NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Clinical guideline
CG90: Depression in adults: treatment and management (update)

Publication date
September 2010

Previous review dates
3 year review: 2012 (no update)

Surveillance report for GE
November 2013

Key findings

<table>
<thead>
<tr>
<th>Potential impact on guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Evidence identified from evidence update</td>
</tr>
<tr>
<td>Evidence identified from literature search</td>
</tr>
<tr>
<td>Feedback from Guideline Development Group</td>
</tr>
<tr>
<td>Anti-discrimination and equalities considerations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No update</th>
<th>Rapid update</th>
<th>Standard update</th>
<th>Transfer to static list</th>
<th>Change review cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Surveillance recommendation
GE is asked to consider the proposal to update the guideline as a standard update. GE are asked to note that this ‘yes to update’ proposal will not be consulted on.
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Centre for Clinical Practice – Surveillance Programme

Surveillance review of CG90: Depression in adults: management and treatment (update)

Recommendation for Guidance Executive

Background information

Guideline issue date: 2010
3 year review: 2012 (no update)

NCC: Mental Health

CG23
Guideline issue date: 2004
Republished: 2007 (amended)
Republished: 2010 (standard update published as CG90)

Main conclusions from previous surveillance review

1. CG90 was previously reviewed for update in 2012. At that review point, limited new evidence was identified which would potentially change the direction of guideline recommendations. However, the new evidence was considered to be insufficient to warrant an update hence the review recommendation was that the guideline should not be considered for an update.

Current (four year) surveillance review

2. A literature search for randomised controlled trials and systematic review was used as the primary source of evidence for this surveillance review. New evidence since the last surveillance review was considered (April 2012 (the end of the search period for the surveillance review) and September 2013) and relevant abstracts were assessed. The identified evidence from the previous 3 year surveillance review
and the Evidence Update on CG90: Depression (published April 2012) were also used as sources of evidence to ensure that the evidence base reflected the lifetime of the guideline. Clinical feedback on the guideline was obtained from 7 members of the GDG through a questionnaire and the chair was also contacted for his opinion on the surveillance decision.

3. New evidence that may impact on recommendations was identified relating to 4 clinical areas within the guideline:

### Clinical area 1: Service delivery – recommendation 1.2

**Q:** In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which models of care produce the best outcomes?

- collaborative care
- stepped care
- case management
- stratified (matched) care
- attached professional model

#### Evidence summary

<table>
<thead>
<tr>
<th>Evidence identified from literature search</th>
<th>GDG/clinical perspective</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>The GDG highlighted the CADET trial, a RCT which compares the clinical effectiveness of collaborative care with usual care (GP decided care-non specified) in the management of patients with moderate to severe depression within UK in primary care had published. Mean depression were significantly lower in participants receiving collaborative care than in those receiving usual care at four months, and at 12 months. Participants receiving collaborative care were significantly more satisfied with treatment than those receiving usual care. However a GDG member indicated that they felt the effect size was fairly small and unlikely to overturn the current recommendations.</td>
<td>The basis of provision of care recommended in CG90 is by a stepped care approach which was established in the original 2004 guideline. Collaborative care is recommended for those with a chronic condition only in CG91 (Depression in a chronic physical health problem). However, for severe depression individuals should be referred to a specialist mental health team for a programme or coordinated multi-professional care. Within CG90 collaborative care was found to be marginally more effective than other comparators (28 RCTs). However, the GDG expressed a desire to see stronger evidence and a cost effectiveness analysis with a comparison to stepped care-before a recommendation for collaborative care could be made. The GDG highlighted the publication of the CADET trial</td>
<td></td>
</tr>
</tbody>
</table>
A small primary care practices in Germany concluded that this approach was cost-effective⁵.

A RCT of a web-delivered care management and patient self-management program for recurrent depression was found to more effective in reducing symptoms compared to specialist mental health care⁶.

As a time point when to reconsider this area for update. A research recommendation 4.8 was also made in relation to collaborative care setting duration minimums and comparator profile.

The CADET trial has now published and indicates that collaborative care is more effective than usual care. This study does not fully meet the research recommendation in the guideline that required a RCT to be of 18 months duration and have a clearly defined stepped care comparator.

The Cochrane review identified in the literature search is likely to contain many of the original RCTS identified in CG90 from 2009 and also contains some trials from individuals with chronic conditions. Collaborative care has a greater effect size for those with a chronic condition.

Clinical area 2: Low intensity psychosocial interventions—recommendation 1.4.2 (1.4.2.1-1.4.2.4)

Q. In depression, does self-guided self-help or peer support improve outcomes compared with other interventions?

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>GDG/clinical perspective</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence identified from Evidence Update</td>
<td>No GDG feedback was provided for this clinical area.</td>
<td>CG90 recommends offering one or more low-intensity psychosocial interventions (specifically, individual guided self-help based on CBT, CCBT 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). This is potentially a low cost, low intensity intervention that could be included. The Evidence Update concluded that there was possible benefits from peer support, self-help delivered</td>
</tr>
</tbody>
</table>
**Clinical area 3: High intensity psychosocial interventions**

Recommendations 1.4.3, 1.5.1.1, 1.5.1.2, 1.5.1.4, 1.5.3.1-1.5.3.7

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), do any of the following (either alone or in combination with pharmacotherapy) improve outcomes compared with other interventions (including treatment as usual): CBT, BT/behavioural activation, Interpersonal therapy (IPT), counselling, problem solving, psychodynamic psychotherapy, family interventions/couples therapy, acceptance and commitment therapy, psychoeducation, systemic interventions, cognitive analytic therapy, solution focussed therapy, self-help (guided).

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>GDG/clinical perspective</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence identified from Evidence update</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two systematic reviews which supported guideline recommendations for psychological interventions for depression were identified (^8,9).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Evidence identified from literature search</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Through the high level RCT search 13 studies relevant to the clinical question were identified. The majority of studies supported current guideline recommendations and provided evidence of the effectiveness of CCBT, MBCT and group CBT (in older individuals) \(^10,11-14\). Additionally new evidence which was judged to be in line with current recommendations on behavioural activation, problem solving and short-term psychodynamic psychotherapy were identified \(^15,16\ 17-19,20\). The evidence on manualised narrative therapy was inconclusive on its effectiveness when compared to wait list control\(^21\). | One GDG member highlighted that the existing guideline has endorsed access to CBT at the expense of access to other equally effective therapies and by depriving patients of choice has also led to continued increases in antidepressant prescribing which the guideline did not recommend this impact has potentially limited the benefits that the guideline could have achieved. | NICE CG90 recommends group-based CBT at Step 2 for people who decline low-intensity psychosocial interventions.
For people with persistent sub threshold depressive symptoms or mild to moderate depression who have not benefited from low level intensity interventions CG90 recommends either an antidepressant or one of the following:
- CBT
- IPT
- Behavioural activation
- Behavioural couples therapy
For those who decline these options then counselling or short term psychodynamic psychotherapy should be considered.

