = 0.029/0.026$ for linear/quadratic terms in adjusted mixed effects modelling). This evidence provides some support for the recommendation of NICE CG90 that bilateral ECT is more effective than unilateral ECT.

Key reference
Kellner CH, Knapp R, Husain MM et al. (2010) Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. British Journal of Psychiatry 196: 226–34
Full text: www.bjp.rcpsych.org/content/196/3/226.full.pdf+html

Transcranial magnetic stimulation

A systematic review of 31 sham-controlled studies of transcranial magnetic stimulation (TMS) by **Allan et al. (2011)** found evidence of moderate efficacy (pooled OR for treatment response [defined as ≤ 50% reduction in MADRS or Ham-D score] of 4.1; 95% CI 2.9 to 5.9), but methodological limitations restricted information on the optimal TMS treatment protocol. There was no evidence (from nine studies) for treatment effects lasting beyond 12 weeks. TMS was well-accepted by patients and was associated with few adverse effects. A systematic review by **Schutter (2010)** evaluated the efficacy of slow-frequency repetitive TMS and found nine double-blind sham-controlled parallel intention-to-treat studies involving 252 patients. The intervention was found to have a moderate positive effect (d = 0.63; 95% CI 0.03 to 1.24), considered comparable to that of fast-frequency repetitive TMS, although there was no consensus on the optimal site for the procedure.

NICE CG90 notes that there are no major safety concerns with TMS used in severe depression, but recommends its use is restricted to research studies until optimal methods are determined. The recent evidence supports this view, although the difficulty of treating patients with severe depression that has failed to respond to other therapies acceptable to patients suggests that TMS may be a therapeutic option as part of specialist team management. The evidence also supports the view that further research is needed to define the optimal protocol.

Key references
Allan CL, Herrmann LL, Ebmeier KP (2011) Transcranial magnetic stimulation in the management of mood disorders. Neuropsychobiology 64: 163–9
Abstract: www.content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowAbstract

Schutter DJLG (2010) Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. Psychological Medicine 40: 1789–95
Abstract: www.journals.cambridge.org/action/displayAbstract?fromPage=online&aid=7908798

2   New evidence uncertainties

No new evidence uncertainties were identified during the Evidence Update process, however current uncertainties for depression in adults can be found at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr.

The NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs) has been established in the UK to publish uncertainties about the effects of treatment that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance and the closely linked guidance on depression in adults with a chronic physical health problem:

- Depression. NICE clinical guideline 90 (2009). Available from www.nice.org.uk/guidance/CG90
- Depression in adults with a chronic physical health problem. NICE clinical guideline 91 (2010). Available from www.nice.org.uk/guidance/CG91

Searches

The literature was searched to identify systematic reviews and RCTs with at least 100 participants relevant to the scope. Searches were conducted of the following databases, covering the dates 1 August 2010 (the end of the search period of the most recent Annual Evidence Update) to 12 September 2011:

- CINAHL
- Cochrane Database of Systematic Reviews – Cochrane Library
- Embase
- MEDLINE
- PsycINFO
- AMED (for St John's Wort only)

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. A single broad search strategy was used, reflecting the breadth of the topic, based on the search strategy used in the reference guidance. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews (www.sign.ac.uk/methodology/filters.html). A single search strategy was used for the Evidence Updates of the clinical guidance on both depression in adults (NICE CG90) and depression in adults with a chronic physical health problem (NICE CG91). The output relevant to each Evidence Update was separated by sifting.

Two other studies (Barbui et al. 2011 and Gartlehner et al. 2011) were identified outside of the literature search. Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser (the chair of the EUAG), and the full search strategies, are available on request from contactus@evidence.nhs.uk
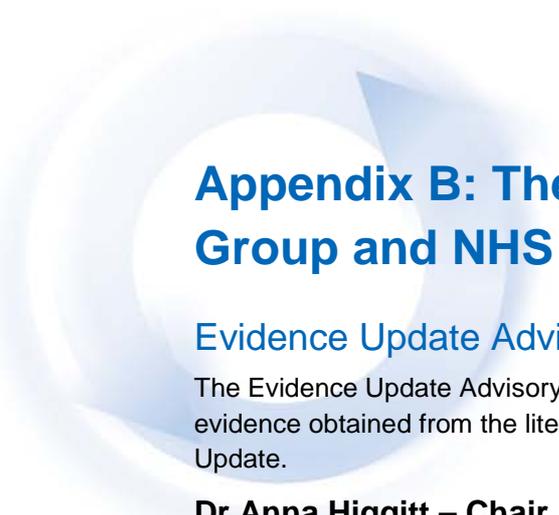
Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp Depression/
2	exp Depressive Disorder/
3	or/1-2
4	(depression or depressive).ti.
5	SAD.ti.
6	melancho*.ab,ti.
7	pseudodementia.ab,ti.
8	reactive depression.ab,ti.
9	dysphori*.ab,ti.
10	or/4-9
11	3 or 10

Figure 1 Flow chart of the evidence selection process
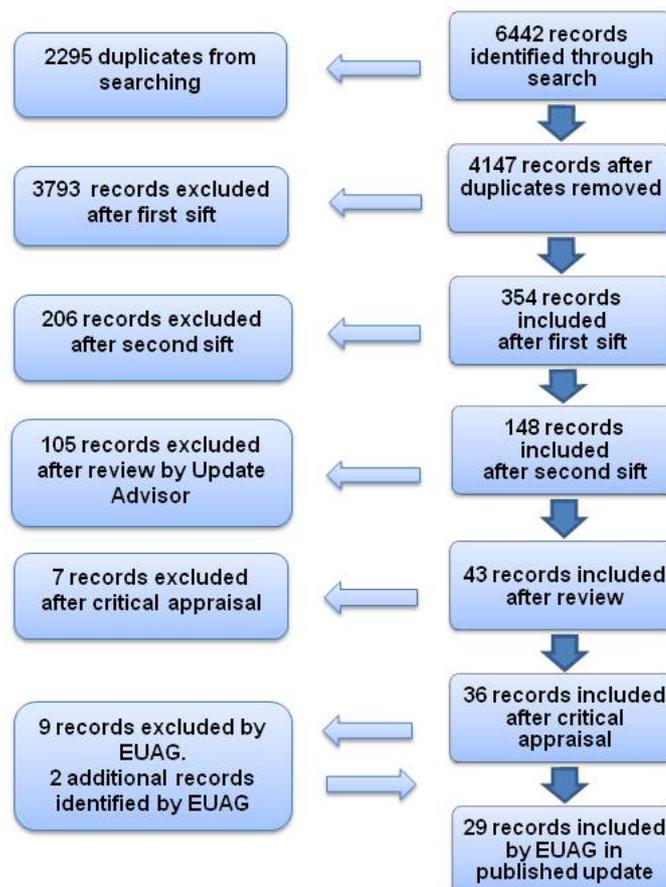
EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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