There is evidence that numerous psychotherapies have similar efficacy. The NMA included 7 therapies and indicated these all were very similar with regard to their effectiveness. This may indicate that the guideline could reflect a greater choice of therapy for Step 2 treatment. This is confirmed by the GDG response that |

However, 1 RCT showed that sertraline was effective in primary-care patients with milder forms of | | |
A network meta-analysis (NMA) which compared the efficacy of 7 psychotherapeutic interventions (198 studies) found that psychotherapeutic interventions was superior to a wait list control. However, relative effects of different psychotherapeutic interventions on depressive symptoms were absent or small.

Likewise, a meta-analysis of 115 studies for CBT for the treatment of adult depression, alone and in comparison with other treatments indicated that CBT is effective. However, CBT was no more or less effective than other psychotherapies or pharmacotherapy. Combined treatment was significantly more effective than pharmacotherapy or psychotherapy alone.

A RCT investigated the effect of telephone-administered vs face-to-face CBT on adherence to therapy and depression outcomes among primary care patients with a major depressive disorder (MDD). CBT over the telephone compared with face-to-face resulted in lower attrition and close to equivalent improvement in depression at post treatment.

In addition 3 studies provided evidence which was in line with current recommendations for the effectiveness of CBT, psycho-educational group program.

In addition there is new evidence relating to the mode of delivery for CBT therapy (either face-to-face or via telephone) which was not addressed in the guideline for this level of care. This new evidence may impact on clinical practice.

The 3 year literature review found a RCT which potentially may address a research recommendation. The efficacy of CBT compared with antidepressants and placebo for persistent sub threshold depressive symptoms. Currently medication is not usually given to these individuals until they have had a Step 1 intervention or had symptoms for greater than 2 years.

Clinical area 4: Pharmacological interventions - recommendations 1.5.2.2-1.5.2.4
Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which drugs (either not covered by the previous guideline or where significant new evidence exists) improve outcomes compared with other drugs and with placebo?

- TCAs
- duloxetine
- desvenlafaxine
- escitalopram
- agomelatine
- St John’s wort
- antipsychotics (for example, quetiapine)

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>GDG/clinical perspective</th>
<th>Impact</th>
</tr>
</thead>
</table>
| **Evidence identified from Evidence Update** | Health economic advice from within CCP indicates that the costs of some of the pharmaceuticals have changed significantly which may affect the results of the health economic model. However, whilst a GDG member noted that there are some new antidepressants on the horizon nothing was currently changing clinical practice. | When an antidepressant is to be prescribed, NICE CG90 advises that it should normally be a SSRI in a generic form. This was based on the evidence presented in CG90 that indicated SSRIs are as effective as other antidepressants and have a favourable risk–benefit ratio. A NMA by Cipriani et al. (2009) identified within CG90 indicated that sertraline had superior efficacy to other SSRIs and other pharmaceutical options, but the study had various limitations and the clinical difference was deemed to be small. This data formed the basis of a health economic model within CG90 the results of which did not take into account adverse events. The health economic analysis indicated that sertraline should be potentially first choice as it was the most cost effective. However the GDG did not make a recommendation for a specific SSRI. The studies identified by the Evidence Update indicate:  
  - There is some support for the current guidance that a generic SSRI is usually the preferred first choice of antidepressant drug. However, there is... |
be inferior to fluoxetine for withdrawals due to adverse events.

- A systematic review on venlafaxine and duloxetine in MDD treatment found both were significantly more effective than placebo. Compared with SSRIs, venlafaxine showed significantly improved response rate but not remission rate; there were no significant differences between venlafaxine and tricyclic antidepressants (TCAs) for efficacy outcomes. Discontinuation due to adverse events was significantly higher with venlafaxine compared with SSRIs 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. Duloxetine resulted in significantly higher discontinuation rates due to adverse events than venlafaxine.

- A Cochrane review of treatment with second-generation antipsychotics in MDD or dysthymia identified 4 RCTs that compared quetiapine monotherapy with placebo. Although significant efficacy benefits of treatment were noted, the authors suggested that the results should be interpreted with caution. Furthermore, acceptability to patients was significantly reduced because of increased adverse events.

### Evidence identified from literature search

**3 Year**

Two systematic reviews indicated that both TCAs and SSRIs are effective for depression treated in primary care and that the benefit of antidepressant medication compared with placebo increases with severity of new evidence which may suggest a more specific choice could be made.

- There is evidence to suggest additional advice on reboxetine may be appropriate.
- There is evidence to support 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.

In addition new evidence identified from the high level literature search indicates that:

- There are very little, if any, differences in efficacy between classes of pharmaceuticals such as SNRIs, SSNIs and third generation drugs. To date there has been no full analysis comparing all different classes of drugs let alone the individual drugs within each class.
- New agents are available that should be considered for Step 2 therapy
- There are new physical treatments and adjunctive treatments that are potentially effective in treating depression.

Other identified evidence indicates that the cost of certain drugs (particularly venlafaxine) have changed since the guideline was published. This may well impact on the cost-effectiveness of certain pharmacological options.
depression symptoms and may be minimal or non-existent, in patients with mild or moderate symptoms\textsuperscript{34,35}.

4 RCTs were identified on the effectiveness of SSRIs in the treatment of adults with depression\textsuperscript{36-39}. These provided an equivocal evidence base for the effectiveness of these agents. As such, the identified new evidence was considered unlikely to change the current guideline recommendations at this time point.

### 4 year

**New antidepressant since guideline 2011**

- **Agomelatine**: 2 studies have meta-analysed the evidence for agomelatine (a melatonergic antidepressant) for treatment of depression\textsuperscript{40,41}. Both analyses indicate that agomelatine is at least as efficacious as escitalopram, fluoxetine, sertraline, venlafaxine and paroxetine in reducing depression scores for response and remission in patients with depression and severe depression.

- **Levomilnacipran sustained release**: 1 RCT demonstrated that levomilnacipran sustained release improves depressive symptoms and functioning relative to placebo in patients with MDD\textsuperscript{42}.

- **Quetiapine** A meta-analysis of 3 RCTs of quetiapine extended release (XR) in adults with MDD indicated that the overall response and remission rates were higher for individuals treated with quetiapine than those with placebo\textsuperscript{43}. Discontinuation rate due to adverse event were greater in the quetiapine group.
An RCT found that long-term functioning and sleep quality in patients with MDD on extended-release quetiapine maintenance treatment following stabilisation with quetiapine XR was significantly improved compared to placebo.\(^4\)

In addition 9 RCTS for unlicensed drugs were identified: 5 RCTs for vortioxetine (Technology Appraisal due to start in 2014), 1 RCT for GSK372475, 1 RCT for ziprasidone, and 2 studies on desvenlafaxine.\(^5\)

**Antidepressant v active comparator +/- placebo**

- 1 Cochrane systematic review which assessed the efficacy of fluoxetine in comparison to monoamine oxidase inhibitors (MOIAs), TCA, SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs) and newer agents (171 studies in total) in individuals with MDD was identified.\(^5\) The review indicated that there may be differences in terms of relative efficacy and tolerability within classes and individual antidepressants particularly in regards to sertraline (more effective) and venlafaxine (less tolerable).

- 1 study indicated that milnacipran (SNRI) and paroxetine (SSRI) showed comparable efficacy in terms of improvement in symptoms of depression in individuals with MDD.\(^5\)

New evidence that was in line with the evidence presented within CG90 was identified for the following antidepressants:
• 1 Cochrane systematic review indicated that amitriptyline is effective in patients with MDD\textsuperscript{65}.
• 1 RCT indicated that duloxetine was effective in reducing symptoms in individuals with non MDD compared to placebo\textsuperscript{66}.
• A meta-analysis comparing desvenlafaxine with venlafaxine indicated that the two drugs were comparable in terms of safety and efficacy in the treatment of depression\textsuperscript{51}.
• 4 RCTs indicate that pioglitazone\textsuperscript{67} oral scopolamine\textsuperscript{68}, triiodothyronine\textsuperscript{69} or gaboxadol\textsuperscript{70} provide no additional benefit compared to antidepressant alone in the treatment of depression.

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which other drugs or physical therapies are effective in treating depression (as monotherapy or augmentation of antidepressants)?

<table>
<thead>
<tr>
<th>Evidence summary</th>
<th>GDG/clinical perspective</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence identified from 4 year literature search</strong></td>
<td>No GDG feedback was provided for this clinical area.</td>
<td>A small number of trials have been identified that have looked at therapies not reviewed within the guideline for depression. It may be worth considering these areas within the scoping process when the guideline is updated.</td>
</tr>
<tr>
<td><strong>New Physical treatments (monotherapy)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• A RCT indicated that laser acupuncture may show some clinical benefit compared to placebo acupuncture for the treatment of major depression\textsuperscript{56}.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• A RCT found that individuals with MDD treated with a single injection of botulinum toxin were significantly less depressed at 6 weeks compared to placebo\textsuperscript{57}.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Augmentation with physical therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• One RCT indicated that augmentation of pharmacological treatment with electrical</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
acupuncture may have some clinical benefit in patients with MDD.

- A RCT indicated that achronotherapeutic intervention (wake and light therapy) was more effective in treating depression symptoms in patients treated duloxetine than exercise. The patients treated with exercise also showed a clinically relevant antidepressant response.

- 2 RCTs and 1 systematic review indicated that facilitated physical activity as an adjunctive treatment for adults with depression in individuals with symptoms of depression was no more effective than usual care.

Combination therapy with other agents

- Two RCTS indicated that augmentation of an antidepressant with another agent (vitamin D, oral creatine monohydrate) was effective in improving depression measures.

**On-going research**

4. The IAPT pbr pilot (payment by results) has published and is now been extended with final results expected by 2016 therefore it is not possible to determine any potential impact on guideline recommendations. However, data from this trial may contribute towards the evidence base relating to management of depression in adults in future surveillance reviews.

**Anti-discrimination and equalities considerations**

5. None identified.

**Implications for other NICE programmes**
6. This guideline relates to a Quality Standard on depression in adults (published 2011).
7. Two of the quality statements are likely to be affected by the proposed areas for update.

**Conclusion**
8. Through the review of CG90 new evidence which may potentially change the direction of guideline recommendations was identified in the following areas:
   a. Service delivery (collaborative care)
   b. Low level psychosocial interventions for depression
   c. High level psychosocial interventions for depression
   d. Pharmacological interventions for moderate to severe depression

9. For all other areas of the guideline no evidence was identified which would impact on recommendations.

**Surveillance recommendation**
10. GE is asked to consider the proposal to update the guideline as a standard update. GE are asked to note that this ‘yes to update’ proposal will not be consulted on.

Mark Baker – Centre Director
Sarah Willett – Associate Director
Katy Harrison – Technical Analyst
Centre for Clinical Practice
November 2013
References


49. **Mahableshwarkar AR, Jacobsen PL, and Chen Y. (2013)** A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. Current Medical Research and Opinion 29:March.


52. **Liebowitz MR, Tourian KA, Hwang E et al. (2013)** A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder. BMC Psychiatry 13.

53. **Papakostas GI, Culpepper L, Fayyad RS et al. (19-7-2013)** Efficacy of desvenlafaxine 50 mg compared with placebo in patients with moderate or severe major depressive disorder: a pooled analysis of six randomized, double-blind, placebo-controlled studies. Int Clin Psychopharmacol.


Appendix 1 Decision matrix
Surveillance and identification of triggers for updating CG90. The table below provides summaries of the new evidence identified for the clinical questions.

### Chapter 5- Case identification

**Q. What methods are effective in identifying people with depression in primary care and community settings, including sexual health clinics, emergency departments, and drug and alcohol services?**

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>

**Q. In which populations (excluding those with chronic physical health problems) should identification methods be used?**

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>

**Q. What are appropriate ways to promote adherence?**

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>

**Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), how can equal access to services for all be ensured? [What promotes access to effective care particularly for people with learning difficulties, acquired cognitive impairment and language difficulties?**

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
<tr>
<td>Evidence update</td>
<td>3 year review</td>
<td>4 year review</td>
<td>Other evidence</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>--------------</td>
<td>----------------</td>
<td>----------</td>
</tr>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>

**Chapter 5 - Service delivery**

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which models of care produce the best outcomes?

- collaborative care
- stepped care
- case management
- stratified (matched) care
- attached professional model
### Evidence update

<table>
<thead>
<tr>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No areas that would ‘impact’ were identified</td>
<td>None identified</td>
<td>New evidence which could potentially impact recommendations</td>
<td></td>
</tr>
<tr>
<td>• A number of areas not specifically covered by CG90 were highlighted:</td>
<td></td>
<td><strong>Collaborative care</strong></td>
<td>The basis of provision of care in CG90 is by a stepped care approach which was established in the original 2004 guideline. Collaborative care is recommended for those with a chronic condition (CG91). However, for severe depression individuals should be referred to a specialist mental health team for a programme or coordinated multi-professional care. Within CG90 collaborative care was marginally more effective than other comparators in CG90 (28 RCTS) but the GDG expressed a desire to see stronger evidence and cost effectiveness with a comparison to stepped care before a recommendation for collaborative care could be made. They highlighted the on-going CADET trial for when to reconsider this area</td>
</tr>
<tr>
<td>• The EU also reported that although unlikely to affect current guidance, limited evidence suggests that there is value in psychiatric assessments to support GPs.</td>
<td></td>
<td><strong>Collaborative care</strong></td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• The EU also found evidence in a systematic review that suggests that pharmacist interventions could improve adherence to antidepressants.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• In addition an RCT on stepped care and an analysis of medication management that supports, CG90 were highlighted.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Collaborative care**

1 Cochrane review (which included 79 trials) demonstrated significantly greater improvement in depression outcomes for adults with depression treated with the collaborative care model in the short-term and long-term. There was evidence of benefit in secondary outcomes including medication use, mental health, quality of life, and patient satisfaction, although there was less evidence of benefit in physical quality of life.

A cluster RCT found that a multi-component programme for managing depression in primary care was more effective in improving treatment response and remission rates than usual care. However, the severity of depression was not significantly different between the groups at the end of treatment.

In addition there were two RCTs that reported on different approaches to offering collaborative care. All approaches were equivalent in their effectiveness.
A cost-effectiveness analysis of depression case management undertaken by healthcare assistants in small primary care practices in Germany concluded that this approach was cost-effective.

A RCT of a web-delivered care management and patient self-management program for recurrent depression was found to more effective in reducing symptoms compared to specialist mental health care.

However, a GDG member indicated that they felt the effect size was fairly small and unlikely to overturn the recommendation.

However, a GDG member indicated that they felt the effect size was fairly small and unlikely to overturn the recommendation.

For update. This study has just published.

A research recommendation was also made in relation to collaborative care setting duration minimums and comparator profile.

The CADET trial has now published and indicates that collaborative care is more effective than usual care. This study does not fully meet the research recommendation in the guideline that required a RCT to be of 18 months duration and have a clearly defined stepped care comparator.

It should also be noted that Cochrane review is likely to contain many/all of the original RCTS identified in CG90 from 2009. It seems likely given the time difference that many of the studies may also include those with chronic conditions. It should be noted that collaborative care is recommended in CG91 for those with a chronic condition as the effect size is greater in this population.
Q. Are different models appropriate to the care of people in different phases of the illness, such as treatment resistant depression and relapse prevention?

<table>
<thead>
<tr>
<th>Evidence Update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>None identified</td>
<td>None identified</td>
<td>Insufficient new evidence which could potentially impact recommendations</td>
<td>None</td>
<td>No new evidence that impacts recommendations</td>
</tr>
</tbody>
</table>

A stepped care relapse prevention program for depression in older people was found to be no more effective that care as usual in one RCT.10

7. Low intensity psychosocial interventions

Q. New intervention: New clinical question: In depression, does self-guided self-help improve outcomes compared with other interventions?

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>New evidence which could potentially impact recommendations</td>
<td>New evidence which could potentially impact recommendations</td>
<td>No new evidence that impacts recommendations</td>
<td>None</td>
<td>New evidence which could potentially impact recommendations</td>
</tr>
</tbody>
</table>

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. A meta-analysis of 7 RCTs of self-guided psychological treatment demonstrated a small but

The same systematic review of self-guided self-help, indicated that self-guided psychological treatment has a small clinical benefit in improving depressive

A RCT which compared self-help for depression via E-mails compared to emails containing depression information was identified13. The
significant effect of self-guided self-help on depression at follow up\textsuperscript{11}. A meta-analysis examined 17 RCTs of psychological treatments in low-income to middle-income countries found an overall benefit of such therapies compared with usual care\textsuperscript{12}. 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 meta-analysis examined 17 RCTs of psychological treatments in low-income to middle-income countries found an overall benefit of such therapies compared with usual care\textsuperscript{12}. 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.

symptomatology\textsuperscript{11}. results suggest that the e-mails were able to increase participants' use of evidence-based self-help, but that this did not improve depression more than an attention control.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|}
\hline
Q. In depression, does guided self-help improve outcomes compared with other interventions? & & & & \\
\hline
Evidence update & 3 year review & 4 year review & Other evidence & Comments \\
\hline
No areas that would 'impact' were identified & None identified & No evidence that conflicts CG90 was identified & None & New evidence is consistent with guideline recommendations \\
One systematic review provides limited evidence supporting guided self-help\textsuperscript{14}. & & & & \\
\hline
Q. Does computerised CBT (CCBT) improve patient outcomes compared with other treatments? & & & & \\
\hline
Evidence update & 3 year review & 4 year review & Other evidence & Comments \\
\hline
None identified & None identified & No evidence that conflicts CG90 & Insufficient evidence provided & New evidence is consistent with \\
\end{tabular}
\end{table}
Three studies that support the guideline recommendations in relation to CCBT were identified.

- A meta-analysis found CCBT to be effective in the short term but there was no significant clinical effect at long term follow-up\(^\text{17}\).
- A systematic review of psychotherapy for sub-clinical depression in older adults found that CCBT was an effective intervention for reducing depressive symptoms in comparison to waiting list control\(^\text{18}\). CCBT was at least as effective as group CBT in reducing depressive symptoms.
- One RCT indicated that delivery of CCBT using a mobile application can result in clinically significant improvements in outcomes for patients with depression\(^\text{19}\).

A GDG member indicated that there is evidence that brief dynamic therapy should be a first-line and that indicates CCBT should not be a first-line treatment. However no references were not provided and have not been identified by surveillance searches for RCTs.

In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), do any of the following improve outcomes compared with other interventions?

- exercise
- support including groups, befriending, and non-statutory provision
- programmes to facilitate employment
<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient new evidence to justify guideline alterations. Peer support</td>
<td>No new evidence that impacts was identified</td>
<td>No new evidence that impacts was identified</td>
<td>None</td>
<td>New evidence is consistent with guideline recommendations</td>
</tr>
<tr>
<td></td>
<td>Physical activity programmes</td>
<td>Physical activity programmes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two studies relevant to the clinical question were identified on physical activity</td>
<td>Three systematic reviews, 2 in older individuals and 1 in all ages of adulthood</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generally they indicated that it may have a short term beneficial effect in adults with depression. This is in keeping with the current recommendations</td>
<td>found that exercise was associated with significantly lowering of depression severity. A systematic review also indicated that walking has a statistically significant, large effect on the symptoms of depression in some populations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity programmes</td>
<td>No new evidence that impacts was identified</td>
<td>No new evidence that impacts was identified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The recommendation for physical activity programmes receives some support from current evidence (2 systematic reviews), and limited evidence also suggests that shorter programmes may be as effective as longer programmes.</td>
<td>No new evidence that impacts was identified</td>
<td>No new evidence that impacts was identified</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Chapter 8 High Intensity psychosocial interventions

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), do any of the following (either alone or in combination with pharmacotherapy) improve outcomes compared with other interventions (including treatment as usual):

- CBT
- BT/behavioural activation
- Interpersonal therapy (IPT)
- counselling/person-centred therapy
- problem solving
- psychodynamic psychotherapy
- Family interventions/couples therapy
- ACT (acceptance and commitment therapy)
- Systemic interventions
- Psychoeducation
- Cognitive analytic therapy (CAT)
- Solution-focused therapy
- Self-help, including guided self-help

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No areas that would 'impact' were identified</td>
<td>New evidence which could potentially impact recommendations</td>
<td>New evidence which could potentially impact recommendations</td>
<td>New evidence which could potentially impact recommendations</td>
<td>New evidence which could potentially impact recommendations</td>
</tr>
<tr>
<td>A systematic review confirms that the psychological interventions appear to have a small but statistically significant additional effect on depression compared with alternative approaches.</td>
<td>CBT</td>
<td>CBT</td>
<td>GDG feedback.</td>
<td>NICE CG90 recommends group-based CBT at Step 2 for people who decline low-intensity psychosocial interventions.</td>
</tr>
<tr>
<td>A meta-analysis which confirms that IPT is an effective high-intensity psychological treatment, in accordance with current guidance was also</td>
<td>Through the high level RCT search numerous studies relevant to the clinical question were identified.</td>
<td>A network meta-analysis (NMA) which compared the efficacy of 7 psychotherapeutic interventions (198 studies) found that psychotherapeutic interventions was superior to a waitlist control. Relative effects of different psychotherapeutic</td>
<td>One GDG member highlighted that the existing guideline has endorsed access to CBT at the expense of access to other equally effective therapies and by</td>
<td>For people with persistent sub threshold depressive symptoms or mild to moderate depression who have not benefited from low</td>
</tr>
</tbody>
</table>
highlighted\textsuperscript{29}.

when compared to CBT or placebo\textsuperscript{30}.

The remaining evidence supported the effectiveness of CCBT, indicated that MBCT showed some effectiveness and group CBT showed some effectiveness in older individuals\textsuperscript{31-35}. Additionally studies on Behavioural activation, Problem solving short-term psychodynamic psychotherapy that were judged to be in line with current recommendations\textsuperscript{36-41}.

interventions on depressive symptoms were absent to small.

A meta-analysis of 115 studies for CBT for adult depression, alone and in comparison with other treatments indicated that CBT is effective \textsuperscript{43}. CBT was no more or less effective than other psychotherapies or pharmacotherapy. Combined treatment was significantly more effective than pharmacotherapy alone. A RCT investigated the effect of telephone-administered vs face-to-face CBT on adherence to therapy and depression outcomes among primary care patients with MDD\textsuperscript{44}. CBT over the telephone compared with face-to-face resulted in lower attrition and close to equivalent improvement in depression at post treatment.

The following evidence is in line with current recommendations:

- A meta-analysis of CBT for depression in older people indicated CBT is effective compared to control\textsuperscript{45}.
- A RCT indicated that a

depriving patients of choice has also led to continued increases in anti-depressant prescribing which the guideline did not recommend this impact has potentially limited the benefits that the guideline could have achieved.

level intensity interventions CG90 recommends either an antidepressant or one of the following:

- CBT
- IPT
- Behavioural activation
- behavioural couples therapy

For those who decline these options then counselling or short term psychodynamic psychotherapy should be considered.

There is evidence that numerous psychotherapies have similar efficacy. The NMA included 7 therapies this would indicate that the guideline may need updating to reflect a greater choice of therapy for Step 2 treatment. This is confirmed by the GDG response that a greater choice of therapy could enhance service provision.

The mode of delivery for CBT therapy either face-to-face or via telephone was not covered in the guideline for this Step level of care. Hence this new evidence may impact
A psycho-educational group program was effective in the short and long-term in treatment for patients with mild depression symptoms\(^\text{46}\). A meta-analysis\(^\text{47}\) indicated that CBT has an enduring effect following termination of the acute treatment. No significant difference in relapse after the acute phase CBT versus continuation of pharmacotherapy after remission was reported.

In addition, the 3 year review found a RCT which potentially may address a research recommendation 8.12.1.3. The efficacy of CBT compared with antidepressants and placebo for persistent sub threshold depressive symptoms. Currently medication is not a given to these individuals until they have had Step interventions.

### Q. Does mode of delivery (group-based or individual) impact on outcomes?

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>

### Q. Are there specific therapist characteristics that improve outcomes?

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>

### Q. Are there specific patient characteristics (for example, anxiety, previous episodes) that predict outcomes?

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>

### Q. Are brief interventions (for example, 6 to 8 weeks) effective?
### Evidence update

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>None identified</td>
<td>None identified</td>
<td>New evidence which could potentially impact recommendations</td>
<td>None</td>
<td>Insufficient new evidence to impact recommendations</td>
</tr>
</tbody>
</table>

#### Pharmacological interventions Chapters 9/10

**Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which**

---

A systematic review and meta-analysis of brief psychotherapy for depression was identified. The systematic review found brief psychotherapies to be more efficacious than control and conclude that depression can be efficaciously treated with 6-8 to sessions of psychotherapy, particularly CBT and problem-solving therapy.

The guideline makes various recommendations about the duration of treatment with high intensity psychological interventions. In general 16-20 sessions over 3-4 months is recommended for most therapies. For those with persistent sub threshold symptoms 6-10 treatments over 8-12 weeks is recommended. It was not clear from the abstract the type of depression included and comparisons were to control only. This evidence was therefore considered to be in line with that already detailed in the guideline.

---

**Q. Are psychological interventions harmful?**

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>
drugs (either not covered by the previous guideline or where significant new evidence exists) improve outcomes compared with other drugs and with placebo?
– TCAs
– duloxetine
– desvenlafaxine
– escitalopram
– agomelatine
– St John’s wort
  – antipsychotics (for example, quetiapine)
### Evidence update

**New evidence that could potentially impacts the recommendations**

A comprehensive meta-analysis to assess the comparative benefits and harms of second generation antidepressants in MDD was identified. The review found no clinically relevant differences in efficacy or effectiveness for the treatment of acute, continuation and maintenance phases of MDD. There were some differences in relation to adverse events and discontinuation rates.

Another study assessed the efficacy of escitalopram in MDD compared with other antidepressant drugs in a systematic review of 6 pooled analyses. Escitalopram was marginally more effective than other antidepressants. A systematic review included both published and unpublished RCTs comparing the SNRIs, reboxetine, with placebo and/or SSRIs. A total of 13 acute treatment trials were included. Reboxetine showed no significant difference in remission rates from placebo. Reboxetine was inferior to placebo for both harm outcomes. Reboxetine was shown to be inferior to SSRIs (fluoxetine, paroxetine and

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New evidence that could potentially impacts the recommendations</strong></td>
<td>No evidence that would impact the recommendations</td>
<td>New evidence which could potentially impact recommendations</td>
<td>New evidence which could potentially impact recommendations</td>
<td><strong>Recs 10.14.1-3</strong></td>
</tr>
<tr>
<td><strong>A comprehensive meta-analysis to assess the comparative benefits and harms of second generation antidepressants in MDD was identified.</strong></td>
<td><strong>Placebo-controlled RCTs of antidepressants</strong></td>
<td><strong>New antidepressant (not reported in CG) drugs since 2011</strong></td>
<td><strong>New evidence which could potentially impact recommendations</strong></td>
<td><strong>The costs of some of the pharmaceuticals have changed significantly which may affect the results of the health economic model.</strong></td>
</tr>
<tr>
<td><strong>2 systematic reviews indicated that both TCAs and SSRIs are effective for depression treated in primary care and that the at the benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or non-existent, on average, in patients with mild or moderate symptoms.</strong></td>
<td><strong>SSRIs</strong></td>
<td><strong>Agomelatine:</strong> 2 studies have meta-analysed the evidence for agomelatine a melatonergic antidepressant, for treatment of depression. Both analyses indicate that agomelatine is at least as efficacious as escitalopram, fluoxetine, sertraline, venlafaxine and paroxetine in reducing depression scores for response and remission in patients with depression and severe depression.</td>
<td><strong>A GDG member noted that there are some new antidepressants on the horizon but nothing changing clinical practice.</strong></td>
<td><strong>A GDG member noted that there are some new antidepressants on the horizon but nothing changing clinical practice.</strong></td>
</tr>
<tr>
<td><strong>4 RCTs were identified. Overall, the evidence is mixed on the effectiveness of SSRIs in the treatment of adults with depression. As such, the identified new evidence is unlikely to change the current guideline recommendations.</strong></td>
<td><strong>Levomilnacipran sustained release:</strong> 1 RCT demonstrated that levomilnacipran sustained release improves depressive symptoms and functioning relative to placebo in patients with severe depression.</td>
<td><strong>The costs of some of the pharmaceuticals have changed significantly which may affect the results of the health economic model.</strong></td>
<td><strong>A GDG member noted that there are some new antidepressants on the horizon but nothing changing clinical practice.</strong></td>
<td><strong>The HE analysis and NMA</strong></td>
</tr>
</tbody>
</table>

### Other evidence

When an antidepressant is to be prescribed, NICE CG90 advises that it should normally be a SSRI in a generic form because SSRIs are as effective as other antidepressants and have a favourable risk–benefit ratio. It should be noted that a meta-analysis by Cipriani et al. (2009) also identified an antidepressant drug (sertraline) with superior efficacy to other SSNRIs and pharmaceutical options although there were limitations to this study and the clinical difference was small. This was incorporated into a health economic model within CG90 the results of which did not take into account adverse events which are a problem for some of these drugs.
citalopram) for remission rates and response rates and reboxetine was inferior to fluoxetine for withdrawals due to adverse events.

A systematic review which assessed 54 RCTs of venlafaxine, 14 RCTs of duloxetine and two direct comparisons in major depression was highlighted\(^6\). Both therapies were significantly more effective than placebo. Compared with SSRIs, venlafaxine showed significantly improved response rate but not remission rate; 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 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. Duloxetine resulted in significantly higher discontinuation rates due to adverse events than venlafaxine.

### Antipsychotic drugs

A Cochrane review of treatment with second-generation antipsychotics in MDD or dysthymia was highlighted\(^7\). Four RCTs compared quetiapine monotherapy with placebo. Although significant efficacy benefits of treatment were noted, the authors suggested that the results should

MDD.

- **Quetiapine** A meta-analysis of 3 RCTs of quetiapine extended release in adults with MDD indicated that the overall response and remission rates were higher for individuals treated with quetiapine than those with placebo\(^8\). Discontinuation rate due to adverse event were greater in the quetiapine group.
- An RCT found that long-term functioning and sleep quality in patients with MDD on extended-release quetiapine maintenance treatment following stabilisation with quetiapine XR was significantly improved compared to placebo\(^9\). In addition the 9 RCTs for unlicensed drugs were identified:
  - 5 RCTs for vortioxetine (Technology Appraisal due to start in 2014)\(^65\) 66 67 68 69, 1 RCT for GSK372475\(^70\), 1 RCT ziprasidone\(^71\) and 2 studies on desvenlafaxine\(^72\) 73.

### Placebo-controlled RCTs of Sertralinine

In addition new evidence indicated that seraltine should be first choice-the GDG did not make a recommendation for a specific SSRI.

The studies identified by the EU indicate:

- Some 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 made.
- There is also evidence to suggest additional advice on reboxetine may be appropriate.
- Whilst the 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.
be interpreted with caution. Furthermore, acceptability to patients was significantly reduced because of increased adverse events. The review also included one RCT 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 augmentation may be considered after initial inadequate response) and this limited evidence supports this view.

### Antidepressants

New evidence that was in line with the evidence presented within CG90 was identified for the following antidepressants:

1. Cochrane systematic review indicated that amitriptyline is effective in patients with major depressive disorder.\(^74\).

1. RCT indicated that duloxetine was effective in reducing symptoms in individuals with non MDD compared to placebo.\(^75\).

#### Antidepressant v active comparator +/- placebo

**Fluoxetine**

1. Cochrane systematic review of fluoxetine in comparison to MOIAs, TCA, SSRIs, SNRIs and newer agents (171 studies in total) in individuals with MDD was identified. The review indicated that there may be differences in terms of relative efficacy and tolerability within classes and individual antidepressants particularly in regards to sertraline and

identified from the high level literature search indicates that:

- There is very little, if any differences in efficacy between classes of pharmaceuticals such as SNRIs, SSNIs and third generation drugs. To date there has been no full analysis comparing all different classes of drugs let alone the individual drugs within each class.

- New agents are available that should be considered for Step 2 therapy.

- There are new physical treatments and adjunctive treatments that are potentially effective in treating depression.
1 study indicated that milnacipran (SNRI) and paroxetine (SSRI) showed comparable efficacy in terms of improvement in symptoms of depression in individuals with MDD⁷⁷.

A meta-analysis comparing desvenlafaxine with venlafaxine indicated that the two drugs were comparable in terms of safety and efficacy in the treatment of depression⁷⁸.

---

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), which other drugs or physical therapies are effective in treating depression (as monotherapy or augmentation of antidepressants)?

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence that could potentially impact recommendations</td>
<td>No evidence that could potentially impact the recommendations</td>
<td>New Physical treatments - Monotherapy</td>
<td>None</td>
<td>A small number of trials have been identified that have looked at therapies not reviewed within the guideline for depression. It may be worth considering these areas within</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo acupuncture indicated for the treatment of major depression.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A RCT found that individuals with MDD treated with a single injection of botulinum toxin were significantly less depressed as measured on the HDRS at 6 weeks compared to placebo.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Combination therapy with other agents**

Two RCTS indicated that augmentation of an antidepressant with another agent (vitamin D, oral creatine monohydrate was effective in improving depression measures.

Whereas 4 RCTs indicated that pioglitazone, oral scopolamine, triiodothyronine, or gaboxadol provided no additional benefit compared to antidepressant alone in the treatment of depression.

**Augmentation with physical therapy**

One RCT indicated that
augmentation of pharmacological treatment with electrical acupuncture may have some clinical benefit in patients with MDD. A RCT indicated that achronotherapeutic intervention (wake and light therapy) was more effective in treating than exercise in reducing depression symptoms in patients with MDD treated with duloxetine. The patients treated with exercise, also had a clinically relevant antidepressant response. 2 RCTs and 1 systematic review indicated that facilitated physical activity as an adjunctive treatment for adults with depression in individuals with symptoms of depression was no more effective than usual care.

11. Factors influencing choice of anti-depressants

Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), to what extent do the following factors affect the choice of drug?
adverse events (in particular, cardio toxicity), including long-term adverse events, discontinuation problems

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence that could potentially impact the recommendations</td>
<td>No evidence that could potentially impact the recommendations</td>
<td>No evidence that could potentially impact the recommendations</td>
<td>None</td>
<td>New evidence is consistent with guideline recommendations</td>
</tr>
<tr>
<td></td>
<td><strong>The pharmacological management of depression with psychotic symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 RCT indicated that mifepristone was no more effective than placebo(^93).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No evidence that could potentially impact the recommendations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Older Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A systematic review of the efficacy of antidepressants older depressed patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>indicated that all classes of antidepressant were more effective than placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>in achieving response(^94). In achieving remission however, only pooling all 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>classes of antidepressants showed a statistically significant difference from</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>placebo.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>The pharmacological management of depression with psychotic symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A systematic review concluded that antidepressant-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>antipsychotic co-treatment was superior to</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^92\)\(^93\)\(^94\)
monotherapy with either drug class in the acute treatment of psychotic depression.19

**Depression, antidepressants and Suicide**

Results from an RCT indicate that fluoxetine increases suicide ideation less than placebo during treatment of adults with minor depressive disorder over a 12 week period.96

---

<table>
<thead>
<tr>
<th>Q. In people whose depression has atypical features, what are the most effective treatment strategies?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence update</strong></td>
</tr>
<tr>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Q. In the treatment of depression (major depressive disorder, dysthymia, sub threshold depression and sub threshold depressive symptoms), do any of the following improve outcomes compared with other interventions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>– ECT</td>
</tr>
<tr>
<td>– TMS (integrate NICE Interventional Procedure Guidance) –</td>
</tr>
<tr>
<td>- light therapy</td>
</tr>
<tr>
<td>– VNS</td>
</tr>
<tr>
<td>– neurosurgery</td>
</tr>
</tbody>
</table>
### Evidence update

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No evidence that could potentially impact the recommendations</strong></td>
<td>None identified</td>
<td>No evidence that could potentially impact the recommendations</td>
<td>None</td>
<td>New evidence is consistent with guideline recommendations</td>
</tr>
<tr>
<td><strong>Sequencing treatments after initial inadequate response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current recommendations for augmentation of antidepressant therapies with antipsychotics appear to be supported by a Cochrane review.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A meta-analysis indicated that adjunctive atypical antipsychotic treatment was significantly more effective than placebo for both response to treatment and remission in patients with non-psychotic unipolar MDD resistant to prior antidepressant treatment.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A pooled analysis of two RCTs in patients with MDD provided evidence to support the NICE CG90 recommendation for augmentation with antipsychotic medication with quetiapine.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**No evidence that could potentially impact the recommendations**

**Sequencing treatments after initial inadequate response**

- A systematic review of the efficacy and safety of aripiprazole, olanzapine/fluoxetine combination, quetiapine, and risperidone for the adjunctive treatment for treatment-resistant MDD in adults indicated all were effective on remission and on clinician-rated depression severity measures. However on measures of functioning and quality of life, these medications produced either no benefit or a very small benefit.
- A systematic review of antidepressant combination for MDD in incomplete responders identified 5 studies with combinations involving mianserin, mirtazapine and desipramine. The review concluded that the practice of using a combination of antidepressants for major depression in incomplete responders is not warranted by the literature.
- A RCT comparing an early switch to a conventional strategy in patients with MDD to duloxetine found no differences in the primary end points.
One RCT indicated that combining pramipexole, and escitalopram for the treatment of MDD resistant depression was no more effective than either agent alone\textsuperscript{102}. Whereas pooled data from 3 RCTs found that adjunctive aripiprazole in patients with MDD who showed minimal response to initial antidepressant therapy was clinically meaningful\textsuperscript{97}. A RCT indicated that vortioxitene (unlicensed) was more effective than placebo in the prevention of relapse in patients with MDD\textsuperscript{103}.

**Adjunctive with psychosocial therapies**

An RCT indicates that CBT as an adjunct to pharmacotherapy for primary care based patients is more effective than TAU for reducing symptoms of depression in individuals with resistant depression\textsuperscript{104}. A small RCT (n=16) that compared MCBT with psycho-education for patients with major depression who did not achieve remission following antidepressant treatment indicated that MBCT was more effective than psycho-education\textsuperscript{105}.

**Adjunctive with Physical interventions**

A patient-level meta-analysis of studies evaluating vagal nerve stimulation therapy for treatment-resistant depression indicated that the augmentation of treatment as usual
with vagal nerve stimulation was produced greater response and remission rates\textsuperscript{106}.

A RCT compared combined and monotherapy of transcranial direct current stimulation (tDCS) with sertraline in individuals with MDD. The combined treatment showed more efficacy than either monotherapy which were comparable\textsuperscript{107}. Whereas in another study tDCS was not effective as an augmentation treatment for resistant MDD\textsuperscript{108}.

Q. In the treatment of depression, which patient characteristics predict response and relapse? For example, childhood trauma, age of onset, number of previous episodes, gender, and so on?

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>No relevant evidence identified</td>
<td>None</td>
<td>No relevant evidence identified</td>
</tr>
</tbody>
</table>

Q. In people whose depression has responded to treatment, what psychological and psychosocial strategies are effective in preventing relapse (including maintenance treatment)?

In people whose depression has responded to treatment, what strategies are effective in preventing relapse (including maintenance treatment)?

<table>
<thead>
<tr>
<th>Evidence update</th>
<th>3 year review</th>
<th>4 year review</th>
<th>Other evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence that could potentially impact the recommendations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychological interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence demonstrating the value of psychological therapies to reduce relapses supports current guidance was identified.</td>
<td>None identified</td>
<td>No evidence that could potentially impact the recommendations</td>
<td>GDG Feedback stated that a number of studies have provided more cautionary evidence about the role</td>
<td>New evidence is consistent with guideline recommendations</td>
</tr>
<tr>
<td><strong>Psychological interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A systematic review by the HTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence appears to support current recommendations for continued therapy to prevent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• 3 systematic reviews confirmed the effectiveness of MBCT in reducing the risk of relapse and support the NICE CG90 recommendation for use of MBCT in relapse prevention for patients at significant risk of relapse\textsuperscript{109-111}.

• A meta-analysis found that adjunctive treatment with IPT significantly reduced the recurrence rate compared with pharmacotherapy alone for relapse prevention\textsuperscript{29}. The EU concluded this may be a consideration for future reviews of NICE CG90.

Medication for relapse prevention
Two meta-analyses (Glue et al. (2010) Kok et al. (2011)) showed that continued therapy with all drug classes reduced the risk of relapse compared with placebo\textsuperscript{112,113}.

Electroconvulsive therapy (ECT)
An RCT provides some support for the recommendation of NICE CG90 that bilateral ECT is more effective than unilateral ECT\textsuperscript{114}.

Transcranial magnetic stimulation
A systematic review by found evidence of moderate efficacy but there was no evidence (from 9 studies) for treatment effects lasting beyond 12 weeks\textsuperscript{115}.

A systematic review found that slow-frequency repetitive TMS had a moderate positive effect considered comparable to that of fast-frequency repetitive TMS\textsuperscript{116}.

found that there was inadequate evidence to determine the clinical effectiveness or cost-effectiveness of low-intensity interventions for the prevention of relapse or recurrence of depression\textsuperscript{117}.

An RCT indicated that MBCT in recurrent depressed patients in addition to treatment as usual was more effective at reducing post-treatment depressive symptoms than TAU\textsuperscript{118}.

Whereas another RCT found that MCBT was comparable to structured patient education in the treatment of recurrent depression in patients in remission from depression\textsuperscript{119}.

Medication for relapse prevention
A Cochrane systematic review\textsuperscript{120} on continuation and maintenance treatments for preventing relapse of depression in older people concluded continuing antidepressant medication for 12 months appears to be helpful.

An RCT indicated that desvenlafaxine was effective of MBCT in preventing recurrences/relapse than would be implied by the firm endorsement of MBCT in the current guideline (references not provided). They then stated that MBCT may not be as effective as previously thought other than in groups with particular features (E.g. unstable recovery, sexual abuse as a child).

It is also not an option that many patients seem to want. No evidence in line with these statements has been found in the surveillance process.

relapse, although further research is needed to determine the optimal treatment regimen.

NICE CG90 recommends individual CBT or MBCT as psychological interventions for relapse prevention in people who are at significant risk of relapse.

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.

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.
compared to placebo in preventing relapse for a 6 month period in individuals with MDD who demonstrated a stable initial 20 week response to desvenlafaxine\textsuperscript{121}.

A RCT indicated that St John's wort was comparable to sertraline in preventing relapse in individuals with MDD\textsuperscript{122}.

**Transcranial magnetic stimulation**
A meta-analysis of high-frequency repetitive TMS indicates that this approach accelerates and enhances the clinical response and remission to antidepressants in major depression compared to sham\textsuperscript{123}.

**ECT**
An RCT indicated that in severe depression, high-dose ultra-brief right unilateral ECT appears to show matching acute antidepressant response to an equally high-dose brief pulse right unilateral ECT\textsuperscript{124}.

### 13 Pharmacological and Psychological interventions for sub threshold depressive symptoms and persistent sub threshold depressive symptoms (dysthymia)
No evidence that could potentially impact the recommendations

A systematic review and meta-analysis that included 6 RCTs of antidepressants (amitriptyline, fluoxetine, isocarboxazid and paroxetine) compared with placebo in patients with minor depression \(^{125}\). There was no significant difference between treatment arms in response to treatment or acceptability.

None identified

None identified

None

New evidence is consistent with guideline recommendations

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.

References for decision matrix


47. Cuijpers P, Hollon SD, Van SA et al. (2013) Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. BMJ Open 3:e002542.


72. Liebowitz MR, Tourian KA, Hwang E et al. (2013) A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder. BMC Psychiatry 13.

73. Papakostas GI, Culpepper L, Fayyad RS et al. (19-7-2013) Efficacy of desvenlafaxine 50 mg compared with placebo in patients with moderate or severe major depressive disorder: a pooled analysis of six randomized, double-blind, placebo-controlled studies. Int Clin Psychopharmacol.


